

Frequency-Specific Modulation of Slow-Wave Neural Oscillations via Weak Exogeneous Extracellular Fields Reveals a Resonance Pattern

 Boateng Asamoah,  Ahmad Khatoun, and Myles Mc Laughlin

ExpORL, Department of neurosciences, The Leuven Brain Institute, Katholieke Universiteit Leuven, Leuven B-3000, Belgium

Single neurons often exhibit endogenous oscillatory activity centered around a specific frequency band. Transcranial alternating current stimulation (tACS) can generate a weak oscillating extracellular field in the brain that causes subthreshold membrane potential shifts that can affect spike timing at the single neuron level. Many studies have now shown that the endogenous oscillation can be entrained when the tACS frequency matches that of the exogenous extracellular field. However, the effect of tACS on the amplitude of the endogenous oscillation has been less well studied. We investigated this by using exogenous extracellular fields to modulate slow-wave neural oscillations in the ketamine anesthetized male Wistar rat. We applied spatially broad extracellular fields of different frequencies while recording spiking activity from single neurons. The effect of the exogenous extracellular field on the slow-wave neural oscillation amplitude (NOA) followed a resonance pattern: large modulations were observed when the extracellular frequency matched the endogenous frequency of the neuron, while extracellular fields with frequencies far away from the endogenous frequency had little effect. No changes in spike-rate were observed for any of the extracellular fields applied. Our results demonstrate that in addition to the previously reported entrainment and Arnold tongue patterns, weak oscillating extracellular fields modulate the amplitude of the endogenous neural oscillation without any changes in spike-rate, and that this modulation follows a frequency-specific resonance pattern.

Key words: entrainment; neural oscillation; neuromodulation; resonance; tACS

Significance Statement

Neural activity often oscillates around specific endogenous frequencies. Transcranial alternating current stimulation (tACS) is a neuromodulation method which biases spike-times and alter endogenous activity. Most tACS studies focus on entrainment effects which occur when tACS and endogenous neural frequencies are matched. In this study we varied the frequency of the applied tACS and investigated its effect on amplitude of the neural oscillation. Our results revealed a resonance pattern where tACS frequencies close to the endogenous frequency caused an increase in neural oscillation amplitude (NOA) specifically at the applied tACS frequency, while applying tACS frequencies farther away caused little or no change in NOA. Furthermore, applying tACS at differing frequencies caused the amplitude of the neural oscillation at the prestimulation endogenous frequency to decrease.

Introduction

Neurons rhythmically fire action potentials thereby engaging in patterned communication with large neural networks (Kandel et al., 2000; Purves et al., 2008; Wang, 2010). The specific pattern

of a neuron's activity gives rise to oscillations which are important as they may facilitate communication between distinct neural populations (Jensen and Colgin, 2007; Cardin et al., 2009; Canolty and Knight, 2010; Dürschmid et al., 2013). Specific oscillatory frequency bands are associated with a behavior or brain region [e.g., β in the motor cortex and γ during cognition (Bouyer et al., 1987; Baker et al., 1997; Benchenane et al., 2011; Li et al., 2012; Senkowski and Gallinat, 2015; Espenhahn et al., 2019) or low frequency under anesthesia and sleep (Achermann and Borbély, 1997; Amzica and Steriade, 1997; Erchova et al., 2002; Lydic and Baghdoyan, 2005; Léger et al., 2018)]. Thus, neural activity is by nature oscillatory and in some cases these oscillations may play a functional role, although this is still debated (Cardin, 2016; Sohal, 2016).

Received Jan. 24, 2022; revised Apr. 18, 2022; accepted May 10, 2022.

Author contributions: B.A. and M.M. designed research; B.A. and A.K. performed research; B.A. and M.M. analyzed data; B.A. wrote the first draft of the paper; B.A. and M.M. edited the paper; B.A., A.K., and M.M. wrote the paper.

This work was supported by Katholieke Universiteit Leuven Research Funding Grants STG/14/024 and EGM-D2929-C24/17/091 and by EIT health innovation by ideas, Neuro-Wear project. B.A. was SB PhD fellow at Research Foundation Flanders (FWO).

The authors declare no competing financial interests.

Correspondence should be addressed to Myles Mc Laughlin at myles.mclaughlin@kuleuven.be.

<https://doi.org/10.1523/JNEUROSCI.0177-22.2022>

Copyright © 2022 the authors

Transcranial alternating current stimulation (tACS) is a noninvasive neuromodulation method which aims to modulate these endogenous neural oscillations, by using scalp electrodes to generate an exogenous extracellular field in the brain, and thus affect behavior (Herrmann et al., 2013; Tavakoli and Yun, 2017). The exogenous extracellular field generated by tACS is weak, typically below 1 V/m (Y. Huang et al., 2017; Lafon et al., 2017; Vöröslakos et al., 2018). Despite this, we (Asamoah et al., 2019) and others (Krause et al., 2019; Johnson et al., 2020) have shown that oscillating extracellular fields in this range can cause neural entrainment (the phase of the neural oscillation becomes aligned to the phase of the exogenous field). Entrainment is mediated by subthreshold shifts in the membrane potential thereby possibly causing an Arnold tongue (Pikovsky et al., 2001; Notbohm et al., 2016; Vosskuhl et al., 2018), i.e., if stimulation amplitude is low, only frequencies close to the endogenous oscillation cause entrainment, but as the stimulation amplitude increases, entrainment occurs to a wider range of stimulation frequencies. However, the effect of the frequency difference between the endogenous neural oscillation and exogenous extracellular field has not been studied in detail.

W.A. Huang et al. (2021) used a ferret model to study the effect of the frequency difference between an exogenous extracellular field and an ongoing alpha oscillation. They found that at very low electric field strengths the alpha oscillation only entrained to the exogenous extracellular field when they were exactly matched in frequency. However, when the electric field strength was increased the alpha oscillation entrained to a broader range of frequencies; thereby indicating that an Arnold tongue-like mechanism may underly some tACS effects. Importantly, they used a control condition where they only stimulated peripheral nerves to rule out costimulation effects.

Most studies to date have focused on how tACS can entrain neural oscillations. However, the effect of tACS on neural oscillation amplitude (NOA) has been less well studied. We know that tACS exerts a subthreshold effect and does not cause spike-rate increases (Vöröslakos et al., 2018; Asamoah et al., 2019; Krause et al., 2019). However, the subthreshold membrane potential shift does cause spikes to change their timing such that the endogenous oscillation becomes entrained to the extracellular field. One could hypothesize that this shift in spike timing would also affect the amplitude of the endogenous neural oscillation. However, these amplitude effects have, to the best of our knowledge, never been systematically investigated.

Here, we used ketamine anesthetized male Wistar rats as a model for slow-wave neural oscillations and studied the effect of changing the frequency of a driving exogenous extracellular field on the oscillatory nature of the slow frequency spiking activity (which is referred to here as the oscillation). When driving the slow-wave oscillations via extracellular fields of different frequencies a resonance pattern was observed. This resonance peak aligned with the dominant frequency of the endogenous slow-wave neural oscillation.

Materials and Methods

Data collection methods were partly described in depth in an earlier publication (Asamoah et al., 2019) and thus are described only briefly here. All methods which were not described in the previous publication are described in detail. For this work, we applied a new analysis to data from the previous publication (Asamoah et al., 2019) as well as to newly collected data which only appears in this publication.

Surgery

Eight male Wistar rats (Janvier Labs) were anesthetized (ketamine and medetomidine-HCl mixture) and placed in a stereotaxic frame. Their scalp was opened and retracted after which a multi-channel recording probe was inserted into the motor cortex through a burr hole craniotomy. Two bone screws placed in the dried skull were used as electrodes to generate exogenous, spatially broad, low-amplitude, extracellular fields in the brain. All procedures were approved by the Katholieke Universiteit Leuven animal ethics committee for laboratory experiments.

Stimulation and recording setup

To generate exogenous electric-fields sinewave currents were delivered via an AM 2200 analog current source (AM Systems). This current source received voltage input from a data acquisition card (NI USB-6216, National Instruments) which was controlled using a custom MATLAB (MathWorks) 2014a software.

A 32-channel silicon probe (E32Tri+R-25-S01-L10 NT, Atlas Neuro) was used to record signals from the brain. Signals were amplified, filtered and digitized using an Intan headstage (RHD2132, Intan Technologies) in combination with an Open Ephys system (Siegle et al., 2017; <http://www.open-ephys.org/store>).

Experimental protocol

Across all recordings the electrode was inserted in the motor cortex at depths ranging from 800 to 2300 μm ; approximately corresponding to cortical layers 4 through 6. We first recorded 1 min with no stimulation (pre-condition). This was immediately followed by the “during-condition” where we delivered 1 min of sinewave electric stimulation through the screw electrodes placed in the skull. The frequencies of the exogenous electric-field (f_{exo}) ranged from 0.3 to 10 Hz. The amplitude of the delivered sinewave ranged from 0.025 to 0.5 mA and were grouped into amplitude levels: ≤ 0.1 mA (Low), > 0.1 but ≤ 0.2 mA (Medium), > 0.2 mA (High). Full list of stimulation parameters delivered are provided in Table 1.

