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Differential effects of oxycodone and venlafaxine on resting state functional connectivity—A randomized placebo-controlled magnetic resonance imaging study

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Summary

Aim: Different mechanisms may be involved in the antinociceptive effects of oxycodone (opioid) and venlafaxine (serotonin-norepinephrine reuptake inhibitor), and the aim of this study was to investigate the effect of these drugs on brain functional connectivity.

Methods: Resting state functional magnetic resonance imaging was acquired in 20 healthy volunteers before and after a 5-day treatment with oxycodone, venlafaxine, or placebo in a randomized, double-blind, crossover study. Functional connectivity analyses were performed between four predefined seeds (dorsal anterior cingulate cortex, rostral anterior cingulate cortex, posterior insula, and prefrontal cortex), and the whole brain.

Results: The overall interpretation was that there were differences between the effects of oxycodone and venlafaxine on functional connectivity. Oxycodone mainly showed decreased functional connectivity between limbic structures and to supralimbic areas (all $P < 0.05$). Venlafaxine also showed decreased functional connectivity between limbic structures and to supralimbic areas, but increased functional connectivity to structures in the midbrain and brain stem was also found (all $P < 0.05$).

Conclusions: Oxycodone and venlafaxine showed differential effects on resting-state functional connectivity as compared to placebo. This supports that the two drugs exert different mechanisms, and that the drugs in combination may exert additive effects and could potentially improve pain therapy.

KEYWORDS
functional connectivity, magnetic resonance imaging, opioid, resting state, serotonin-norepinephrine reuptake inhibitor

1 | INTRODUCTION

Chronic pain is often treated with opioids, but other drug classes such as the serotonin-norepinephrine reuptake inhibitors (SNRIs) have also shown analgesic effects. The effects of opioids are mediated by activation of opioid receptors, mainly present in supraspinal, spinal, and peripheral levels of the nervous system. SNRIs are thought to exert their effect primary on serotonergic and noradrenergic pathways.[1] Thus, different mechanisms may be involved in the antinociceptive effect of the two drug classes. Oxycodone is a mu-opioid receptor agonist, and venlafaxine is an SNRI (antidepressant) with an analgesic effect. The antinociceptive mechanisms of

venlafaxine are not fully elucidated, but it has been suggested to be related to the opioidergic system.[1-4]

Functional magnetic resonance imaging (fMRI) has been widely used to study brain activity, and the interest of using fMRI to study the modulation of neuronal activation by drug administration is growing. Resting-state fMRI (RSfMRI) is one approach to investigate drug mechanisms in terms of functional connectivity between brain regions during resting state; however, limited studies on drug effects on functional connectivity exist[5-7]. Gorka et al investigated the effect of oxycodone on functional connectivity from two seeds of interest, the dorsal anterior cingulate cortex (dACC), and the rostral anterior cingulate cortex (rACC) and demonstrated that oxycodone decreased functional connectivity to insula.[6]

As oxycodone and potentially venlafaxine have impact on the opioidergic system, we hypothesized that oxycodone and venlafaxine reveal both similar, but to some extent also different effect on functional connectivity. Recently we used magnetic resonance spectroscopy to show that oxycodone and venlafaxine decreased the concentration of the neurotransmitter glutamate in the anterior cingulate cortex, insula, and prefrontal cortex.[8] As these regions are also rich in opioid receptors, they were selected for the current study.[9-11] Accordingly, the aim of this study was to investigate the effect of oxycodone and venlafaxine treatment on functional connectivity in these regions of interest in healthy volunteers as compared to placebo.

2 | METHODS

Twenty healthy male subjects (mean age 24.6 ± 2.5 years) were MRI scanned in a randomized, double-blind, three-way crossover study. They were treated with oxycodone, venlafaxine, or placebo and scanned on day one (before each treatment) and after 5 days of treatment. The "wash-out" periods between treatments were at least 1 week. The study was carried out at Department of Radiology, Aalborg University Hospital, Denmark and at MechSense, Department of Gastroenterology and Hepatology, Aalborg University Hospital, Denmark.

2.1 | Experimental protocol

All subjects underwent a routine health screening conducted by a medical doctor to exclude subjects with any pain and nervous system related conditions, and subjects with a history of abuse or mental disorders were also excluded. Subjects gave written, informed consent before enrollment and could withdraw from the study at any time. Inclusion criteria were male, age between 20 and 35 years, normal medical examination, ability to read and understand Danish and of Scandinavian origin.

