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Epilepsy & Behavior 92 (2019) 269–275

Contents lists available at ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

Severe seizures as a side effect of deep brain stimulation in the dorsal peduncular cortex in a rat model of depression

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ARTICLE INFO

Article history:
Received 27 September 2018
Revised 29 December 2018
Accepted 4 January 2019
Available online 4 February 2019

Keywords:
High frequency (HF)
Deep brain stimulation (DBS)
Ventromedial prefrontal cortex (vmPFC)
Dorsal peduncular cortex (DPC)
Seizure

ABSTRACT

Deep brain stimulation (DBS) has shown to have antidepressant effects in both human trials and animal studies. However, the optimal target and the underlying therapeutic mechanisms remain to be determined. In this study, we investigated if high frequency (HF) DBS in the dorsal peduncular cortex (DPC) alleviates depressive-like behavior in an experimental model of depression. Surprisingly, HF DBS in the DPC caused acute induction of seizures in ~40% of animals stimulated with clinically relevant stimulation parameters. Reducing the stimulation's amplitude by 50% did not alter seizure occurrence. Electroencephalographic (EEG) recordings showed seizures up to Racine stage IV lasting up to 4 min after cessation of stimulation. We conclude that HF DBS in the DPC is not suitable for mood-related experiments in rats but could be a potential model for seizure induction.

1. Introduction

Major depression is a common mental disorder affecting more than 300 million people worldwide [1]. Despite advances in antidepressant treatment, 10–30% of the patients show an inadequate respond to therapy. This treatment-resistant depression (TRD) is diagnosed when a patient shows a poor or unsatisfactory response to two to four medications and psychotherapy treatment sessions [2]. For these patients' alternative treatments are widely investigated. Deep brain stimulation (DBS) is one of these treatment options initially showing promising results in different open-label trials. Nevertheless, more recent randomized controlled trials could not replicate these positive findings [3]. Factors that contribute to these varying results include differences in study design, stimulation settings, patient selection, and targets for DBS. Regarding the latter, there is no consensus about the best target for DBS in treating TRD. To get a better insight into the neurobiology of depression and to study potentially better targets for DBS, further investigation of the different neuronal circuits involved in mood is needed. We previously showed that DBS of the ventromedial prefrontal cortex (vmPFC) caused antidepressant effects in behavior in a rat model of depression [4]. The vmPFC is part of the prefrontal cortex (PFC) and consists of multiple interconnected regions fulfilling numerous functions such as the regulation of emotion, decision making, the process of extinction and fear conditioning, and self-directed cognition [5]. In rodents, the mPFC can be subdivided into four major subdivisions namely the dorsal anterior cingulate cortex, the prelimbic (PreL) cortex, the infralimbic (IL) cortex, and the dorsal peduncular cortex (DPC), each fulfilling different functions [6,7]. Further dissection of the pathways causing the antidepressive effects may give important insights into the neurobiology of this behavior. In this study, we used an experimental model of depression induced by 'chronic unpredictable stress (CUS)'. This model mimics the pathway to depression by chronic exposure to various unpredictable stressors inducing a range of behavioral and physiological changes parallel to symptoms of depression. Our aim was to electrically stimulate the DPC with DBS which is understudied. We expected to see different antidepressive behavioral effects when stimulating the DPC then what is seen with stimulating the IL and PreL subregions. We believe that multiple small microcircuits are responsible for different traits seen in depression and that stimulating the DPC would alleviate particular traits. However, no behavioral research has yet been done about the specific function of the DPC. Our hypothesis was that the different

Abbreviations: AcbC, midrostrocaudal level of the nucleus accumbens core; AcbS, dorsal caudomedial shell of the nucleus accumbens; AP, anteroposterior; BDA, biotinylated dextranamine; BLA, basolateral nucleus of the amygdala; BST, bed nucleus of stria terminalis; CeA, central nucleus of the amygdala; CUS, chronic unpredictable stress; DBS, deep brain stimulation; dlPAG, dorsolateral periaqueductal gray; DPC, dorsal peduncular cortex; DV, dorsoventral; EEG, electroencephalographic; FST, forced swim test; HF, high frequency; HCE, home cage emergence; IL, infralimbic; ML, mediolateral; mPFC, medial prefrontal cortex; NAc, nucleus accumbens; PFC, prefrontal cortex; PreL, prelimbic; SEM, standard error of the mean; SIT, sucrose intake test; SPC, sulcal prefrontal cortex; SPT, sucrose preference test; STN, subthalamic nucleus; TRD, treatment-resistant depression; VMH, ventromedial hypothalamus; vmPFC, ventromedial prefrontal cortex; VS, ventral striatum.