Spike sorting

We performed spike sorting using the Klusta suite (Rossant et al., 2016). Klusta took in the raw neural data and bandpass filtered it between 300 and 3000 Hz. This filtering removed the artifact created by the exogenously applied electric-fields. The data were then automatically clustered, after which clusters were manually inspected. Only well isolated clusters were considered putative single units and used for further analysis.

Data analysis: data preparation

After isolation of putative single units, we extracted spike-times. To characterize the oscillatory nature of the slow frequency spiking (here referred to as slow-wave oscillation) we first down sampled the spike-train to 100 Hz (Fig. 1, second row of all panels). We then calculated the autocorrelation of the down sampled spike-train (Fig. 1, third row) and performed the fast Fourier transform (FFT) on the autocorrelation signal (Fig. 1, fourth row). A clear peak around 1 Hz shows the dominant frequency (Fig. 1, red dot) of the neural oscillation. In the pre-condition (top left panel) this peak defined the frequency of the endogenous neural oscillation (f_{endo}) and the NOA at this endogenous frequency ($\text{NOA}_{f_{\text{endo}}}$). The frequency of exogenous field was denoted f_{exo} . The NOA at the exogenous frequency was denoted $\text{NOA}_{f_{\text{exo}}}$ in the pre-condition and as $\text{NOA}_{f_{\text{exo}}-\text{dur}}$ in the during-condition. To quantify the effect of exogenous extracellular field on oscillation at the exogenous frequency we calculated the change in NOA at the exogenous frequency as $\Delta\text{NOA}_{f_{\text{exo}}} = \text{NOA}_{f_{\text{exo}}-\text{dur}} - \text{NOA}_{f_{\text{exo}}-\text{pre}}$. We also calculated this for $\text{NOA}_{f_{\text{endo}}}$ as $\Delta\text{NOA}_{f_{\text{endo}}} = \text{NOA}_{f_{\text{endo}}-\text{dur}} - \text{NOA}_{f_{\text{endo}}-\text{pre}}$. The endogenous oscillation frequency differed slightly from one neuron to the next. Therefore, for population level comparisons we calculated the frequency difference (f_{diff}) such that $f_{\text{diff}} = f_{\text{exo}} - f_{\text{endo}}$. This allowed us to assess the effect of the exogenous frequency given the endogenous frequency at the group level.

Table 1. List of recorded neurons with the frequencies and amplitudes of the exogenous signal

Neuron	Amplitude (mA)	Frequency (Hz)									
1	0.1	0.4	0.8	1.2	1.6	2	2.4	2.8	3.2	3.6	4
2	0.1	0.4	0.8	1.2	1.6	2	2.4	2.8	3.2	3.6	4
3	0.1	0.4	0.8	1.2	1.6	2	2.4	2.8	3.2	3.6	4
4	0.1	0.4	0.8	1.2		2	2.4	2.8		3.6	4
5	0.1	0.4	0.8				2.4	2.8			
6	0.1	0.4						2.8			
7	0.1	0.4						2.8			
8	0.1	1	2	3	4	5	6	7	8	9	10
9	0.1	1	2	3	4	5	6	7	8	9	10
10	0.1	1	2	3	4	5		7	8	9	
11	0.1	1	2	3		5			8	9	
12	0.1	1	2	3		5					
13	0.1		2								
14	0.025	0.4	0.8								
	0.05	0.4	0.8	1.2	1.6	2	2.4	2.8	3.2	3.6	4
15	0.05	1.2	1.6	2	2.4	2.8	3.2	3.6	4		
16	0.05	2.4									
17	0.1	0.4	1.2		3.6		10				
	0.05	3	6								
18	0.1	0.4									
19	0.1	4									
	0.2	4									
20	0.1	4									
	0.2	4									
21	0.1	4									
22	0.1	1	4	5	6	7	8	10			
23	0.1	1	6	8	10						
24	0.1	1	6								
25	0.06	1.8									
	0.12	1									
	0.12	4									
26	0.15	1	2	3	6	7	8	9			
27	0.15	1	2	3	6	7	8	9			
28	0.15	2	6	7	9						
29	0.15	6	7	9							
30	0.15	7	7								
31	0.15	7	7								
32	0.25	0.6	1.2	1.6	2.4	3					
33	0.25	0.6	1.2	1.6	2.4	3					
34	0.25	0.6	1.6	2.4	3						
35	0.25	0.6	1.6	2.4							
36	0.25	1.6									
37	0.1	0.5	2	2.5	3.5	4	4.5	7	8	9	10
38	0.1	2	3.5	4.5	7	8	9	10			
39	0.1	2	4.5	7							
40	0.1	2									
41	0.2	0.3	0.6	0.9	1.2	1.8	2.4	2.7	3		
42	0.2	0.3	0.6	0.9	1.2	2.4	2.7	3			
43	0.2	0.3	0.6	0.9	2.7						
44	0.2	0.6									
45	0.2	1.5	2.5	3.5	4.5	5	5.5				
46	0.2	1.5	2.5	3.5	4.5	5.5					
47	0.2	5.5									
48	0.2	0.5	1	1.5	2	2.5	3	3.5	4	4.5	5
49	0.2	0.5	1	1.5	2	2.5	3	3.5	4	4.5	5
50	0.2	0.5	1	1.5	2	2.5	3	3.5	4	4.5	5
51	0.2	0.5	1	1.5	2	2.5	3	3.5	4	4.5	5
52	0.2	0.5	1	1.5	2	2.5	3	3.5	4	4.5	5
53	0.2	0.5	1.5	2	3.5	4.5					
54	0.2	0.5	2	4.5							
55	0.2	0.5	2								
56	0.2	0.5									
57	0.15	0.5	1	2.5	3	3.5	5				

(Table continues.)

Table 1. Continued

Neuron	Amplitude (mA)	Frequency (Hz)									
58	0.15	1	5								
59	0.08	0.75	1.5								
60	0.18	1	2	2.5	3	3.5	4.5	5			
61	0.18	1	4.5								
62	0.05	2									
	0.1	2									
	0.3	2									
	0.5	2									
63	0.1	2									
	0.3	2									
64	0.1	2									
65	0.12	2									
66	0.12	2									
67	0.12	2									
68	0.2	1.5									
69	0.2	1.5									
70	0.2	1.5									
71	0.2	1.5									
72	0.2	1.5									
73	0.2	1.5									
74	0.2	1.5									
75	0.1	1									
76	0.15	2									
77	0.2	1.5									
78	0.2	1.5									
79	0.2	1.5									
80	0.2	1.5									
81	0.2	1.5									
82	0.2	1.5									
83	0.2	2.1									
84	0.2	2.1									
85	0.25	1.8									
86	0.25	1.8									
87	0.25	1.8									
88	0.025	1.6									
89	0.1	1.6									
90	0.25	1.6									
91	0.12	2									
92	0.1	1.4									
	0.2	1.4									
93	0.2	1.4									
94	0.1	1.5									
95	0.1	1.5									
96	0.1	1.5									
97	0.2	2									
	0.5	2									
98	0.2	2									
	0.5	2									
99	0.2	2									
	0.5	2									
100	0.2	2									
	0.5	2									
101	0.2	2									
	0.5	2									
102	0.2	2									
	0.5	2									
103	0.2	2									
	0.5	2									
104	0.2	2									
105	0.2	2									
106	0.05	1.6									
	0.025	1.6									
	0.1	1.6									
	0.2	1.6									

(Table continues.)

Table 1. Continued

Neuron	Amplitude (mA)	Frequency (Hz)
107	0.05	1.6
	0.025	1.6
	0.1	1.6
	0.2	1.6
108	0.05	1.6
	0.025	1.6
	0.2	1.6
109	0.05	1.6
110	0.05	1.6
111	0.05	1.5
	0.15	1.5
	0.25	1.5
112	0.05	1.5
	0.15	1.5
	0.25	1.5
113	0.05	1.5
	0.15	1.5
	0.25	1.5
114	0.05	1.5
	0.15	1.5
	0.25	1.5
115	0.05	1.5
	0.15	1.5
	0.25	1.5
116	0.05	1.5
	0.15	1.5
	0.25	1.5
117	0.05	1.5
	0.15	1.5
	0.25	1.5
118	0.05	1.5
	0.15	1.5
	0.25	1.5
119	0.05	1.5
	0.15	1.5
120	0.05	1.5
121	0.05	1.5
122	0.25	1.5
123	0.25	1.5
124	0.25	1.5
125	0.05	1.5
	0.15	1.5
	0.25	1.5
126	0.05	1.5
127	0.05	1.5
128	0.05	1.5
	0.15	1.5
129	0.05	1.5
	0.15	1.5
	0.25	1.5
130	0.05	1.5
	0.15	1.5
	0.25	1.5
131	0.05	1.5
	0.15	1.5
	0.25	1.5
132	0.15	1.5
	0.25	1.5
133	0.05	1.5
	0.15	1.5
	0.25	1.5
134	0.15	1.5
	0.25	1.5
135	0.15	1.5

(Table continues.)

