Neural Responses Display More Heterogeneities to Stimuli Under Natural Conditions: implications for population coding

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Statement of Contribution

This study was designed by Dr. Maurice Charon. The data was collected by Dr. Michael Metzen.

Kejin (Vicky) Zhu analyzed data and wrote this thesis. Dr. Maurice Chacron edited the writing.

Abstract

Growing evidence from single unit recordings shows that sensory systems have adapted to the complex statistics of the natural environment in which the organism lives. However, it is now widely accepted that behavioral responses are determined from the activities of large neural populations. Here we investigated how populations of neurons encode naturalistic stimuli and artificial stimuli in the electrosensory system of the weakly electric fish *Apteronotus leptorhynchus*. We performed multiunit recording in the hindbrain region and quantified information transmitted by neural populations. Overall, we found that more information was transmitted about naturalistic stimuli than artificial stimuli of equivalent frequency content. Further analysis revealed that this occurred because neural responses were more heterogeneous during naturalistic stimulation, as evidenced from reduced signal correlations, as opposed to changes in noise correlations. Our results thus suggest that electrosensory neural populations have adapted to the statistics of natural envelope stimuli such as to better encode these than artificial sinusoidal stimuli.

Résumé

Des preuves croissantes provenant d'enregistrements d'unités uniques montrent que les systèmes sensoriels se sont adaptés aux statistiques complexes de l'environnement naturel dans lequel vit l'organisme. Cependant, il est maintenant largement admis que les réponses comportementales sont déterminées à partir des activités de grandes populations neuronales. Nous avons étudié ici comment les populations de neurones encodent les stimuli et les stimuli artificiels dans le système électrosensoriel du poisson faiblement électrique *Apteronotus leptorhynchus*. Nous avons effectué des enregistrements multi-unités dans la région du cerveau postérieur et quantifié les informations transmises par les populations de neurones. Dans l'ensemble, nous avons constaté que davantage d'informations étaient transmises sur des stimuli naturels que sur des stimuli artificiels de contenu fréquentiel équivalent. Une analyse plus approfondie a révélé que cela se produisait parce que les réponses neuronales étaient plus hétérogènes pendant la stimulation naturaliste, comme en témoigne la réduction des corrélations de signaux, par opposition aux changements dans les corrélations de bruit. Nos résultats suggèrent donc que les populations neuronales électrosensorielles se sont adaptées aux statistiques des enveloppes naturelles de manière à mieux les encoder que les stimuli artificiels.

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List of Abbreviations

AM - amplitude modulation

cf – coding fraction

Circ STD – circular standard deviation

CLS – centrolateral segment

CMS – centromedial segment

EA – electrosensory afferent

EGP - eminentia granularis posterior

ELL – electrosensory lateral line lobe

EOD – electric organ discharge

JAR – jamming avoidance response

LS – lateral segment

MS – medial segment

nP - nucleus praeminentialis

TS - torus semicircularis

Introduction

The natural world is made up of stimuli with complex statistics, and biological systems must be adaptive to environmental changes for animal survival. How neurons encode natural stimuli to give rise to perception and behavior remains a central question in neuroscience. Growing evidence from single unit recordings shows that sensory systems have adapted to the statistics of the natural environment (Huang et al., 2019). However, how large populations of neurons encode natural stimuli cannot be ascertained from single unit recordings. This is because single neurons are not fully informative about the stimuli, and neural populations can offer more accurate representations of the stimuli (Averbeck et al., 2006; Paradiso, 1988; Schneidman et al., 2003). Therefore, we investigated how sensory information from the naturalistic environment is decoded by neural populations to guide behavior using the electrosensory system of weakly electric fish as a model.

Weakly electric fish actively generate electric fields and perceive the environment by detecting perturbations of these fields (Hitschfeld et al., 2009; Krahe & Maler, 2014). Specifically, electroreceptors on the skin detect objects in the environment and sense social signals from other conspecifics (Hupe & Lewis, 2008). The anatomy of the fish brain is well studied (Maler et al., 1991), the behavior of the fish can be easily picked up by electrodes in the water as they consist of changes in the electric organ discharge (EOD), and the electrosensory stimuli can be easily mimicked in the lab (Huang et al., 2019). In this study, we decided to use weakly electric fish as the animal model due to these advantages as well as important similarities with other sensory modalities such as audition, vision, and vestibular (see (Chacron et al., 2011; Clarke et al., 2015; Krahe & Maler, 2014; Maler, 2009) for review). We used the South American wave

type weakly electric fish *Apteronotus leptorhynchus* of either sex, which is also commonly known as the brown ghost knifefish. This fish emits continuous EOD. The brain region studied is the hindbrain electrosensory lateral line lobe (ELL), which is one synapse away from the electroreceptor afferents on the skin. We recorded neural activities in ELL simultaneously using Neuropixels, a probe that allows large scale multi-unit recording. Before showing the results from this study, we will review some background information and previous literature about population coding, the electrosensory system as well as electrosensory stimuli.