The study was approved by the local Ethics Committee (N-20130011) and the Danish Medicines Agency (201300017030) and monitored by the Good Clinical Practice unit at Aalborg and Aarhus University Hospitals, Denmark. The study was conducted according to the Declaration of Helsinki and registered with the European Clinical Trials Database (EudraCT 2013-000170-30).

2.2 | Drug administration

Oxycodone (10 mg extended release, "Accord," Accord Healthcare, Salzburg, Austria), venlafaxine (37.5 mg extended release, "Stada," Stada Nordic ApS, Herlev, Denmark), and placebo (8 mm tablets) were orally administered. Tablets were over-encapsulated in DBcaps®, Swed.orange, size AA, "Capsugel®, Basel, Switzerland." Capsules were administered once on day 1 and day 5, and twice a day on day 2-4 (8 doses in total with twelve hours in between). Medication was handled, packed, and delivered by Hospital Pharmacy, Central Denmark Region, Denmark.

2.3 | Brain imaging

Magnetic resonance imaging data were acquired on a 3T GE scanner (GE Signa HDxt, General Electric, Milwaukee, WI, USA) with a standard eight-channel head coil. The head was fixed using foam pads. A high-resolution T1-weighted structural scan was acquired (TR/TE: 9.0 ms/3.6 ms, flip angle: 14°, field of view (FOV): 25 cm, matrix: 320 × 320, and voxel size: 0.8 × 0.8 × 1.0 mm). Resting-state fMRI was acquired for 6:32 minutes as 192 volumes of gradient echo planar images (TR/TE: 2000 ms/30 ms, flip angle: 90°, FOV: 24 cm, matrix: 64 × 64, and voxel size: 2.5 × 2.5 × 3.8 mm). Four dummy scans were acquired for all functional scans prior to scanning of the 192 volumes. Volunteers were instructed to remain awake and to lie in the most relaxed position with closed eyes.

2.4 | Resting-state functional connectivity data analyses

The fMRI data were preprocessed and analyzed using SPM12 (Wellcome Trust Centre for Neuroimaging, London, UK). Images were slice timing corrected, realigned to correct for head movement, structural images and functional images were coregistered, segmented into CSF, white matter and gray matter, normalized to a standard brain in the MNI (Montreal Neurological Institute, Montreal, Canada), and smoothed (full width at half maximum = 8 mm). The functional connectivity (CONN) toolbox,[12] www.nitrc.org/projects/conn, was used for connectivity analyses. Effects of nuisance covariates, cerebrospinal fluid, white matter, and motion parameters (including the first derivative), obtained during realignment were regressed from the data. The data were band-pass filtered to 0.008-0.09 Hz. Seed-to-voxel first-level analyses for all subjects were performed by calculating the temporal correlation between blood-oxygen-level-dependent signals from four predefined seeds to all voxels in the brain. The predefined seeds were: (i) the dorsal anterior cingulate cortex (dACC) (10 mm sphere around center MNI coordinates (0, 6, 40); (ii) rostral anterior cingulate cortex (rACC) (10 mm sphere around center MNI coordinates (0, 46, 2); (iii) right posterior insula (insula) (10 mm sphere around center MNI coordinates

(37, −27, 12); and (iv) right prefrontal cortex (PFC) (10 mm sphere around center MNI coordinates (14, 48, 28)). The MarsBar toolbox was used to extract seeds.[13] The second-level analyses were performed in SPM12. Differences in functional connectivity across the three baselines (before treatments) were investigated for each seed using paired sample t tests. Treatment effects were investigated using paired sample t tests between treatment sessions (placebo vs oxycodone, placebo vs venlafaxine), and the directions of effects were investigated (placebo > oxycodone; placebo < oxycodone; placebo > venlafaxine; placebo < venlafaxine). We used a primary threshold ($P < 0.005$) and cluster-extent based thresholding with k > 220 voxels. The MNI coordinates (X, Y, Z) for the maximum t-value (obtained from the *t* tests) in each activated area were presented together with the number of voxels and the z-value.

3 | RESULTS

Due to logistic challenges, one subject missed an MRI scan before venlafaxine treatment, and another subject missed a scan after oxycodone treatment. Furthermore, one subject was excluded due to high level of movements (>2.5 mm and/or 2.5 degrees). Consequently, 18 subjects were included for analyses between baseline scans, 18 subjects were included for analyses of the oxycodone effects, and 19 subjects were included for analyses of the venlafaxine effects.