Table 1. Continued

Neuron	Amplitude (mA)	Frequency (Hz)
136	0.15	1.5
137	0.15	1.5
138	0.3	1.5
139	0.1	1.5
	0.2	1.5
	0.3	1.5
140	0.3	1.5
141	0.3	1.5
142	0.1	1.5
	0.2	1.5
	0.3	1.5
143	0.1	1.5
	0.3	1.5
144	0.1	1.5
	0.3	1.5
145	0.1	1.5
	0.2	1.5
	0.3	1.5
146	0.1	1.5
	0.2	1.5
	0.3	1.5
147	0.1	1.5
	0.3	1.5
148	0.2	1
149	0.1	1.5
	0.2	1.5
	0.3	1.5
150	0.1	1.5
	0.1	1.5
151	0.08	1.5
	0.18	1.5
	0.28	1.5
152	0.08	1.5
	0.18	1.5
	0.28	1.5
153	0.08	1.5
	0.18	1.5
154	0.08	1.5
	0.18	1.5
155	0.18	1.5
156	0.18	1.5
157	0.18	1.5
158	0.4	1.5

Neurons were recorded from all eight rats.

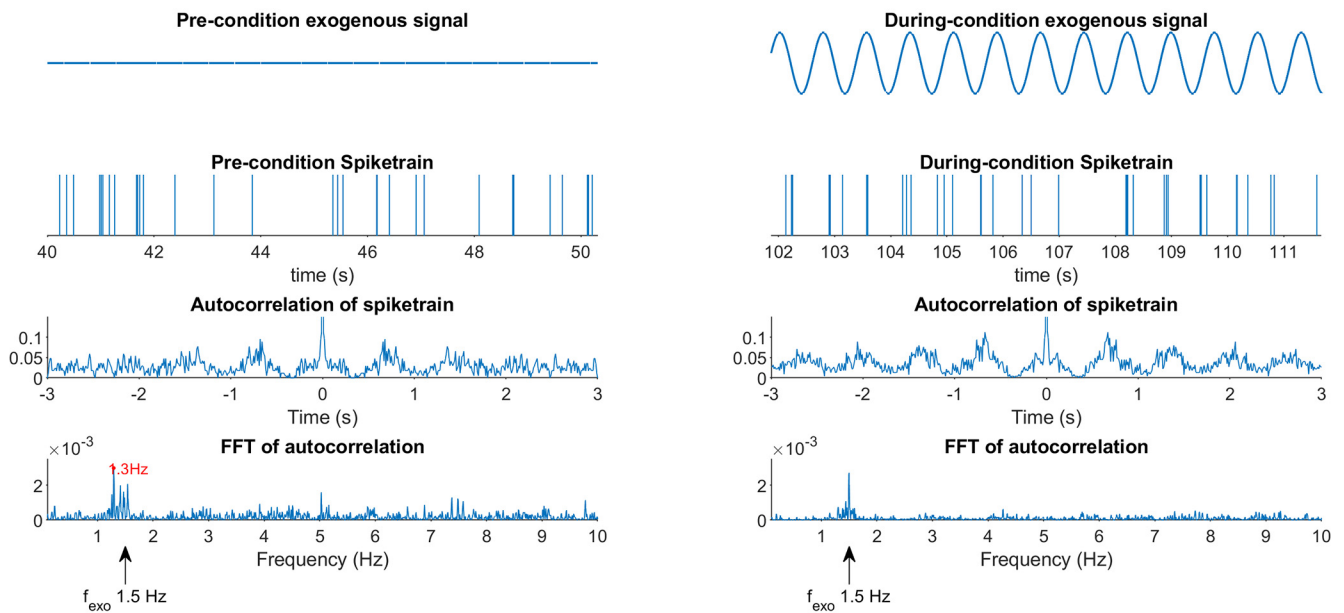
Data analysis: linear model and statistics

To test whether ΔNOA depended on f_{diff} we applied a linear model. F_{endo} could be either higher or lower than f_{exo} ; therefore, f_{diff} has both negative and positive values. Based on a visual inspection of the data, we predicted the same linear relationship for both negative and positive f_{diff} values. We tested this prediction by separating the negative f_{diff} data (negative f_{diff} condition) from the positive (positive f_{diff} condition). For the negative condition we took the absolute values of f_{diff} , thus making the sign of both relationships equal. We ran a linear model with the f_{diff} conditions as independent and the ΔNOA as dependent variables and tested the interaction between the two conditions. This allowed us to test whether ΔNOA was differently modulated by f_{diff} condition (negative vs positive). This was not the case (see Results, Positive and negative frequency difference equally modulate NOA).

Therefore, to simplify the statistics and increase statistical power, we performed all further analyses using the absolute f_{diff} values ($|f_{\text{diff}}|$; see under Results: NOA increase depends on exogenous extracellular field frequency and amplitude). We used a linear model to test whether ΔNOA was dependent on $|f_{\text{diff}}|$. For statistical comparisons we applied either a linear model or the Wilcoxon signed-rank and where appropriate corrected p values for multiple comparisons using the Bonferroni approach. α -Value was always 0.05.

In the graphs showing individual datapoints, we zoomed in to show the bulk of the data (Figs. 2, 3, top two rows, 4, 5, 6, lower row). As such some outliers are not shown. However, all data were taken into account for analysis.

Exogenous frequency close to endogenous frequency



Exogenous frequency far from endogenous frequency

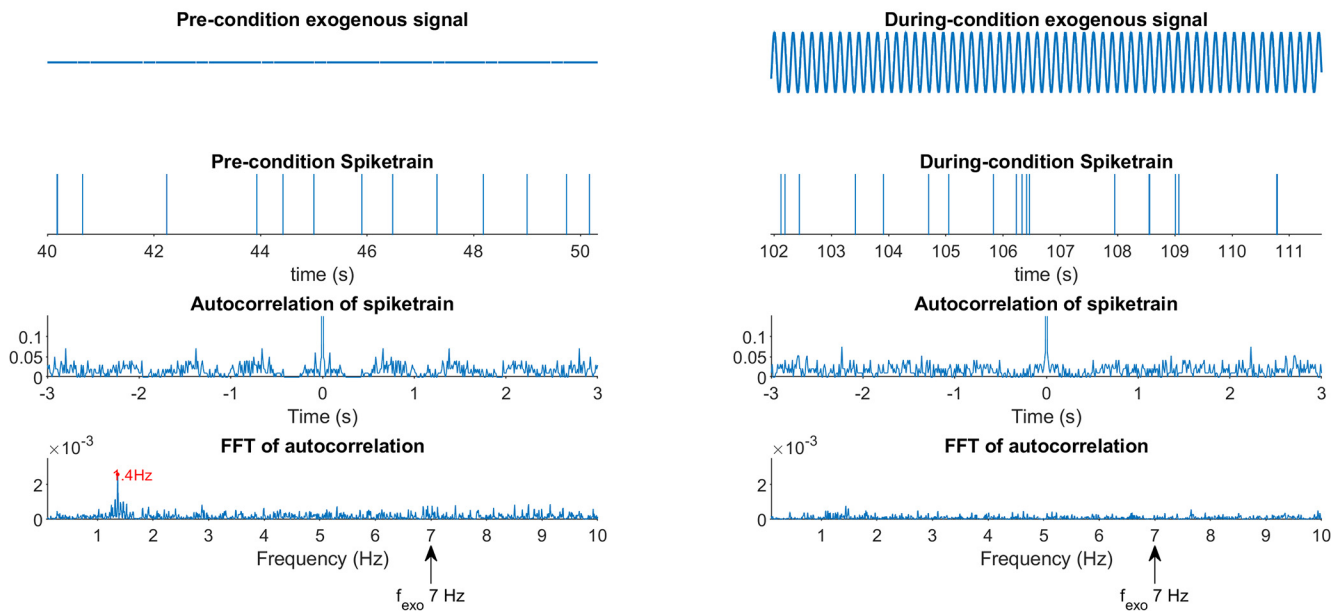


Figure 1. Quantification of neural oscillation (spiking rhythmicity) amplitude and frequency from an action potential recording. The upper left panel shows how the pre-condition recording was analyzed to quantify the endogenous neural oscillation. The first row depicts the exogenous field which is flat because there was no field applied in this condition. The second row depicts the recorded spike-train with each vertical line indicating the time of an action potential. The autocorrelation of the spike-train was calculated (third row) followed by the Fourier transform of the autocorrelation (fourth row). A dominant neural oscillation close to 1 Hz is apparent. We extracted the largest peak of the Fourier spectrum (red dot) to define the endogenous neural oscillation frequency (f_{endo}) and its amplitude ($\text{NOA}_{f_{\text{endo}}}$). The upper right panel shows how the same process was used to quantify the during-condition oscillation from the same neuron when an exogenous field was applied with a frequency close to the endogenous frequency. Note how the dominant frequency of the neural oscillation now shifts to move closer to the frequency of the exogenous field (f_{exo} ; arrow points to f_{exo}). The amplitude of the neural oscillation at exogenous frequency was defined as $\text{NOA}_{f_{\text{exo}}}$. The bottom two panels show data from the pre (left) and during (right) conditions for a neuron where the frequency of the exogenous field was further away from the endogenous frequency (f_{endo}). Here, we note that the dominant frequency in the during-condition is similar to that in the pre-condition (red dot), albeit lower, and does not shift to match the frequency of the exogenous field. This means that the amplitude of the neural oscillation at the exogenous frequency ($\text{NOA}_{f_{\text{exo}}}$) is small. The first two rows of all panels are zoomed in to better visualize the exogenous field and its relation to the spikes-train. Both neurons were stimulated at the High level.