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https://doi.org/10.1016/j.yebeh.2019.01.007
1525-5050/

regions of the vmPFC are responsible for different modalities of mood-related behavior such as anhedonia, anxiety, behavioral despair, and motivation. This could be critically important for the treatment of various mood-related disorders such as depression and will give the opportunity to integrate a symptom-based treatment.

2. Material and methods

2.1. Subjects

We used male rats (300–400 g; Sprague Dawley, n = 29, Envigo), housed in standard Individual Ventilated Cages (IVC) in a controlled environment (temperature 22 °C, humidity 59 (rH)) using a 12/12-h reversed dark/light cycle (light on 07 AM–07 PM). After DBS surgery, all animals were housed individually. Food and water were given *ad libitum*, except during the CUS model when the given stressor related to food or water intake. All the experiments were carried out in accordance with the Animal Experiments and Ethics Committee of Maastricht University.

2.2. Electrode construct

All stimulation electrodes were custom made by the engineering department (IDEE) of Maastricht University [8]. A DBS electrode consists of a bilateral construct of two concentric bipolar coaxial gold-coated stimulation electrodes containing a platinum–iridium inner wire; shaft diameter 0.3 mm, tip (core) diameter 0.08 mm, with an interelectrode distance of 1.2 mm.

2.3. Electrode implantation

Following an induction of isoflurane anesthesia, rats were placed into a stereotactic frame and their body temperature was kept a 37 °C using a thermoregulated heating pad. Throughout the whole surgical procedure, rats were sedated with 2,5% isoflurane inhalation anesthesia. Initially, a bur whole in the skull was made, and the DBS electrode construct was implanted into the DPC (anteroposterior (AP): +3.00 mm. mediolateral (ML): ±0.60 mm dorsoventral (DV): 5.00 mm), according to the brain atlas of Paxinos and Watson 6th edition [9]. After surgery, all animals were given a postoperative recovery period before introducing the stress protocol.

2.4. The CUS model

The CUS protocol was executed as described before [4]. The stressors given consisted of soiled-cage bedding with 300 ml of cold water (4 °C), intermittent illumination every 2 h during their dark cycle, stroboscopic light (2.5 Hz), food or water deprivation, housing in mouse cages, and paired-housing where the rat alternatingly was the intruder or resident and a condition with no stressor. Each stressor lasted between 10 and 14 h and was given in a random order at an unpredictable time during both the morning and evening. Stressors were given for 3 consecutive weeks.

2.5. DBS stimulation parameters

We used clinically relevant stimulation parameters with a biphasic and monophasic, bipolar high frequency (HF) stimulus (100 Hz) with a stimulation amplitude of 100 μA and a pulse width of 100 μs. For a precise delivery of the stimulus we used an A-M systems model 3800 8 channel stimulator connected to stimulus isolation units' model 3820.

For our experiments, we have chosen an acute stimulation paradigm since we previously showed antidepressant effects upon acute DBS in the PFC in a rat model of depression [4]. It is debatable if a chronic stimulation paradigm should be used to measure antidepressive-like effects of DBS. We focused on the acute antidepressant effects of DBS which has been published before. Jimenez-Sanchez et al. has shown that acute DBS in the IL cortex of healthy rats, alleviates behavioral despair in the forced swim test (FST) and reduces the latency to feed in the novelty-suppressed feeding test (NSFT) [10].

2.6. Behavioral testing

During behavioral testing, animals received either stimulation or sham stimulation. For sham stimulation, the animals were attached to a DBS cable without attachment to the stimulator. In all our experiments, animals were stimulated 15 min before behavioral testing and during the entire behavioral test.

2.6.1. Sucrose intake test (SIT)

The day before testing, all animals were habituated to a 1% sucrose solution instead of water for 1 h. This was followed by a period of 14 h of food and water deprivation, starting at the beginning of their dark phase. After the 14 h fasting period, all animals were offered a 1% sucrose solution for 1 h. The sucrose intake was calculated from the total amount of 1% sucrose solution consumed divided by the bodyweight of the animal (g/kg).