3.1 | Treatment effects on functional connectivity

To verify the changes in functional connectivity to be treatment related, functional connectivity of measurements before treatments were compared. No significant differences in functional connectivity of areas relevant for the treatment response (as reported below for oxycodone and venlafaxine treatment) were seen between the baseline scans. Differences in baseline connectivity were confined to the occipital cortex, lingual gyrus, intracalcarine cortex, middle temporal gyrus, parahippocampal gyrus, and temporal pole (all $P < 0.05$), see Table S1.

The effects of oxycodone and venlafaxine treatment on functional connectivity from the predefined seeds (dACC, rACC, insula, and PFC) to other brain regions are presented in Tables 1-4, respectively and in Figure 1. To provide an overview, the overall trends of the treatment effects are summarized in Table 5.

3.2 | Oxycodone

Significant *decreased* functional connectivity (compared to placebo) was found for oxycodone treatment (i) between dACC and insula and parietal regions, (ii) between rACC and frontal regions, (iii) between insula and operculum and parietal regions, and (iv) between PFC and posterior cingulate and parietal regions (all $P < 0.05$). Significant *increased* functional connectivity was found (i) between dACC and anterior cingulate regions, (ii) between rACC and frontal regions, and (iii) between PFC and anterior cingulate and parietal regions (all $P < 0.05$). Overall, oxycodone mostly affected functional connectivity in limbic and supralimbic regions.

3.3 | Venlafaxine

Significant *decreased* functional connectivity (compared to placebo) was found for venlafaxine treatment (i) between dACC and posterior cingulate, parietal regions, and frontal regions, (ii) between rACC and insula/operculum and frontal regions, (iii) between insula and parietal regions, and (iv) between PFC and insula/operculum and parietal regions (all $P < 0.05$). *Increased* functional connectivity was found (i) between dACC and frontal regions, rACC, and frontal regions and (ii) between

TABLE 1 Functional connectivity between dACC and other voxels in the brain

Region name	X	Y	Z	Voxels	Z-score	P_{uncorr}
Oxycodone<placebo						
Superior parietal lobule, left	−28	−48	76	908	4.21	<0.001
Supramarginal gyrus, right	64	−34	38	813	4.08	<0.001
Insula	42	2	2	325	3.32	0.010
Oxycodone > placebo						
Precentral gyrus	−4	−22	58	598	3.91	0.001
Anterior cingulate gyrus	2	40	18	245	3.69	0.021
Venlafaxine < placebo						
Superior frontal gyrus, left	−8	44	34	637	3.95	0.001
Supramarginal gyrus, left	−68	−48	26	512	3.84	0.002
Middle frontal gyrus, left	−52	26	40	311	3.72	0.010
Posterior cingulate gyrus	2	−24	38	278	3.66	0.014
Venlafaxine > placebo						
Superior frontal gyrus, right	22	5	54	223	3.61	0.024

Oxycodone < placebo, decreased functional connectivity; Oxycodone > placebo, increased functional connectivity, same nomenclature for venlafaxine.

TABLE 2 Functional connectivity between rACC and other voxels in the brain

Region name	X	Y	Z	Voxels	Z-score	P_{uncorr}
Oxycodone < placebo						
Middle temporal gyrus, left	−64	−8	−22	381	4.15	0.006
Frontal medial cortex, left	14	44	−6	544	4.02	0.002
Oxycodone > placebo						
Middle frontal gyrus, left	−18	12	36	767	4.28	<0.001
Middle frontal gyrus, right	22	4	40	791	3.80	<0.001
Venlafaxine < placebo						
Insula, left	−44	−22	2	1384	4.94	<0.001
Parietal operculum, right	58	−32	22	374	4.64	0.007
Insula, right	54	2	−8	1356	4.08	<0.001
Superior frontal gyrus, right	16	2	70	292	3.76	0.014
Frontal orbital gyrus/inferior frontal gyrus	44	30	−6	231	3.23	0.026
Venlafaxine > placebo						
Cerebellum	−26	−94	−38	480	4.47	0.003
Superior frontal gyrus	2	56	46	361	3.49	0.007
Lingual gyrus	0	−76	−2	432	3.34	0.004