Literature Review

Population coding and neural correlations

It is generally agreed that behavioral responses are determined from the activities of large neural populations (Averbeck et al., 2006; Kohn et al., 2016). Though single unit recordings contribute tremendously to our current understanding in system neuroscience, they are limited in helping us understand how neurons represent the natural environment. For example, population of neurons in the primary visual cortex (V1) predict visual discrimination more accurately than that of single neurons (Paradiso, 1988). Therefore, how activities of large population of neurons are combined stays a central yet complicated question in neuroscience (Bannister & Larkman, 1995a, 1995b; Gjorgjieva et al., 2016). Technical constraints limited researchers to simultaneously record from large populations of neurons, meaning that usually only neurons responded strongly to a test stimulus were hand-picked for analysis. Therefore, many studies considered neurons as single units and reported single unit statistics (e.g., firing rates). Recent technologies in the form of high-density electrode arrays have opened the door

for simultaneous large-scale recordings of neural populations (Steinmetz et al., 2021). Therefore, we performed multi-unit recoding from ELL pyramidal cell populations in the hindbrain.

Neural responses to sensory stimuli are variable. As such, neural activities are not the same for each trial even when the same stimulus is presented repeatedly. Therefore, it is impossible to accurately decode the stimulus using one single noisy neural response. The brain needs to decode the stimulus in the presence of the noise and computes some estimate of the stimulus using population of neural activities. If noise is not correlated, population coding would be relatively easy to understand. However, noise is correlated in the brain. Therefore, we were interested in understanding the role of pairwise correlation between neurons, especially noise correlation, in encoding different stimuli, since previous work suggested that correlation could impact population coding (Averbeck et al., 2006).

There are two types of pairwise correlation between spike counts of neurons. First, signal correlation represents the correlation between the average responses of two neurons. These are due to similarities in stimulus-response properties. On the other hand, noise correlation is correlation between the trial-to-trial variabilities to repeated stimulus presentations and is due to shared synaptic inputs (Averbeck et al., 2006). Note that noise correlation is found ubiquitously across systems and species, though its function remains unclear (Cohen & Kohn, 2011; Doiron et al., 2016). Some theoretical frameworks argued that noise correlation limits the amount of information neurons could encode (Abbott & Dayan, 1999; Sompolinsky et al., 2001; Zohary et al., 1994), while some other studies suggested that noise correlation could be

beneficial for neural representation of the stimulus (Franke et al., 2016; Lin et al., 2015; Zylberberg et al., 2016).

The understanding of the role of noise correlation in information transmission evolved throughout the years. It can be detrimental (Averbeck & Lee, 2006; Ecker et al., 2010), beneficial (Franke et al., 2016; Lin et al., 2015; Zylberberg et al., 2016) or no effect on information transmission (Nirenberg & Latham, 2003; Wu et al., 2001). It depends on many factors, such as stimulus features (Chacron & Bastian, 2008), learning (Gu & Lin, 2011) and attention (Cohen & Maunsell, 2009). The effect of noise correlation on information transmission depends on the relationship between signal and noise correlation, or correlation structure. When noise and signal correlation are both positive or both negative, noise correlation is detrimental (Averbeck & Lee, 2006), but when noise and signal correction have opposite signs (i.e., one is positive and the other one is negative), the effect becomes beneficial (Averbeck et al., 2006). Here, we decoded the spike train of neural population and compared the performance of information transmission that do and do not take neural correlation into account. This helped us gain more understanding on how brain carries out computations efficiently in the presence of noise.