Data analysis: entrainment calculation

We calculated entrainment by using the phase lock value (PLV) metric. This metric is previously extensively described (Lachaux et al., 1999; Brittain et al., 2013; Krause et al., 2019; Mc Laughlin et al., 2022). A cycle histogram was created with 30 phase bins where each spike was assigned

a bin on the basis of when the spike occurred. PLV was then calculated using the following equation:

$$\text{PLV} = \left| \sum_b R_b e^{i\theta_b} \right|$$

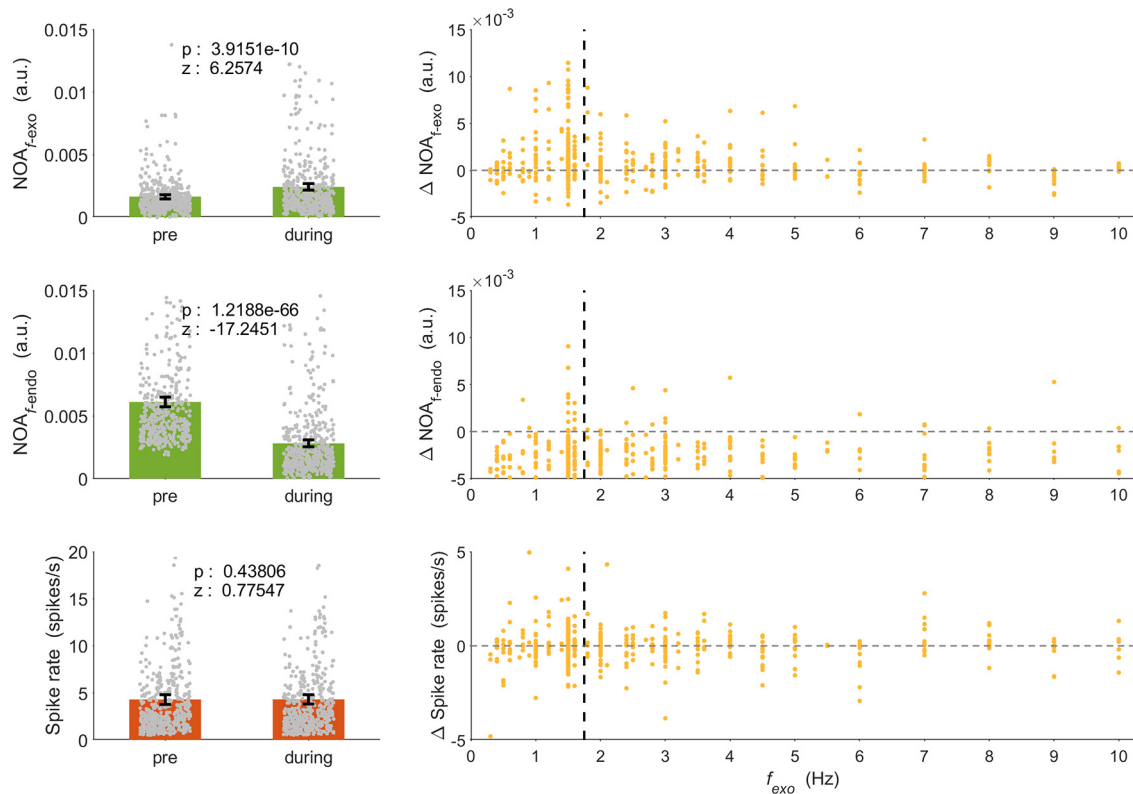


Figure 2. Exogenous fields affect NOA. In the upper left panel, NOA at the exogenous frequency (NOA_{f-exo}) increased when an exogenous field was applied (during-condition) as compared with the preexogenous condition (two-sided Wilcoxon signed-rank). The upper right panel shows that this increase appeared strongest when the exogenous frequency was close to the endogenous oscillation frequency (dashed vertical line shows median endogenous frequency of 1.7483; measured before the exogenous field was applied). Visually it appears that the largest NOA_{f-exo} values tend to be around this endogenous frequency. The NOA of the endogenous oscillation NOA_{f-endo} decreased as a response to the exogenous field (middle left panel). However, as shown in the middle right panel this decrease did not appear to be frequency dependent. The shifts in NOA s were not because of spike-rate changes overall (lower left panel) nor did there seem to be frequency dependent spike-rate changes (lower right panel). Descriptive statistics are in Table 2.

Where θ_b was the center of bin b and R_b the normalized magnitude of bin b . As such for PLV calculation R_b was the likelihood that a spike fell in bin b . To determine entrainment, we calculated PLV in the pre-condition (PLV_{pre}) and during-condition (PLV_{dur}) separately. We then subtracted PLV_{dur} from PLV_{pre} to get entrainment. For the pre-condition, we assumed a sine wave that matched the during-condition sine wave in phase and frequency.

Results

Quantification of neural oscillation response to weak exogenous extracellular fields

Figure 1 shows two examples of how the recorded spike train was analyzed to quantify the oscillatory nature of the slow frequency spiking activity rhythmicity (here, neural oscillation) in the pre (left panels) and during (right panels) conditions. In the upper left panel, the top row shows the applied exogenous extracellular field (flat in the pre-condition). The second row shows the spike train, the third row shows the autocorrelation of the spike train. A clear low frequency oscillation is visible in both the spike train and autocorrelation. To quantify this, we calculated the FFT (fourth row) and extracted the largest peak in the pre-condition to define the dominant frequency of the endogenous neural oscillation (f_{endo}) and its amplitude (NOA_{f-endo}). The two top panels show an example of how the neural oscillations responded when the frequency of the applied exogenous extracellular field (f_{exo}) was close to f_{endo} . The bottom two panels show an example response when the frequency difference (f_{diff}) between f_{endo} and f_{exo} was large. We found that when f_{diff} was

small the frequency of the neural oscillation tended to shift toward that of the exogenous extracellular field (f_{exo}). This caused a decrease in the NOA at the endogenous frequency (NOA_{f-endo}) and an increase in the NOA around the exogenous frequency (NOA_{f-exo}). However, when f_{diff} was large very little frequency shift was observed. There was no increase in the amplitude at the exogenous frequency but there was a decrease in the NOA at the endogenous frequency.

Exogenous extracellular fields modulate slow-wave NOA

We quantified these effects at the group level for all recordings ($n = 473$, generated from 158 neurons which came from all rats; see Materials and Methods, Experimental protocol, and Table 1). Figure 2, upper left panel, shows the mean NOA_{f-exo} in the pre-condition ($NOA_{f-exo-pre}$) and during-condition ($NOA_{f-exo-during}$) as bars (for descriptive statistics on all bar graphs, see Tables 2, 3) as well as the individual datapoints in gray. Overall, there is an increase in the amplitude of the neural oscillation at the exogenous frequency (NOA_{f-exo} ; $z = 6.2574$, $p = 3.9151 \times 10^{-10}$; two-sided Wilcoxon signed-rank). This is accompanied by a decrease in the amplitude of the neural oscillation at the endogenous frequency (NOA_{f-endo} ; middle left panel, $z = -17.2451$, $p = 1.2188 \times 10^{-66}$; two-sided Wilcoxon signed-rank). Note that this data are grouped and the effects may be frequency dependent (see next section). The upper right panel shows the change in oscillation amplitude at the exogenous frequency between the pre-condition and during-condition (ΔNOA_{f-exo}) as a function of the frequency of the exogenous extracellular field (f_{exo}). Visually it appears that