TABLE 3 Functional connectivity between insula and other voxels in the brain

Region name	X	Y	Z	Voxels	Z-score	P_{uncorr}
Oxycodone < placebo						
Opercular cortex, right	58	−10	12	1944	4.04	<0.001
Postcentral gyrus, left	−40	−24	40	676	3.65	0.001
Superior temporal gyrus, right	−70	−30	2	587	3.53	0.001
Precentral gyrus, left	−40	−18	58	227	3.15	0.030
Oxycodone > placebo	NS					
Venlafaxine < placebo						
Postcentral gyrus, left	−52	−28	44	877	5.03	<0.001
Venlafaxine > placebo						
Thalamus	6	−16	10	475	4.29	0.003
Cerebellum	24	−54	−48	549	3.68	0.001
Brain stem	8	−14	−18	225	3.60	0.026
Cerebellum	18	−86	−52	424	3.54	0.004

NS, nonsignificant.

insula and thalamus and brain stem (all $P < 0.05$). Overall, venlafaxine mostly affected functional connectivity in the limbic system and in deeper structures (thalamus and brain stem).

4 | DISCUSSION

We investigated the effect of oxycodone and venlafaxine on cingulate, insula, and prefrontal functional connectivity to other brain regions. In comparison with placebo, functional connectivity was affected by both active treatments and involved all the predefined brain areas. The effect of oxycodone on functional connectivity was more pronounced in the limbic and supralimbic system, whereas the effect of venlafaxine on functional connectivity was more pronounced in the limbic system and in deeper structures (thalamus and brain stem).

4.1 | Drug effects on functional connectivity

Previous studies have shown MRI resting-state functional connectivity to be useful to evaluate drug action on the central nervous system.[5,14,15] Oxycodone is a mu-opioid receptor agonist, and a number of previous studies have reported that cingulate, insula, and prefrontal cortex are rich in opioid receptors.[9-11] ACC, especially, has high opioidergic binding potential, and it has previously been demonstrated that oxycodone treatment reduced functional connectivity

TABLE 4 Functional connectivity between PFC and other voxels in the brain

Region name	X	Y	Z	Voxels	Z-score	P_{uncorr}
Oxycodone < placebo						
Precuneus/posterior cingulate gyrus, left	−18	−50	8	379	4.10	0.004
Temporal occipital cortex, left	−20	−52	−16	445	3.92	0.002
Postcentral gyrus, right	12	−44	78	260	3.84	0.014
Paracingulate gyrus	6	42	−10	256	3.54	0.015
Cerebellum	10	−40	−28	402	3.48	0.003
Oxycodone > placebo						
Precentral gyrus, left	−40	−6	46	1954	5.05	<0.001
Superior parietal gyrus, right	38	−48	48	361	4.39	0.005
Precentral gyrus, right	46	4	34	351	3.97	0.006
Middle temporal gyrus, left	−64	−60	4	293	3.64	0.010
Superior parietal lobule, left	−38	−54	50	270	3.60	0.013
Anterior cingulate/paracingulate	−16	12	38	251	3.34	0.016
Venlafaxine < placebo						
Opercular cortex, left	−42	−10	18	276	3.55	0.016
Venlafaxine > placebo						
Supramarginal gyrus, left	−64	−44	44	248	3.36	0.021