The electrosensory system of weakly electric fish

The wave type weakly electric fish *Apteronotus leptorhynchus* are nocturnal and have poor vision, thus rely heavily on active electric sense. They generate weak electric organ discharge of a few millivolts and form an electric field around their body. Perturbations of the electric field causes changes in EOD frequency and amplitude, which are detected by the tuberous electroreceptors on the fish's skin (Chacron, 2006). Their electroreceptors are connected to an

afferent through a synapse. There are two classes of tuberous electroreceptors in wave type fish. The T-type or the time coders, code the phase, thus coding for the frequency of the EOD. The P-type or the probability coders, code for the amplitude of EOD. Since this project studies the amplitude modifications of EOD and envelopes, we will focus on P- type electroreceptors (Chacron, 2006; Wessel et al., 1996).

The electrosensory afferent (EA) carries information from electroreceptors to hindbrain, and projects to the ELL region. ELL has four parallel segments, centromedial segment (CMS), centrolateral segment (CLS), lateral segment (LS) and medial segment (MS). CMS, CLS and LS process inputs from tuberous electroreceptor afferents. MS process inputs from ampullary electroreceptors, which will not be discussed here. ELL pyramidal cells from all three maps (CMS, CLS and LS) are analyzed in this project. These brain maps are further divided into three layers, superficial, intermediate, and deep layers. In addition, pyramidal cells can be divided as ON-type cells who receive direct synaptic input from EA, and OFF-type cells who receive inputs from EA via intermediate inhibitory interneurons. ON cells increase firing rates in response to EOD amplitude increases and OFF-type cells decrease firing rates when EOD amplitude decreases (Maler, 1979).

Pyramidal cells are the sole output neurons in the ELL, and these cells from all three maps project to neurons in midbrain *torus semicircularis* (TS). Neurons in TS further project to even higher brain regions for further processing. In addition to the feedforward inputs from EA, the ELL pyramidal cells receive extensive excitatory and inhibitory feedback inputs from higher brain regions. TS neurons also project to *nucleus praeminentialis* (nP), a major feedback area in midbrain. The stellate cells in nP directly project back to ELL pyramidal cells and forms a direct

closed feedback loop. The other major feedback source is the indirect pathway, where deep pyramidal cells project to nP, the multipolar cells in the nP project to the *eminentia ranularis posterior* (EGP). Granule cells in the EGP project back to the apical dendrites of the pyramidal cells in ELL (Maler, 1979).

Electrosensory signals in weakly electric fish

As mentioned above, the wave-type weakly electric fish sense perturbations of their electric field to detect the natural environment. These perturbations cause frequency or amplitude modulations (AM) of the EOD (Carlson & Kawasaki, 2006), making themselves as the first order stimuli while the EOD is referred as the zeroth order stimulus. Frequency and amplitude modulations are processed differently, and this study focus on amplitude modulations, also referred as "beats". These modulations can be results of detecting small objects or prey items in the electric field, but one fish's own EOD can also be modulated when two conspecifics are in proximity (< 1m) of one another (Bastian et al., 2002; Bastian & Nguyenkim, 2001; Engler et al., 2000). Due to the constructive and destructive perturbations, the resulting AM has a frequency of the frequency difference of the two fish's EOD. One behavior example demonstrating the effect of AM is the jamming avoidance response (JAR). When two fish come into close proximity, and their EOD frequencies are too close, the two fish will jam each other's signal. The jamming will result in sensory confusion as the fish cannot effectively electro-locate. Therefore, one of the fish will either increases or decrease its EOD frequency to increase the frequency difference between itself and its neighbors' discharge, thus avoiding jamming and sensory confusion (Kawasaki, 1997).

However, in natural environments, two fish seldom stay stationary next to each other. When two fish move close to each other, the AM is further modulated at a lower frequency to give rise to a second order stimulus, also referred to as the envelope stimulus (Stamper et al., 2013; Stamper, Roth, et al., 2012). The frequency of the envelope is much lower than the frequencies of the AM, usually ranging from 0.03 Hz to 1 Hz. This kind of movement envelope carries information about the relative distance and movement between the two conspecific fish (Metzen & Chacron, 2014; Stamper et al., 2013). Previous studies reveal that the power of the movement envelopes decays as a function of envelope frequencies (Fotowat et al., 2013; Metzen & Chacron, 2014). In other words, there are more power in low frequency envelopes, or low frequency envelopes occur more often than high frequency envelopes in natural environment (Fig. 1b right). One important feature of natural stimuli is that the decay in power from low to high envelope frequencies occur in a power law fashion. This is not a unique feature in the electrosensory system, it is similar in other sensory modalities (Carriot et al., 2017; Lundstrom et al., 2010). Note that there is another kind of envelope, the social envelope. It occurs when three or more stationary fish are in close proximity. This social envelope contains two prominent AMs, and it contains higher frequencies than 1 Hz (Stamper et al., 2013). Social envelopes are not the focus of this thesis.