2.6.2. Home-cage emergence (HCE) test

In this test, the home-cage of the animal was opened and placed in an open field. An iron grid was placed over the edge of the home-cage to ease leaving the home-cage. The total amount of time it takes for the animal to get out of their home-cage onto the iron grid was measured. The session lasted for 10 min. If the rat did not escape its home cage within these 10 min, the rat was given a score of 600 s.

2.7. Statistical analysis

All the data are represented as mean ± standard error of mean (SEM), and the analyses were performed with IBM SPSS Statistics 24. Normality and homogeneity of variance of the data were checked using the Kolmogorov–Smirnov test and normality plots. The data of our behavioral tests were analyzed using either a one-way analysis of variance (ANOVA), a Kruskal–Wallis H test, or Mann–Whitney U-test, as appropriate. All P-values < 0.05 were considered significant.

3. Results

3.1. CUS model

To test for CUS susceptibility, we performed a SIT right before the onset of CUS and 3 weeks after the onset of CUS. Rats exposed to the CUS model, showed less increase in 1% sucrose solution consumption over time compared to the nonstressed control animals. This finding

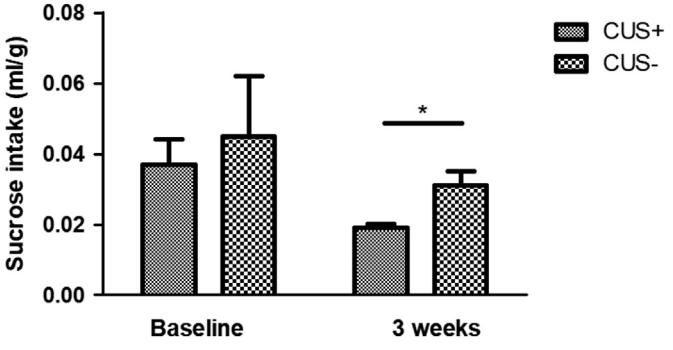

Fig. 1. Sucrose intake test before and after 3 weeks of CUS. Results of the SIT at t = 0 baseline and after 3 weeks of CUS. Data are represented as means ± s.e.m. (CUS+ n = 18, CUS+ sham n = 6, CUS− n = 6). *p < 0.05. CUS+ chronic unpredictable stress, CUS− nonstressed controls.

indicates a state of anhedonia in the rats undergoing the CUS model for 3 consecutive weeks (Fig. 1).

At baseline (t = 0), no significant difference between the group of stressed (CUS+) and nonstressed (CUS−) animals was found (Mann–Whitney U, U = 65.50, z = −0.338, p = 0.736). After 3 weeks of CUS, the 1% sucrose consumption levels showed a significant difference between the CUS+ and CUS− animals (Mann–Whitney U, U = 14.500, z = −2.953, p = 0.003).

3.2. Behavioral testing

After 3 weeks of CUS, we started behavioral testing for all animals. Part of the stressed animals (n = 18) underwent HF DBS, and part of the stressed animals (n = 6) served as sham controls (CUS+ sham) being coupled to a DBS cable but not to the stimulator. For HF DBS, biphasic bipolar stimulation with a frequency of a 100 Hz an amplitude of a 100 μA, and a pulse width of a 100 μs was given. The animals not undergoing CUS (n = 6) served as a nonstressed control group and therefore were also not stimulated. One animal in the CUS+ DBS group was excluded from behavioral analysis since its electrode was not placed in the DP region.

The HCE test showed no significant effect between the three groups, but a trend can be seen after the second day of testing between the CUS+ DBS and CUS− groups, where the stressed group undergoing HF DBS tends to remain longer in their home-cage than the nonstressed controls (HCE1: 1.572(2) = 0.456 and HCE2: 5.591(2) = 0.061, P < 0.05 (Fig. 2)). Since no significant differences were found, we cannot speak of a neophobia effect of DBS in the DPC.

Sucrose intake test with HF DBS in the DPC was executed in which surprisingly, 5 out of the 17 stimulated animals showed involuntary movements and seizure-like behavior upon start of HF DBS in the 15 min of prestimulation. A significant difference between the different groups was found (one-way ANOVA, 4.741(3,24) = 0.010, p < 0.05) in which the significant effect was seen between the CUS+ DBS animals experiencing seizures and the CUS− group (p = 0.007) (Fig. 3). A trend towards less 1% sucrose intake between the animals experiencing involuntary movements upon DBS and the CUS+ sham control group was seen (p = 0.089). No significant difference was seen between the CUS+ DBS sham and CUS− groups.