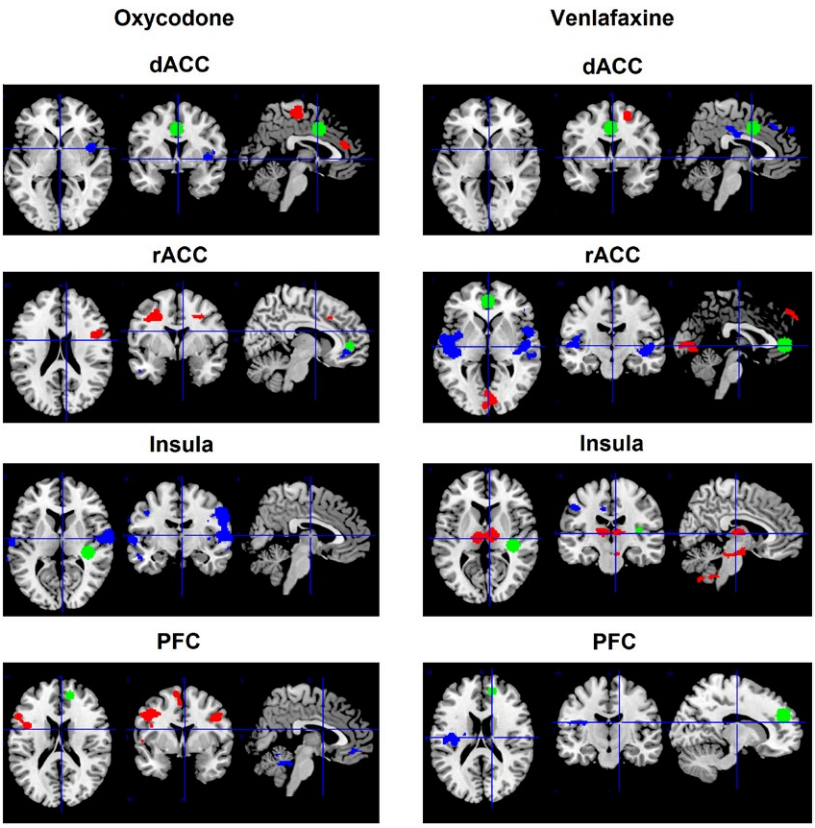

FIGURE 1 Treatment effects on functional connectivity between preselected seeds (the dorsal anterior cingulate cortex (dACC), the rostral anterior cingulate cortex (rACC), the right posterior insula (insula) and the right prefrontal cortex (PFC)) and other voxels in the brain for oxycodone (left column) and venlafaxine (right column) as compared to placebo. Green: preselected seed; Blue: decreased functional connectivity as compared to placebo; Red: increased functional connectivity as compared to placebo. The presented results are cluster-extent based thresholded (k > 220) with primary threshold of $P < 0.005$. Note that the seeds of interest (green) are the same size (10 mm sphere) for all preselected seeds, and not visible in all slices as the selected slices focus on the brain regions with changes in connectivity

between dACC/rACC and insula.[6] In this study, we demonstrated that oxycodone decreased functional connectivity in the limbic system. In line with Gorka et al we found reduced functional connectivity between dACC and insula for oxycodone treatment and furthermore functional connectivity was decreased between insula and opercular cortex. ACC and insula work together in the salience network and integrate interoceptive information with emotional salience and awareness.[16,17] Moreover, ACC and insula are regions well known to be important in pain processing.[18] Increased functional connectivity between ACC and insula during rest has been

TABLE 5 Summary of the overall treatment effects (as compared to placebo) on functional connectivity between dACC, rACC, insula, and PFC cortex and relevant brain regions

	dACC	rACC	Insula	PFC
Insula/operculum regions	Oxycodone ↓	Venlafaxine ↓	Oxycodone ↓	Venlafaxine↓
Cingulate regions	Oxycodone ↑ (a) Venlafaxine ↓ (p)			Oxycodone ↓ (p) ↑ (a)
Parietal regions	Oxycodone ↓ Venlafaxine ↓		Oxycodone ↓ Venlafaxine ↓	Oxycodone ↓↑ Venlafaxine ↓
Frontal regions	Venlafaxine ↓↑	Oxycodone ↓↑ Venlafaxine ↓↑		
Thalamus/brain stem			Venlafaxine ↑	

dACC, dorsal anterior cingulate cortex; rACC, rostral anterior cingulate cortex; PFC, right prefrontal cortex; ↓, decreased functional connectivity; ↑, increased functional connectivity; ↓↑, decreased and increased functional connectivity has been found within the region; (a), anterior region; (p), posterior region.

demonstrated in chronic pain conditions,[19,20] and in an acute pain model, we showed increased activity in ACC, insula, and thalamus in healthy volunteers, whereas morphine (mu-opioid receptor agonist) decreased activity in insula, ACC, and inferior parietal cortex.[21] Even in absence of painful stimulation, we demonstrated in the present study that oxycodone decreased functional connectivity in these brain regions. Hence, we may infer that modulation of functional connectivity in these brain regions could be related to activation of opioid receptors and hence changed neuronal activity in these regions. Furthermore, in our recent magnetic resonance spectroscopy study, decreased concentration of the neurotransmitter glutamate was observed in response to oxycodone treatment (and a trend for venlafaxine treatment) in the insula, ACC, and prefrontal cortex.[8] In addition to this, in two EEG source localization studies, which used the same cohort of healthy volunteers as this study, we showed frontal shift of cingulate activity in response to oxycodone treatment in the cingulate-operculum network underlying nociceptive withdrawal reflex evoked potentials and an increase in cingulate activity coupled with a decrease in operculum activity,[22] and we observed a decrease in insula and frontal gyrus activity underlying tonic pain following oxycodone treatment.[23] It can also be proposed then, that the shifts and changes of activity seen in the previous surface EEG studies could be related to the changes in functional connectivity as observed in our present MRI study. We found both increased and decreased functional connectivity from cingulate to frontal regions. Increased functional connectivity between dACC and frontal regions has previously been shown in response to oxycodone treatment, and this has been suggested to reflect acutely increased cognitive control over subjective pain unpleasantness.[6] As overall reduced functional connectivity was seen for all seeds of interest to parietal regions, this may indicate an inhibition of neuronal activity, which may be central in inhibition of pain processing, when pain is present.