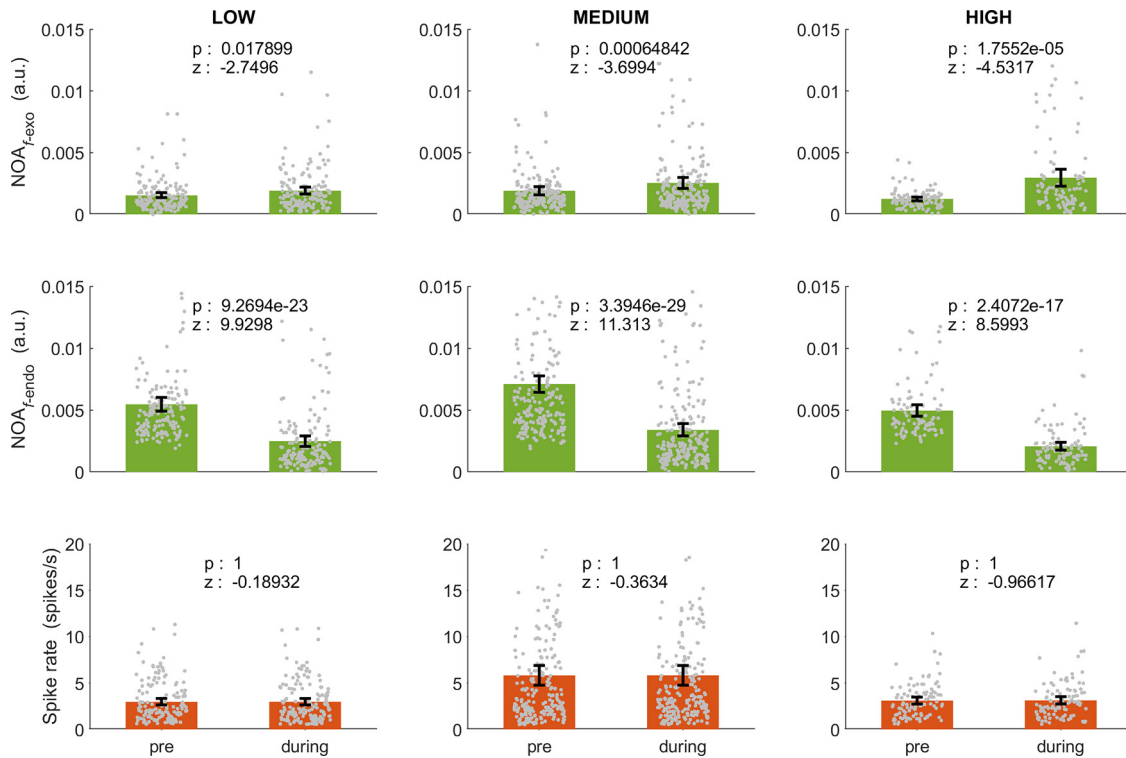


Figure 3. NOA and spike-rate in the pre-condition and during-condition for different exogenous field amplitude groups, Low, Medium, and High. For all groups, NOA at the exogenous field frequency (NOA_{f-exo}) increased (upper row). This was accompanied by a decrease of the endogenous NOA (NOA_{f-endo}; middle row). However, spike-rates did not change (lower row). Bars show the mean and error bars show 95% confidence intervals. All statistics are two-sided Wilcoxon signed-rank with a Bonferroni correction ($n = 3$). Descriptive statistics are in Table 3.

Table 2. Descriptive statistics for bar graphs in Figure 2

	Mean _{Pre}	Mean _{During}	CI _{Pre}	CI _{During}
NOA _{f-exo}	0.0016508	0.0024294	0.0014823–0.0018192	0.0021553–0.0027034
NOA _{f-endo}	0.0061087	0.0028156	0.0057303–0.0064872	0.0025343–0.0030969
Spike rate	4.3061	4.3199	3.7912–4.821	3.8061–4.8336

the largest increases in oscillation amplitude occur when the frequency of the exogenous extracellular field is closest to the ongoing endogenous oscillation frequency (median = 1.7483 Hz, indicated vertical dashed line). The middle right panel shows the change in oscillation amplitude at the endogenous frequency between the pre-condition and during-condition (Δ NOA_{f-endo}) as a function of f_{exo} . For most exogenous frequencies tested Δ NOA_{f-endo} decreased. Noticeably, when Δ NOA_{f-endo} increased, it tended to happen when the frequency of the exogenous extracellular field (f_{exo}) was very close to the endogenous frequency (f_{endo}) of the neural oscillation. The bottom two panels show the effect of the exogenous extracellular field on spike-rate. We observed no effect on spike-rate at the population level (lower right panel: $z = 0.77547$, $p = 0.43806$, two-sided Wilcoxon signed-rank). Plotting the spike-rate change as a function of f_{exo} also did not appear to reveal any frequency dependence. Error bars depict 95% confidence intervals. These results show that weak extracellular fields can modulate endogenous slow-NOA and that these effects may depend on the frequency of the extracellular field.

The effect of stimulation amplitude on neural oscillation

To also assess stimulation amplitude effects, we divided the data into three groups: Low (156 recordings), Medium (217 recordings), and High (100 recordings) amplitude exogenous extracellular field

Table 3. Descriptive statistics for bar graphs in Figure 3

		Mean _{Pre}	Mean _{During}	CI _{Pre}	CI _{During}
NOA _{f-exo}	Low	0.0015416	0.001918	0.001337–0.0017461	0.001637–0.002199
	Med	0.0019122	0.0025482	0.0015857–0.0022387	0.002093–0.003003
	High	0.0012538	0.0029692	0.0011103–0.0013973	0.002268–0.003671
NOA _{f-endo}	Low	0.0054616	0.0024896	0.0049161–0.0060071	0.002071–0.002909
	Med	0.0071064	0.0033942	0.0064372–0.0077757	0.002891–0.003897
	High	0.0049531	0.0020686	0.0044826–0.0054237	0.001749–0.002389
Spike rate	Low	2.9695	2.9823	2.6233–3.3157	3.6322–3.3324
	Med	5.8213	5.8286	4.7432–6.8694	4.785–6.8722
	High	3.1033	3.1326	2.7459–3.4606	2.7548–3.5103

(see Materials and Methods, Experimental protocol). In Figure 3, the changes in NOA followed the same pattern as in Figure 2, left column (all data grouped). Specifically, within each amplitude group NOA_{f-exo} increased significantly between the pre-condition and during-condition. This increase was largest in the High group and smallest in the Low. For NOA_{f-endo} the levels decreased in all amplitude groups. No changes were observed in spike-rate for any of the groups. Descriptive statistics are shown in Table 2.

Positive and negative frequency difference equally modulate NOA

Since the endogenous frequency (f_{endo}) of neurons could be slightly different we used the frequency difference (f_{diff}) between the endogenous and exogenous frequencies (f_{exo}) as outcome measure. We tested whether the change in NOA at the exogenous field frequency (Δ NOA_{f-exo}) depended on the frequency difference (f_{diff}) between the exogenous extracellular field (f_{exo})