No test for locomotion has been done, but we observed that animals displaying seizures upon DBS showed less explorative behavior and were less active during the postictal phase. This decrease in locomotion lasted between 5 and 15 min depending on the severity of their seizure (Supplementary videos 1 and 2). High frequency DBS was stopped when a seizure was observed and continued when the animal did not show seizure-like behavior anymore.

During further behavioral testing, we observed that more CUS+ animals receiving HF DBS began to display seizure-like behavior (~40%, n = 7 out of n = 17). Seizures were observed in 5 out of 17

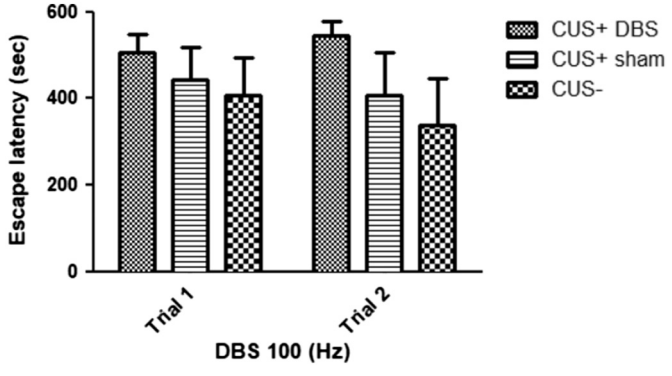

Fig. 2. Home cage emergence test with DBS. Results of the HCE test during DBS on two consecutive days. Data are represented as means ± SEM (CUS+ DBS n = 17, CUS+ sham n = 6, CUS− n = 6). *p < 0.05. CUS+ chronic unpredictable stress, CUS− nonstressed controls. No seizure occurrence was seen.

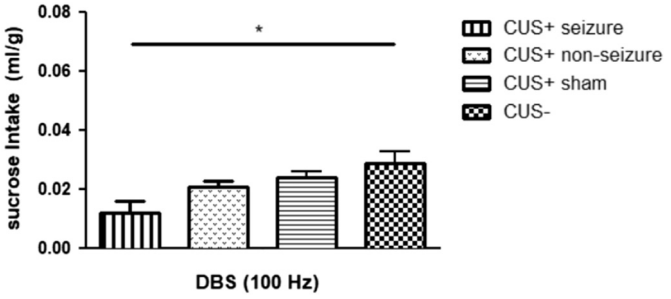

Fig. 3. Sucrose intake test with DBS. Results of the SIT during DBS. Data are represented as means ± SEM (CUS+ DBS seizure n = 5, CUS+ DBS nonseizure n = 11, CUS+ sham n = 6, CUS− n = 6). *p < 0.05. CUS+ chronic unpredictable stress, CUS− nonstressed controls.

animals after a total amount of HF DBS of 50 min consisting of two HCE trials with prestimulation. Two more animals showed seizure-like behavior during the up following food intake (FI) test after a total amount of 125 min of stimulation per animal. Because of the severity of the seizures, these behavioral tests were aborted.

Seizure-like behavior was not seen in the nonstimulated animals confirming that the observed involuntary movements were due to stimulation. Because of severe seizure-like behavior, all animals were given a wash out period of two weeks without DBS followed by a reduction in the stimulations amplitude by 50% (from 100 μA to 50 μA). Nevertheless, the animals who had displayed seizures before still did so at an amplitude of 50 μA. Thereafter, we switch towards a monophasic approach which did not prevent the occurrence of seizures. We stopped further behavioral testing because of persisting seizures in already affected animals and the development of seizures in unaffected animals. Seizures were not observed in previous animal studies applying DBS to the PFC, and therefore, more adaptation in stimulation parameters did not seem valuable at that time (reference Anthony paper). We decided to acquire electroencephalographic (EEG) recordings upon DBS in the affected animals to investigate if indeed this seizure-like behavior could be classified as seizures.

3.3. Seizure induction

To classify the observed seizure-like behavior, EEG recordings were made during both biphasic and monophasic DBS. During baseline measurements, the rats were not stimulated but EEG recordings were made to record background EEG activity. Before DBS, the rats showed no signs of discomfort with normal explorative and washing behavior. When starting DBS, rats immediately froze and subsequently showed facials movements (Racine stage I) and head nodding (Racine stage II), quickly followed by a forelimb clonus (Racine stage III) with rearing (Racine stage IV) and a full generalized clonus with falling (Racine stage V). Electroencephalographic recordings showed typical seizure activity. Approximately 1 min after DBS was turned off, the rats still displayed automatisms comprised of facial movements and postictal behavior while the EEG signal normalized. Normal explorative behavior started approximately 2–4 min after cessation of DBS (Fig. 4).