Natural stimuli vs artificial stimuli

Past research, through use of artificial stimuli, has provided much of our understanding in how systems process sensory information. Black and white gratings, an example of artificial stimuli, are often used in visual system research (Ferster & Miller, 2000; Wright & Johnston, 1982). In the electrosensory system, artificial stimuli consist of a noisy carrier which is modulated at

specific envelope frequencies and can be easily constructed in the lab. Though these artificial stimuli contribute substantially to the current knowledge of how sensory neurons represent the stimuli in the brain, they are not ideal in studying perception. Artificial stimuli are not behaviorally relevant, the information of these stimuli may not be decoded by or may be differently decoded by downstream neurons. More studies in system neuroscience are moving to using natural stimuli both in the electrosensory system as well as other sensory modalities (Einhauser & Konig, 2010; Huang et al., 2019; Kayser et al., 2004; Nelken, 2004). In fact, this move can be supported by other previous research, which has shown that sensory systems have adapted to the complex statistics of the natural stimuli (Attneave, 1954; Rieke et al., 1996; Simoncelli & Olshausen, 2001; Wark et al., 2007). In this project, the natural stimulus, described by Huang et al. (2019), mimicked the relatively simple natural movement envelope stimulus. The natural envelope is not sinusoidal and contains a whole spectrum of temporal frequencies. The power of the stimuli decays as a power law of increasing frequencies (Fotowat et al., 2013; Metzen & Chacron, 2014; Yu et al., 2012).

Sensory processing of envelopes

We know that artificial envelopes elicit behavioral responses that track the stimulating envelope. This means that the neurons must retain and process the detailed time course of sensory information to guide behavior (Metzen & Chacron, 2014). Though no previous research has shown if this is also the case for naturalistic stimuli with changing statistics, we know that both types of stimuli elicit behavior responses indicating that there must be sensory processing happening at the neural level. How is sensory information processed at each step of the sensory pathway? At the level of the peripheral, EAs respond to envelopes frequencies ranging

from 0.05 Hz to 1 Hz (Metzen & Chacron, 2015). EAs fire within the range of 200 to 600 Hz and increase their firing rates linearly with increasing EOD amplitudes within that range. When EOD amplitude is high, EAs respond with nonlinear phase locking (Chacron et al., 2005a; Gussin et al., 2007; Metzen, Krahe, et al., 2016). Metzon and Chacron (2019) discuss further details on the tuning properties of EAs to movement sinusoidal envelopes. In previous research, it was also shown that correlated activities of EAs can encode information of envelopes (Metzen et al., 2015); this corresponds with the fact that hundreds of EA units can synapse onto one single ELL pyramidal cell. Since EAs carry information to ELL, the next step is to review how ELL neurons respond to different stimuli.

ELL has heterogeneous populations of pyramidal ON- and OFF-type cells from three different maps across three layers (Maler et al., 1991). Both ON- and OFF-type cells respond with similar phase preference (Huang & Chacron, 2016; Huang et al., 2016). However, the tuning to envelopes varies greatly for different cell populations, but in general, ELL pyramidal cells display high-pass tuning and phase lead to the movement envelope (Huang & Chacron, 2016). One might assume that ELL neural responses are mediated by nonlinear integration of afferents. However, ELL cells receive large amounts of feedback from higher brain regions, and their responses are also shaped by the descending feedback pathways. Previous studies revealed that descending inputs result in increases in firing rate of pyramidal cells, and this could mediate adaptive optimized coding of natural stimuli in weakly electric fish (Huang et al., 2019; Metzen & Chacron, 2019).

Efficient coding

To efficiently encode stimuli, sensory systems adapt their coding strategies. For example, retinal ganglion cells change their firing rates adaptively to changes in the mean or variance of a Gaussian white noise stimulus (Smirnakis et al., 1997). This is seen across sensory modalities and species (Brenner et al., 2000; Carriot et al., 2022; Maravall et al., 2007; Nagel & Doupe, 2006). In weakly electric fish, it was found out that the power spectrum of ELL pyramidal cells was temporally white, or independent of frequency within the range of relevant envelope frequencies (Huang et al., 2019; Metzen & Chacron, 2019). The high pass tuning properties of LS superficial pyramidal cells compensate for the decaying power law statistics of the stimulus, forming a close match between the increase in neural gain and the decrease in stimulus power, thus the resulting power spectrum is white. Theoretical studies suggests that a white spectrum maximize information transmission (Rieke et al., 1996). In this study, we quantified the information transmitted by neural populations to assess the efficiency of coding of different stimuli.