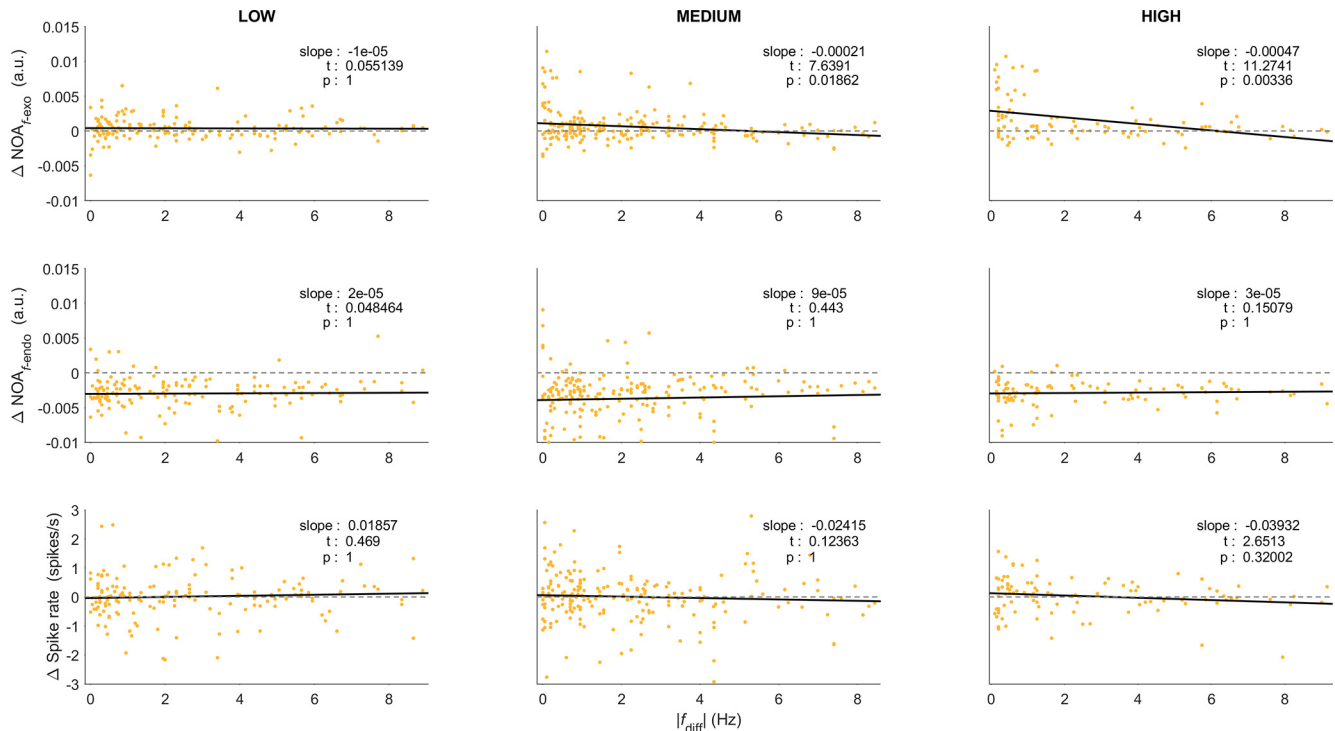


Figure 4. The change in NOA at the exogenous frequency (ΔNOA_{f-exo}) was dependent on the amplitude and frequency of the exogenous extracellular field. The columns show from left to right; Low, Medium, and High exogenous extracellular field amplitudes. NOA_{f-exo} increased for all levels (Fig. 3). However, a resonance pattern was only observed at the Medium and High levels such that when $|f_{diff}|$ was small ΔNOA_{f-exo} tended to be large. However, when $|f_{diff}|$ was large ΔNOA_{f-exo} tended to be small. At the Low level ΔNOA_{f-exo} did not depend on $|f_{diff}|$ (upper row). Although NOA_{f-endo} was affected by the exogenous field (Figs. 2, middle left panel, 3, middle row), in the middle row NOA_{f-endo} never depended on $|f_{diff}|$. The lower row shows that no spike-rate changes were observed for any of exogenous extracellular field amplitudes tested. Nor was there any dependency on $|f_{diff}|$.

and the endogenous neural oscillation (f_{endo}). Since f_{diff} could be negative or positive we first tested (see Materials and Methods, Linear model and statistics) whether negative f_{diff} differently modulated ΔNOA_{f-exo} compared with positive f_{diff} . This was not the case ($t = 0.68711$, $p = 0.98471$). We also found no differential modulation by the negative and positive f_{diff} conditions for ΔNOA_{f-endo} ($t = 1.458$, $p = 0.291$) nor Δ spike-rate ($t = -0.52784$, $p = 0.59786$). Therefore, we performed all further analyses using the absolute f_{diff} values ($|f_{diff}|$), thus simplifying the analysis and increasing statistical power.

NOA increase depends on exogenous extracellular field frequency and amplitude

Figure 4, upper row, shows ΔNOA_{f-exo} as a function of $|f_{diff}|$ for the Low, Medium, and High groups. The Low group did not have a statistically significant slope (slope: $-1e-5$, CI_{slope} : -0.000121 – $9.5e-5$, $t = 0.055139$, $p = 1$). The Medium group did show a significant slope (slope: -0.00021 , CI_{slope} : -0.000365 to $-6.1e-5$, $t = 7.6391$, $p = 0.01862$), as did the High group (slope: -0.00047 , CI_{slope} : -0.000745 to -0.000191 , $t = 11.2741$, $p = 0.00336$). This indicates that the observed changes in NOA at the exogenous frequency are dependent on $|f_{diff}|$. Stated in other words, the changes in NOA, at the exogenous field frequency (ΔNOA_{f-exo}), caused by the extracellular field showed a resonance pattern centered around the endogenous neural oscillation frequency (f_{endo}). Furthermore, this resonance pattern depended on the amplitude of the extracellular field, with stronger extracellular fields causing larger increases in the neural oscillation when the endogenous and exogenous frequencies were close. We tested whether the ΔNOA_{f-exo} depended on stimulation amplitude. This was not the case Low to Medium ($t = -1.1399$, $p = 0.255$); Medium to High ($t = -0.4290$,

$p = 0.668$). There is, however, a clear trend with an increasing slope as the stimulation amplitude increases.

Oscillation responses correlate with entrainment

Entrainment is the adjustment of the phase of one oscillatory signal to the phase of another. In this analysis, we tested whether the amplitude of the neural oscillation in responses to the external stimulation was related to the neuron's entrainment. In Figure 5, entrainment (PLV) is plotted as a function of the endogenous NOA (NOA_{f-endo}). There was a statistically significant positive correlation such that as NOA_{f-endo} increased so did entrainment (p values: Low, $3.40e-17$; Medium, $2.77e-30$; High, $1.32e-24$).

Endogenous oscillation amplitude decreases as a response to exogenous extracellular field application

NOA_{f-endo} decreases (Figs. 2, middle left panel, 3, middle row) however did not depend on $|f_{diff}|$. Figure 4, middle row, ΔNOA_{f-endo} showed no significant slopes (Low, slope: $2e-5$, CI_{slope} : -0.000152 – 0.00019 , $t = 0.048464$, $p = 1$; Medium, slope: $9e-5$, CI_{slope} : -0.000173 – 0.000349 , $t = 0.443$, $p = 1$; High, slope: $3e-5$, CI_{slope} : -0.000115 – 0.000171 , $t = 0.15079$, $p = 1$).

Importantly, the results indicate that the largest changes in NOA_{f-exo} observed at small $|f_{diff}|$ values were not because of spike-rate changes at those frequencies; (Low, slope: 0.01857, CI_{slope} : -0.035001 – 0.072145 , $t = 0.469$, $p = 1$; Medium, slope: -0.02415 , CI_{slope} : -0.15955 – 0.11125 , $t = 0.12363$, $p = 1$; High, slope: -0.03932 , CI_{slope} : -0.087231 – 0.0086 , $t = 2.6513$, $p = 0.32002$). This implies that the NOA increases were because of subthreshold modulation of the neural membrane. The reported statistics in this section were conducted with a linear model and p values Bonferroni corrected for three comparisons.

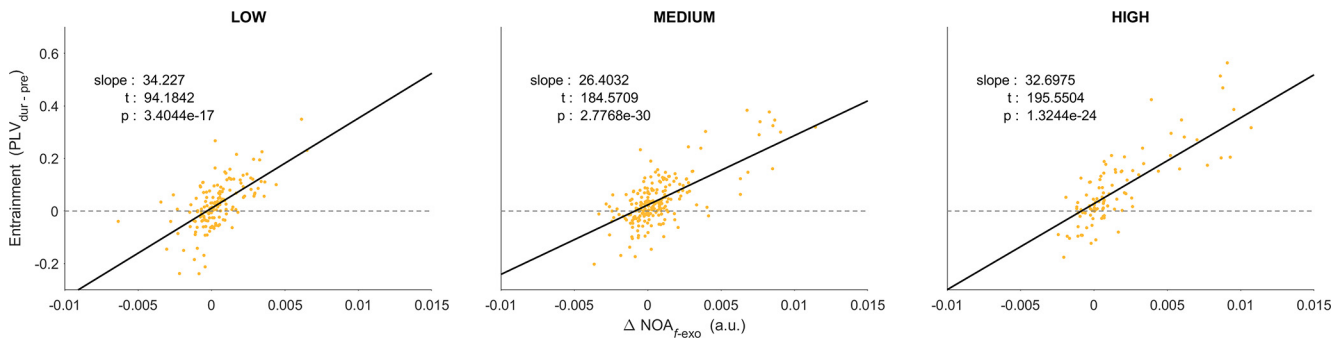


Figure 5. Oscillation amplitude change at the stimulation frequency correlates with entrainment. For all panels entrainment is plotted as a function of the change in NOA at the stimulation frequency. The positive correlation shows that when oscillation amplitudes increased neurons tended to become more entrained.