3.4. Electrode localization

Electrodes were traced in the DPC in 94% of the rats undergoing DBS, with a 100% accuracy in the rats experiencing seizures upon stimulation (n = 7) (Fig. 5). Two animals were excluded from analysis because of misplacement (n = 1) or detachment of the electrode construct (n = 1).

3.5. Histological examination

In a few cases, some scar tissue around the electrode construct has been seen. However, this was not more than what is usually seen in other DBS experiments in our laboratory [8]. No hemorrhage or signs

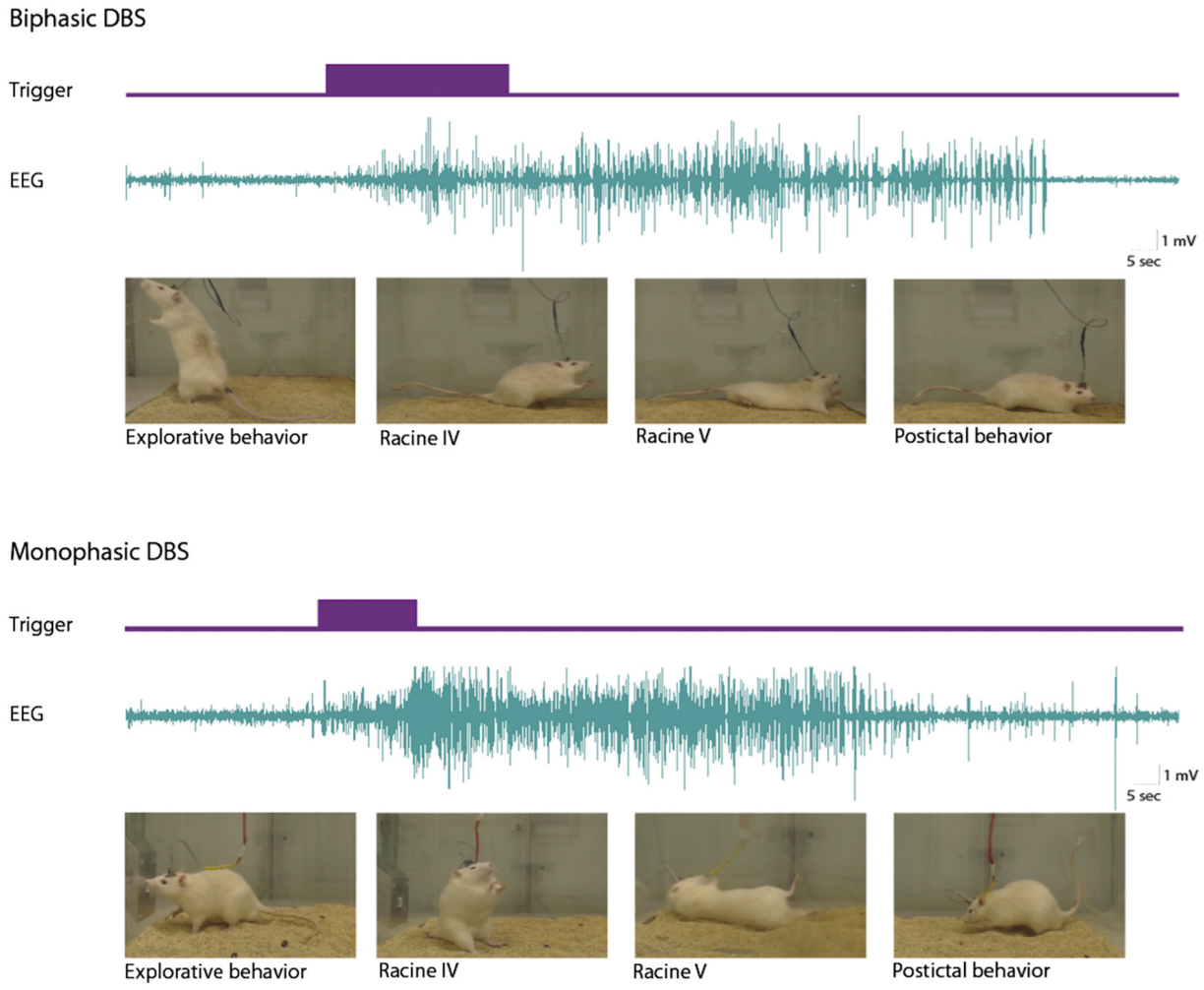

Fig. 4. Seizure induction upon DBS. Electroencephalographic recording during biphasic and monophasic bipolar DBS in de DPC with a frequency of 100 Hz, an amplitude of 100 μA, and a pulse width of 100 μs. Seizure induction (blue) can be seen right after the onset of the stimulus (purple) and continues for approximately 1 min after the stimulation has stopped. Behavior is scored with the inclusion of Racine scores for epileptic seizures seen on the added pictures.

of infection around the electrodes were seen during postmortem evaluation of the PFC.