Venlafaxine is an antidepressant drug, which modulates the serotonergic and noradrenergic pathways, and is believed to involve descending pain inhibitory systems.[3] It is still not elucidated how this mechanism differentiates from opioidergic pathways, and a complex interaction between several neurotransmitter systems might be involved in the underlying mechanisms for the antinociceptive effects of venlafaxine. Similar to oxycodone, venlafaxine demonstrated decreased functional connectivity in the limbic system. In particular, decreased functional connectivity was observed between rACC and insula, which may indicate the involvement of opioidergic pathways at least to some extent. Previous studies have proposed that venlafaxine improves attention, motor activity, and response time.[24] To observe the effects of venlafaxine on the human motor cortex, a study using fMRI in combination with different motor tasks showed that one-week treatment improved the finger-tapping rate and increased the activations of contralateral primary sensorimotor cortex, contralateral premotor cortex, and contralateral supplementary motor area.[25] On the other hand, the authors found the activation of the parietal cortices was decreased. Another study in duloxetine (SNRI) in healthy volunteers showed reduced functional connectivity between the medial prefrontal cortex and the lateral parietal cortex.[26] We also found venlafaxine to reduce functional connectivity to parietal regions. Additionally, using the same cohort of healthy volunteers as in the present study, in our previous EEG study involving spinal and cortical evoked potentials, we observed a decrease in latencies induced by venlafaxine treatment,[27] and in an EEG study involving tonic pain, we observed a decrease in alpha activity induced by venlafaxine treatment, which was correlated to decrease in pain scores.[23] The observed changes in the surface EEG could be related to changes in functional connectivity observed in our present MRI study. Consequently, it could be speculated that these changes in functional connectivity to venlafaxine treatment are centrally involved in the mechanisms of pain relief. Finally, we observed that venlafaxine increased functional connectivity from insula to thalamus and the brain stem. This increased functional connectivity may present a part of the thalamic feedback loop of descending pain inhibition resulting in reduction of pain signaling. However, experiments involving pain are needed to verify this.

4.2 | Methodological considerations

In this study, we investigated the effect of oxycodone and venlafaxine on functional connectivity during resting state, and we demonstrated drug induced changed functional connectivity. An important advantage of estimation of functional connectivity during rest, and not during task (eg, painful stimulation), is that the estimated effects are not confounded by, for example, anticipation, performance, or other task-induced confounders. On the other hand, as this study did not include pain models or subjects with chronic pain, the analgesic effects of the drugs cannot be distinguished and further research is needed to address that aspect.

As we used a hypothesis-driven seed-based method and a relatively small sample size, we used a liberal primary threshold ($P < 0.005$)[12] followed by a cluster-extent based thresholding method. An advantage of using cluster-extent based thresholding is higher sensitivity in identifying significant regions, but low spatial specificity is a disadvantage, and accurate inferences about the true activation are difficult.[28]

The treatment period of 5 days for venlafaxine may not be sufficient to reach the maximal effect in the brain and should optimally have been longer (ie, at least 2 weeks).[29] However, this study was conducted in healthy subjects, and it was not feasible to treat for longer than 5 days for ethical reasons. Moreover, effects of venlafaxine on the pain system have been observed already after few days of treatment.[30] Another study found that a single dose of a serotonin reuptake inhibitor dramatically altered functional connectivity in the human brain.[31] Hence, although the longer treatment is desired for the maximal clinical effect, we believe that the five-day treatment in this study was long enough to observe relevant changes in the central nervous system.

5 | CONCLUSIONS

In this placebo-controlled study in healthy subjects, the effects of oxycodone and venlafaxine treatment on functional connectivity were investigated. Functional connectivity was affected by both treatments involving all the investigated brain regions. Differential effects of oxycodone and venlafaxine on resting-state functional connectivity were found supporting that venlafaxine exerts different mechanisms compared to oxycodone. Thus, future drug development for pain treatment could be improved as both drugs can be used as monotherapy, but also in combination with different mechanisms can be targeted. However, future studies involving pain are needed to support this idea.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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