Methods

Animal Care

This study was conducted using the weakly electric fish *Apteronotus leptorhynchus* of either sex (n = 2). The animals were purchased from tropical fish suppliers and were housed in groups of 2 to 10 in tanks. The water temperature is kept between 26 - 29 °C in all tanks, and the conductivities of tank water were kept at 300 – 800 μS/cm, according to published guidelines (Hitschfeld et al., 2009). All animal procedures were approved by McGill University's animal care committee.

Surgery

Surgical procedures have been described in detail previously (Chacron et al., 2003; Huang et al., 2018; Metzen et al., 2015; Toporikova & Chacron, 2009). During each experiment, one fish was injected intramuscularly with 0.1 - 0.5 mg of tubocurarine chloride hydrate (sigma). Then, the animal was placed in a tank (30 cm *30 cm*10 cm) filled with water from the animal's home tank. The fish was respirated with heated, oxygenated water through a mouth tube at a consistent flow rate of ~10 mL/min. Before surgery, the head of the fish is stabilized by gluing a metal post to the skull, and the fish was locally anesthetized at its head with lidocaine (5%; AstraZeneca, Mississauga, ON, Canada). A 5 mm^2 window craniotomy was performed to expose the ELL in the hindbrain.

Recording

Neuropixels probes (Imecinc., Leuven, Belgium) were inserted into the brain as done previously when recording from single ELL pyramidal cells within the LS of the ELL (Huang et al., 2019; Wang & Chacron, 2021). The probe advanced to a depth between 1500 μm and 2000 μm into

the hindbrain at approximately 45° angle with respect to the sagittal plane (Maler et al., 1991). Recording started at least 30 minutes after the placement of the probe to ensure brain tissue settling. It was likely that the majority of the neurons recorded were from LS, but it was possible that neurons from all three maps were recorded. All neurons were pulled for data analysis.

Stimulation

During an experiment, we played both artificial and naturalistic stimuli. Since the EOD of the fish is neurogenic, it is not affected by the curare injection. The stimuli consisted of AMs of the animal's own EOD. They were generated through a triggering function to emit sine waves at a frequency 30-40 Hz higher than the fish's EOD frequency, using the animal's EOD zero-crossing points. This allowed synchronization of the sine wave and the EOD. The sine waves were then multiplied by the stimulus waveform (MT3 multiplier; Tucker Davis Technologies), isolated from ground (A395 linear stimulus isolator; World Precision Instruments), and then delivered through a pair of chloritized silver wire electrodes placed 15 cm away from the fish's body on either side (Fig. 1a). A dipole was placed near the skin of the fish to estimate the signals the electroreceptors on the skin of the fish would pick up. The intensity of the stimuli was modified so that the changes in EOD amplitude were ~20 % of the baseline level, as done previously (Metzen et al., 2016). The EOD of the fish was picked up by another pair of electrodes placed near the head and the tail of the fish. The artificial stimuli consisted of a carrier, which were composed of 5-15 Hz noise (4th order Butterworth filter) carrier waveform (i.e., AM). The amplitude of the AM were further modulated at frequencies of 0.05, 0.1, 0.25, 0.5, 0.75 and 1Hz, forming the second order signals that mimic natural movement envelopes. The

frequencies were selected to represent the envelope signals from fish movements (Metzen & Chacron, 2014; Stamper et al., 2013). Under natural conditions, the power spectrum of noisy envelopes decay as a power law. The power law exponent varies depending on the speed and relative position of the fish. The mean exponent was found to be -0.8 (Huang et al., 2019; Metzen & Chacron, 2014). The naturalistic stimulus used in this project shared this characteristic of the noisy envelopes, its power spectrum decayed as a power law with the exponent of -0.8.