4. Discussion

The present study showed that HF DBS in the DPC can induce seizures while using clinically relevant stimulation parameters with both biphasic and monophasic stimulation paradigms. Because of the disabling side effect of HF DBS in this region, we initially reduced our stimulation amplitude with 50%. However, seizure occurrence persisted. We switched to a monophasic stimulation paradigm which unfortunately did not alter seizure occurrence.

A possible trend can be seen in the HCE test where the stressed animals undergoing DBS tend to spend a longer time in their home-cage than the nonstressed controls. Since the number of animals per group is relatively low, increasing the amount of animals per group might show stronger results. No seizure-like behavior was seen during the HCE test, however, it is possible that minor mouth and facial movements have been missed and that the longer latency might still be related to discomfort upon stimulation. Another possibility is the interference of DBS in the DPC upon memory, since a trend only becomes visible after a second trial of the HCE test.

For the SIT test, the CUS+ animals undergoing DBS show a significant decrease in sucrose intake compared to the nonstressed controls. This feature could possibly be due to a postictal phenomenon since less movement could be observed in the first few minutes after a seizure in some of the animals. HF DBS was stopped when a seizure was observed and only continued when no seizure-like behavior was seen anymore, however, this could last up to 15 min which might interfere with a 60 min SIT trial. No significant difference was seen between the CUS+ sham group and nonstressed controls. Since we divided the CUS+ group into a DBS and sham group, a possible explanation could be that the group sizes of CUS+ sham ($n = 6$) and CUS− ($n = 6$) are too small to show the differences in sucrose intake as was shown before with the SIT without stimulation. More abundant seizures where observed when starting the Sucrose Preference Test (SPT) and FI test. We aborted our behavioral paradigm and could not continue with our planned behavioral test such as the FST and elevated zero maze.

We conclude that HF DBS of the DPC in the rat is not a suitable stimulation paradigm to investigate changes in mood-related behavior. Other stimulation parameters might still be relevant and need to be investigated before further conclusions can be drawn. However, HF DBS of the DPC could potentially be used as a model for seizure induction.

Seizure induction following cortical stimulation has been seen before in literature [11], however, previous research stimulating the vmPFC in rats did not show this finding [4]. Experiencing seizure behavior upon cortical stimulation in our experimental model of depression was therefore unexpected and was extensively described in this paper