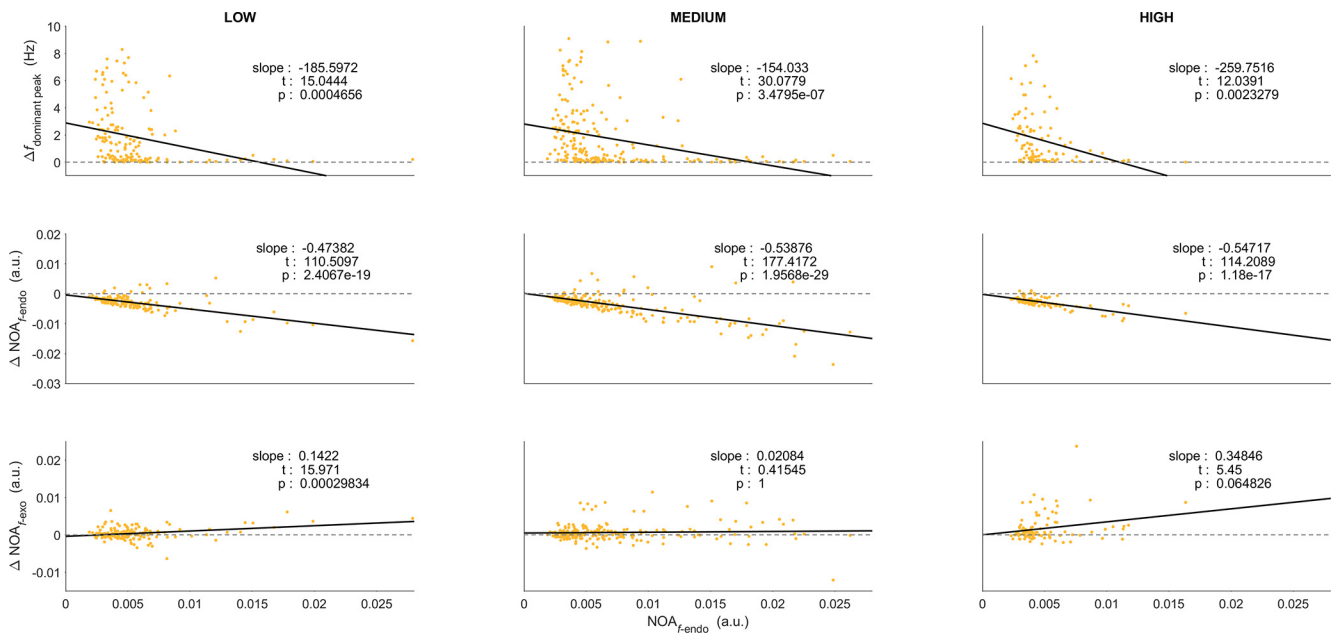


Figure 6. Responses to stimulation depends on amplitude of the ongoing endogenous oscillation ($\text{NOA}_{f\text{-endo}}$). The upper row shows the shift in dominant frequency as a function of $\text{NOA}_{f\text{-endo}}$. Frequency shifts tended to be large when $\text{NOA}_{f\text{-endo}}$ was low. However, when $\text{NOA}_{f\text{-endo}}$ was high-frequency shifts were smaller. In the middle row, $\Delta \text{NOA}_{f\text{-endo}}$ is plotted as a function of $\text{NOA}_{f\text{-endo}}$. There is a clear relationship where larger $\text{NOA}_{f\text{-endo}}$ results in smaller $\Delta \text{NOA}_{f\text{-endo}}$. In the lower row, changes in the NOA at the stimulation frequency ($\Delta \text{NOA}_{f\text{-exo}}$) is plotted as a function of $\text{NOA}_{f\text{-endo}}$. There appears no clear relationship between $\text{NOA}_{f\text{-endo}}$ and $\Delta \text{NOA}_{f\text{-exo}}$.

We also tested whether there was a relationship between the amplitude of the endogenous ongoing oscillation ($\text{NOA}_{f\text{-endo}}$) and the response to the exogenous stimulation. Figure 6, upper row, shows the shift in the frequency of the highest NOA from prestimulation to during-stimulation ($\Delta f_{\text{dominant oscillation}}$) on the y-axis. The analysis shows that frequency tended to shift from the ongoing endogenous oscillation when this ongoing endogenous oscillation was weak before application of the exogenous stimulation. However, as the ongoing endogenous oscillation increased in strength this shift tended to be smaller. Figure 6, middle row, shows the change of the NOA of the endogenous oscillation ($\Delta \text{NOA}_{f\text{-endo}}$) on the y-axis. There appears a clear correlation where larger $\text{NOA}_{f\text{-endo}}$ responded to stimulation with larger $\Delta \text{NOA}_{f\text{-endo}}$. In the lower row of Figure 6, we also compared $\text{NOA}_{f\text{-endo}}$ to the change in oscillation amplitude at the stimulation frequency ($\Delta \text{NOA}_{f\text{-exo}}$). There is only a trend where larger $\text{NOA}_{f\text{-endo}}$ tended to result in larger $\Delta \text{NOA}_{f\text{-exo}}$; this is however not significant. Taken together, this implies that when the ongoing endogenous oscillation is weak the dominant frequency can be easily shifted. At the same time

changes in $\text{NOA}_{f\text{-endo}}$ remain small. On the other hand, strongly oscillating neurons tend to remain close to their endogenous frequency (f_{endo}). However, their $\text{NOA}_{f\text{-endo}}$ can show large shifts.

Discussion

In this study we applied low-amplitude, spatially broad, exogenous extracellular electric fields of varying frequencies and amplitudes and measured their effect on the oscillatory nature of the low frequency spiking activity (here referred to as neural oscillation) in the rat motor cortex. We showed that these extracellular fields can modulate NOA and frequency in an *in vivo* model. Interestingly, the largest changes in NOA occurred when the frequency of the exogenous extracellular field was closest to that of the ongoing endogenous oscillation. Specifically, when the difference between the endogenous and exogenous frequencies (f_{diff}) was small the change in NOA tended to be large. However, when the frequency difference was large the change in NOA was small. Notably, the endogenous oscillation amplitude

decreased when we applied stimulation. It appears that the stimulation tends to disrupt the ongoing periodicity in the spiking. Possibly that the neuron attempts to follow the frequency of the external stimulation thereby reducing its natural oscillating frequency. This implies that the electric stimulation actually drives the neuron away from its natural frequency to follow the frequency of the external stimulation. This manipulation is however limited; when exogenous field frequency (f_{exo}) was far away from ongoing endogenous frequency (f_{endo}) NOA at f_{endo} tended to be low (Fig. 4).

There are currently a number of ongoing debates about how tACS effects are mediated in human subjects. When tACS is applied via scalp electrodes in humans the current passes through the skin, skull and cerebrospinal fluid before generating a weak extracellular field in the brain. We have recently shown (Asamoah et al., 2019) that some tACS motor system effects can be caused by stimulation of peripheral nerves in the scalp. Some studies have claimed that the extracellular field generated in the brain by tACS is too weak to effect ongoing neural oscillations in humans (Lafon et al., 2017; Vöröslakos et al., 2018). Other studies in awake macaques have claimed that the extracellular fields in the brain of a similar amplitude to those in humans can cause neural entrainment (Johnson et al., 2020; Vieira et al., 2020). These studies added controls to rule out peripheral nerve costimulation. In this study we placed the stimulating electrodes directly on the rat skull and ensured that the skull was always dry. This means that we can be sure the results presented here were because of the weak oscillating extracellular field in the brain and not caused by costimulation of peripheral nerves.

We presented extracellular fields at three different amplitude ranges, Low, Medium, and High. In previous work, we have shown that the Low amplitude resulted in extracellular fields which peaked at 0.9 V/m. This is in the same range as the extracellular fields generated by tACS in humans. While we did not observe a resonance pattern at these Low amplitudes (Fig. 4), we did observe a significant effect on the NOA (Fig. 3). The resonance effects only appeared at the Medium and High amplitudes, which correspond to electric field strengths of 1–2 and 2–5 V/m, respectively. These electric field strengths would not be reached in humans using standard tACS approaches. This implies that, in principle, these frequency-specific modulations would be difficult to achieve. However, electric field strength in the brain typically increases with increasing stimulation intensity. Using high-amplitude tACS could increase electric field strengths to sufficient levels. Combining this with a topical anesthetic would then reduce the contribution of peripheral nerves (Khatoun et al., 2018). Another approach in human studies is to use minimally invasive methods such as epicranial stimulation (Khatoun et al., 2019). These approaches have the potential to increase electric field strength by bypassing the skin. Notably, endogenous oscillation decrease occurred also at the Low stimulation amplitude. This implies that human studies that aim to decrease endogenous oscillations can achieve this with relatively low electric field strengths.

A recent paper by W.A. Huang et al. (2021) showed the presence of an Arnold tongue pattern when using tACS to entrain α oscillations in the ferret brain. They showed that weak extracellular fields of around 0.5 V/m needed to be matched exactly to the frequency of the ongoing neural oscillation to cause neural entrainment. However, when the amplitude of the extracellular field was increased entrainment could occur across a wider range of frequencies. The authors used a control condition where they only stimulated on the skin to rule out effects

of peripheral nerve stimulation. Our results build on this and show that in addition to frequency-specific entrainment effects, tACS can cause frequency-specific amplitude effects. These frequency-specific entrainment and amplitude effects are likely linked with higher levels of entrainment causing spikes to be more patterned which in turns leads to higher oscillation amplitudes. This is supported by the analysis in Figure 5, where we show a strong correlation between oscillation amplitude increases and entrainment levels. It is important to note that both the Huang and colleagues' study and our work did not find any increases in spike-rate. Thus, the changes in NOA do not occur because of action potential induction, but rather because of spike timing shifts caused by the exogenous extracellular field. More experiments are needed to fully probe these mechanisms.