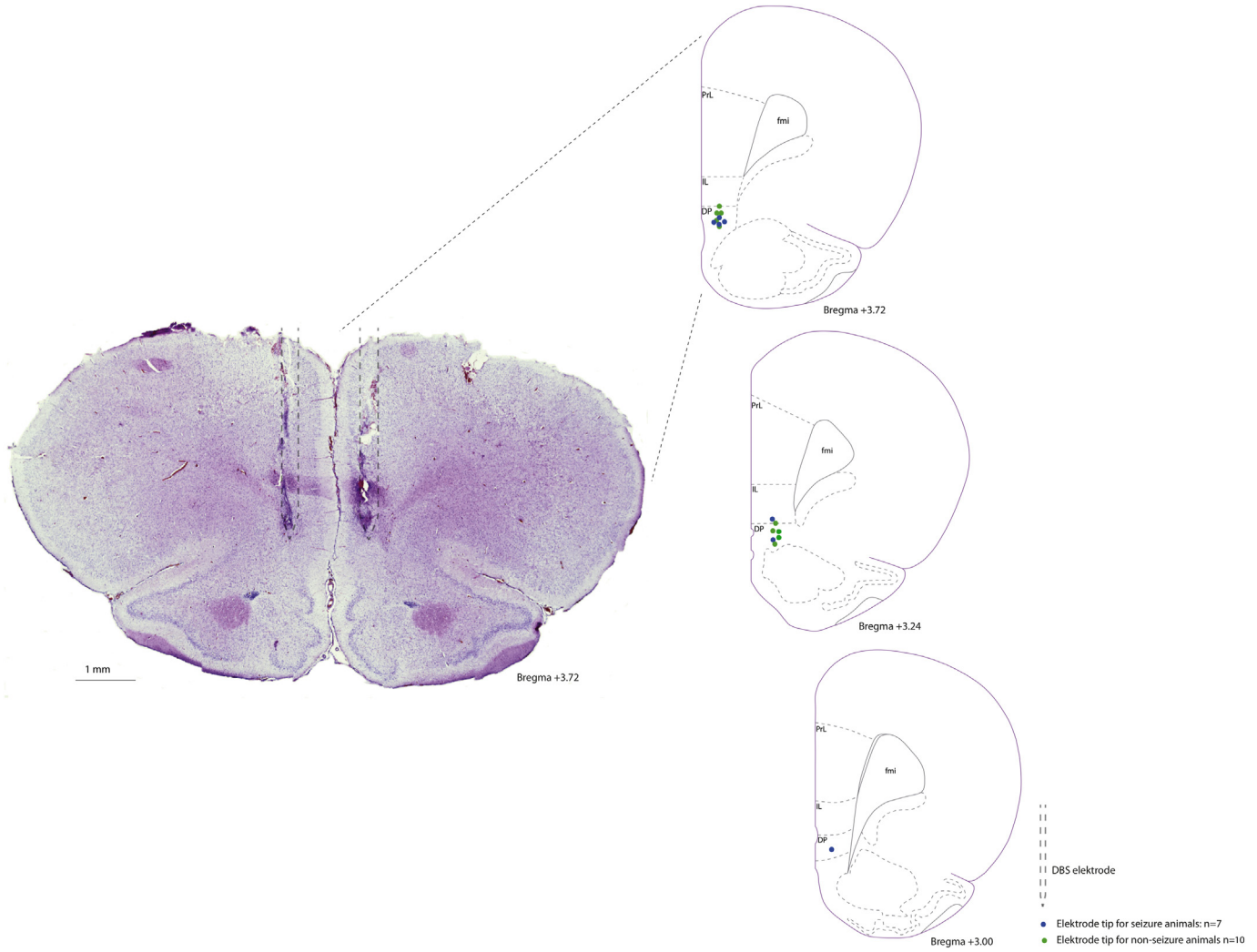

Fig. 5. DBS electrode localization. Electrode localization in stimulated animals showing both nonseizure and seizure behavior upon DBS. A green circle indicates the electrode localization of an animal not experiencing seizures, while a blue circle indicates the electrode localization of an animal experiencing seizures upon DBS.

to broaden our knowledge of this unforeseen finding and to prevent cases like this in the future.

The DPC has not been widely investigated so far, therefore, we chose the stimulation parameters based on our previous experience with DBS experiments and stimulation in the PFC [4,8]. The DPC seems to be far more sensitive to DBS than the IL and PreL regions, therefore conventional DBS parameters do not seem to be appropriate for this region. However, the parameters used are clinically relevant, and we have not experienced seizures so far in any of the regions used such as the subthalamic nucleus (STN), the nucleus accumbens (NAc), the dorsolateral periaqueductal gray (dlPAG), and the ventromedial hypothalamus (VMH) [12–14]. In contrast, similar parameters used for DBS in the anterior nucleus of the thalamus have shown to be effective in animal models of epilepsy [15] and patients with drug-refractory epilepsy [16]. Nevertheless, our findings show that when given into the DPC, these stimulation parameters are potent seizure inducers. Different stimulation parameters could however change the incidence of seizure induction and should be tested before investigation of the DP as a target for mood disorders is abandoned.

Our findings may be useful for investigating the role of the PFC in the generation of seizures and potentially a model for frontal lobe epilepsy. As opposed to stimulating temporal structures as performed in the amygdala kindling and poststatus epilepticus models [17], this model might have the advantage that classical structures involved in seizure induction remain undamaged by chemical or electrical lesioning, and therefore, its action during seizures can be investigated using histological, imaging, or electrophysiological measures. In addition, this model represents more a frontal seizure model than the widely applied models of temporal seizures.

4.1. Other reports of stimulation-induced seizures

The mechanism behind seizure induction when stimulating the DPC remains unclear. Previous research has shown that partial kindling of the PFC in rats with ±11 after discharges of 5s stimulus train of 60 Hz frequency, a pulse duration of 0.5 ms, and a 600- to 800-μA intensity, propagated into the hippocampus, and NAc where postictal activity lasted for >5 min [18]. However, the stimulation intensity used in their experiments was far greater than the intensity used in our experiments. Furthermore, current spread in this experiment was larger given that monopolar electrodes were used, while we stimulated with a bipolar electrode construct.

Nakamura-Palacois et al. have shown convulsion induction and behavioral responses such as head shaking upon bilaterally electrical activation (ten 30-s trains, 60 Hz, 80–100 μA) of the mPFC using monopolar electrodes, influenced by both diazepam and haloperidol [11]. Low-

frequency pulse stimulation in the cortex (2 ms monophasic, square wave pulses, frequency 9 Hz, intensity 400–800 μA) with monopolar constructs has been used as a procedure for inducing seizures by a different group [19]. Other researchers observed seizures during cortex self-stimulation acquisition in the sulcal prefrontal cortex (SPC) and medial prefrontal cortex (mPFC), but these seizures were not seen below currents of 100 μA [20].

Unlike other studies, we used a bipolar electrode constructs where the distance between the cathode and anode is approximately 50 μm. Therefore, the current spread should be significantly less in our experiments. Nevertheless, we do see overt seizures induced by direct stimulation in the PFC, possibly caused by its connections to the limbic system.

4.2. Anatomical connections of the DPC

Since we lack a precise description of the DPC, tissue properties may differ substantially from those of the IL and PreL vmPFC subregions. Previous research has shown direct projections from the DPC to the trigeminal brainstem sensory nuclear complex and other brain stem nuclei; where retrograde tracing by Fluorogold showed labeling of the rostrocaudal middle level of DP when injected into the rostro-dorsomedial part of the laminae I/II of the trigeminal subnucleus caudalis (rdm-I/II-Vc). Anterograde labeling with biotinylated dextranamine (BDA) into the mid-PD showed bilaterally labeling in the rdm-I/II-Vc, periaqueductal gray and solitary tract nucleus, and ipsilaterally in the parabrachial nucleus and trigeminal mesencephalic nucleus. Also, BDA-labeled axons and terminals were found reciprocally between the mid-PD and ipsilateral most caudal level of the granular and the dysgranular insular cortex. These projections indicate a role for intraoral and perioral sensory processing, including nociceptive processing [21].

Retrograde labeling from the ventral striatum (VS), dorsal caudomedial shell of the nucleus accumbens (AcbS) the midrostrocaudal level of the nucleus accumbens core (AcbC), the parabrachial nuclei, the medial lateral septum, the bed nucleus of stria terminalis (BST), the lateral hypothalamus, the mediodorsal thalamus, and the basolateral and central nucleus of the amygdala (BLA, CeA) to the DPC has been shown [22,23].

Knowing that there are retrograde connections to the limbic system and in particular the amygdala, a region also known for kindling, the assumption that the current density upon stimulation in the PFC spreads into and activates the limbic system causing overt seizures become more plausible.

4.3. Functional connections of the DPC

Despite the IL and PreL subregions of the vmPFC, the DPC is relatively unexplored [24]. Up to now, no actual functional connectivity studies of the DPC have been executed. A functional connection between the vmPFC and the basolateral nucleus of the amygdala (BLA) was shown in rats using optogenetics and electrophysiological recordings [25]. However, no clear distinction of the DPC has been made. Functional differences for dorsal and ventral subregions of the mPFC in controlling attention has been shown [26]. In their research, lesioning either the ventral (DPC and tenia tecta) or dorsal (prelimbic and infralimbic cortices) subregion resulted in differences in five-choice serial reaction time performance.

5. Conclusions

In summary, current results show that HF DBS in the DPC in rats has a high incidence of inducing seizures. The stimulation paradigms used are clinically relevant and do not seem to induce seizures in other brain regions. Reducing the stimulations amplitude did not alter seizure occurrence. Investigating mood-related behavior upon HF DBS in the DPC in rodents therefore does not seem viable using the current clinically accepted stimulation parameters.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yebeh.2019.01.007.

Conflict of interest

All authors declare to have no conflict of interest.

Acknowledgments

We would like to thank Prof. J. Prickaerts and Dr. A. Lim for their expertise and advice concerning the Chronic Unpredictable Mild Stress Model and behavioral paradigms described in this manuscript. This work was supported and funded by the school for Mental Health and Neuroscience (MHeNS) of the University of Maastricht (UM).

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