In conclusion, we have shown that in addition to previously observed entrainment and Arnold tongue effects, weak exogenous extracellular fields in a similar range to those generated by tACS in humans, can also cause frequency-specific effects on the NOA, with the largest oscillation amplitude modulations occurring when the frequency of the extracellular field is matched to the frequency of the endogenous oscillation. As such we show that neurons engaged in slow-wave oscillations prefer external inputs in the frequency range of the slow wave.

References

- Achermann P, Borbély AA (1997) Low-frequency (<1Hz) oscillations in the human sleep electroencephalogram. *Neuroscience* 81:213–222.
- Amzica F, Steriade M (1997) The K-complex: its slow (<1-Hz) rhythmicity and relation to delta waves. *Neurology* 49:952–959.
- Asamoah B, Khatoun A, Mc Laughlin M (2019) tACS motor system effects can be caused by transcutaneous stimulation of peripheral nerves. *Nat Commun* 10:266.
- Baker SN, Olivier E, Lemon RN (1997) Coherent oscillations in monkey motor cortex and hand muscle EMG show task-dependent modulation. *J Physiol* 501:225–241.
- Benchenane K, Tiesinga PH, Battaglia FP (2011) Oscillations in the prefrontal cortex: a gateway to memory and attention. *Curr Opin Neurobiol* 21:475–485.
- Bouyer JJ, Montaron MF, Vahnée JM, Albert MP, Rougeul A (1987) Anatomical localization of cortical beta rhythms in cat. *Neuroscience* 22:863–869.
- Brittain JS, Probert-Smith P, Aziz TZ, Brown P (2013) Tremor suppression by rhythmic transcranial current stimulation. *Curr Biol* 23:436–440.
- Canolty RT, Knight RT (2010) The functional role of cross-frequency coupling. *Trends Cogn Sci* 14:506–515.
- Cardin JA (2016) Snapshots of the brain in action: local circuit operations through the lens of γ oscillations. *J Neurosci* 36:10496–10504.
- Cardin JA, Carlén M, Meletis K, Knoblich U, Zhang F, Deisseroth K, Tsai L-H, Moore CI (2009) Driving fast-spiking cells induces gamma rhythm and controls sensory responses. *Nature* 459:663–667.
- Dürschmid S, Zaehle T, Kopitzki K, Voges J, Schmitt F, Heinze HJ, Knight RT, Hinrichs H (2013) Phase-amplitude cross-frequency coupling in the human nucleus accumbens tracks action monitoring during cognitive control. *Front Hum Neurosci* 7:635.
- Erchova IA, Lebedev MA, Diamond ME (2002) Somatosensory cortical neuronal population activity across states of anaesthesia. *Eur J Neurosci* 15:744–752.
- Espenhahn S, van Wijk BCM, Rossiter HE, de Berker AO, Redman ND, Rondina J, Diedrichsen J, Ward NS (2019) Cortical beta oscillations are associated with motor performance following visuomotor learning. *Neuroimage* 195:340–353.
- Herrmann CS, Rach S, Neuling T, Strüder D (2013) Transcranial alternating current stimulation: a review of the underlying mechanisms and modulation of cognitive processes. *Front Hum Neurosci* 7:279–213.
- Huang Y, Liu AA, Lafon B, Friedman D, Dayan M, Wang X, Bikson M, Doyle WK, Devinsky O, Parra LC (2017) Measurements and models of electric fields in the in vivo human brain during transcranial electric stimulation. *Elife* 6:e18834.

- Huang WA, Stitt IM, Negahbani E, Passey DJ, Ahn S, Davey M, Dannhauer M, Doan TT, Hoover AC, Peterchev AV, Radtke-Schuller S, Fröhlich F (2021) Transcranial alternating current stimulation entrains alpha oscillations by preferential phase synchronization of fast-spiking cortical neurons to stimulation waveform. *Nat Commun* 12:3151.
- Jensen O, Colgin LL (2007) Cross-frequency coupling between neuronal oscillations. *Trends Cogn Sci* 11:267–269.
- Johnson L, Alekseichuk I, Krieg J, Doyle A, Yu Y, Vitek J, Johnson M, Opitz A (2020) Dose-dependent effects of transcranial alternating current stimulation on spike timing in awake nonhuman primates. *Sci Adv* 6:eaz2747.
- Kandel ER, Schwartz JH, Jessel TM (2000) *Principles of neural science*, Ed 4. New York: McGraw-Hill.
- Khatoun A, Breukers J, Op de Beeck S, Nica IG, Aerts J-M, Seynaeve L, Haeck T, Asamoah B, Mc Laughlin M (2018) Using high-amplitude and focused transcranial alternating current stimulation to entrain physiological tremor. *Sci Rep* 8:4927.
- Khatoun A, Asamoah B, Mc Laughlin M (2019) Investigating the feasibility of epicranial cortical stimulation using concentric-ring electrodes: a novel minimally invasive neuromodulation method. *Front Neurosci* 13:773–712.
- Krause MR, Vieira PG, Csorba BA, Pilly PK, Pack CC (2019) Transcranial alternating current stimulation entrains single-neuron activity in the primate brain. *Proc Natl Acad Sci U S A* 116:5747–5755.
- Lachaux JP, Rodriguez E, Martinerie J, Varela FJ (1999) Measuring phase synchrony in brain signals. *Hum Brain Mapp* 8:194–208.
- Lafon B, Henin S, Huang Y, Friedman D, Melloni L, Thesen T, Doyle W, Buzsáki G, Devinsky O, Parra LC, A. Liu A (2017) Low frequency transcranial electrical stimulation does not entrain sleep rhythms measured by human intracranial recordings. *Nat Commun* 8:1–13.
- Léger D, Debellemanni E, Rabat A, Bayon V, Benchenane K, Chennaoui M (2018) Slow-wave sleep: from the cell to the clinic. *Sleep Med Rev* 41:113–132.
- Li S, Bai W, Liu T, Yi H, Tian X (2012) Increases of theta–low gamma coupling in rat medial prefrontal cortex during working memory task. *Brain Res Bull* 89:115–123.
- Lydic R, Baghdoyan HA (2005) Sleep, anesthesiology, and the neurobiology of arousal state control. *Anesthesiology* 103:1268–1295.
- Mc Laughlin M, Khatoun A, Asamoah B (2022) Detection of tACS entrainment critically depends on epoch length. *Front Cell Neurosci* 16:806556.
- Notbohm A, Kurths J, Herrmann CS (2016) Modification of brain oscillations via rhythmic light stimulation provides evidence for entrainment but not for superposition of event-related responses. *Front Hum Neurosci* 10:10.
- Pikovsky A, Rosenblum M, Kurths J (2001) *Synchronization: a universal concept in nonlinear sciences*. Cambridge: Cambridge University Press.
- Purves D, Augustine GJ, Fitzpatrick D, Hall WC, LaMantia A-S, McNamara JO, White LE (2008) *Neuroscience*, Ed 4. Sunderland: Sinauer Associates, Inc.
- Rossant C, Kadir SN, Goodman DFM, Schulman J, Hunter MLD, Saleem AB, Grosmark A, Belluscio M, Denfield GH, Ecker AS, Tolias AS, Solomon S, Buzsáki G, Carandini M, Harris KD (2016) Spike sorting for large, dense electrode arrays. *Nat Neurosci* 19:634–641.
- Senkowski D, Gallinat J (2015) Dysfunctional prefrontal gamma-band oscillations reflect working memory and other cognitive deficits in schizophrenia. *Biol Psychiatry* 77:1010–1019.
- Siegle JH, López AC, Patel YA, Abramov K, Ohayon S, Voigts J (2017) Open Ephys: an open-source, plugin-based platform for multichannel electrophysiology. *J Neural Eng* 14:045003.
- Sohal VS (2016) How close are we to understanding what (if anything) γ oscillations do in cortical circuits? *J Neurosci* 36:10489–10495.
- Tavakoli AV, Yun K (2017) Transcranial alternating current stimulation (tACS) mechanisms and protocols. *Front Cell Neurosci* 11:214.
- Vieira PG, Krause MR, Pack CC (2020) tACS entrains neural activity while somatosensory input is blocked. *PLoS Biol* 18:e3000834.
- Vöröslakos M, Takeuchi Y, Brinyiczki K, Zombori T, Oliva A, Fernández-Ruiz A, Kozák G, Kincses ZT, Iványi B, Buzsáki G, Berényi A (2018) Direct effects of transcranial electric stimulation on brain circuits in rats and humans. *Nat Commun* 9:483.
- Vosskuhl J, Strüder D, Herrmann CS (2018) Non-invasive brain stimulation: a paradigm shift in understanding brain oscillations. *Front Hum Neurosci* 12:211.
- Wang XJ (2010) Neurophysiological and computational principles of cortical rhythms in cognition. *Physiol Rev* 90:1195–1268.