Data analysis

The neural recordings were digitized at 30 kHz using spikeGLX (Janelia Research Campus). Then, we filtered the recordings, and sorted the spikes using Kilosort (Steinmetz et al., 2021). Phy 2 (https://github.com/cortex-lab/phy) was used to manually curate the sorting results to select for ELL pyramidal neurons based on known characteristics of these neurons from single unit recording (Huang et al., 2019; Marquez & Chacron, 2020; Metzen et al., 2018). Over the two fish, we sorted 33 neurons in total. The spike times were converted into binary sequences using a bin of width 0.5 ms for further analysis. A Matlab script was written for specific analysis. It was found out that neurons only respond to the naturalistic stimulus with higher amplitude. Neurons fired spontaneously for lower amplitude of the stimulus, as the filtered firing rate curves were not tracking the low amplitude stimulus. Therefore, a cut-off of 1 (arbitrary unit) was used to select for responses when neurons were truly responding to the stimulus (see fig 2. a). Only responses to stimulus which amplitudes were higher than 1 were selected for further analysis.

Binary sequences of the spike train were filtered using a second order butter filter in Matlab to create the filtered firing rate. Behavior traces were calculated as the filtered changes in EOD frequencies. For artificial stimuli, linear system identification techniques were used to compute the sensitivity (i.e., the gain) and the phase of the neural responses in relation to the stimuli. We used a sinewave to fit the cycle histogram of the stimulus to get the firing rate modulation and then divided that to the stimulus envelope amplitude to obtain the gain. The phase was calculated from the phase histogram. For the naturalistic stimulus, the gain was calculated as the ratio of the amplitude of the filtered firing rate and the amplitude of the stimulus obtained from the recording dipole. Specifically, the filtered binary was fitted to the stimulus using a straight line, and the slope of the line was the gain. The phase of the response was calculated using the lag between the cross correlation of the filtered binary and the stimulus. The lag in time was converted into phase in degree, and phase fell outside a cycle was adjusted by subtracting multiples of 2pi for the analysis. Circular standard deviation (circ STD) was calculated as the square root of minus 2 times the log of the mean of the phase divided by the number of data points. A circ STD value close to 0 means little variation in phase values. The neuronal responses of 80% of the neurons from the neuron population were bootstrapped for 50 times to provide more data points for the circular STD analysis. Each time, a different group of neurons were selected.

We used the stimulus reconstruction technique to estimate the time – varying envelope $e(t)$ of the stimuli. Spike trains of each neuron recorded during stimulation were convolved with unique kernels, and then summed up to estimate the envelope signals (Dan et al., 1998; Krahe

et al., 2002; Massot et al., 2011; Warland et al., 1997). The kernels were selected to minimize the mean square error (ε), as previously shown (Abbott & Dayan, 1999; Rieke et al., 1996).

$$\varepsilon^2 = [e(t) - e_{est}(t)]^2 \quad (1)$$

Coding fraction (cf) reflects the fraction of the stimuli that were correctly recovered from neural responses. It was calculated as 1 minus the ratio of the error between the estimated stimuli and the original stimuli and the standard deviation of the original stimuli. It ranges from 0 to 1, the closer the value to 1, the better the reconstruction. Coding fraction was calculated for different population size. For each size, all possible combinations of neurons from the population were selected for cf calculation. The means of the different combinations were reported in the figure. The error bar was the stand error of the different combinations. The cfs for each dataset were calculated separately, and the mean values were reported. Since the population size of each data set was different (n = 15 and n = 18), the size of the smallest dataset (n=15) was used for the mean calculation. 80% of neurons at the maximum population size (n=15) were bootstrapped for 50 times to show maximum information recovered from the neural responses. Extra data points were discarded for this analysis.

Correlation between different pairs of the neuron were calculated and reported in the figures. Signal and noise correlation were calculated as Pearson's correlation coefficient:

$$\boldsymbol{r}_{\boldsymbol{ij}} = \frac{\boldsymbol{Cov}(\boldsymbol{S_i}, \boldsymbol{S_j})}{\sqrt{\boldsymbol{Var}(\boldsymbol{S_i})\boldsymbol{Var}(\boldsymbol{S_j})}} \quad (2)$$

Where S represents the spike trains, i and j represent different neurons. The overall correlation between pairs of neurons were calculated using the spike trains. To calculate signal and noise correlation, we first randomly permuted 20 cycles of the spike train sequences to shuffle out

the noise. Then we computed the average correlation between the shuffled sequences over 20 realizations, which was equal to the signal correlation coefficient. The residual sequences were calculated as the average firing rate sequences over all trials minus the mean firing rate sequence for each trial (Metzen & Chacron, 2021), and noise correlation was computed as the correlation coefficient between the firing rate residual sequences.

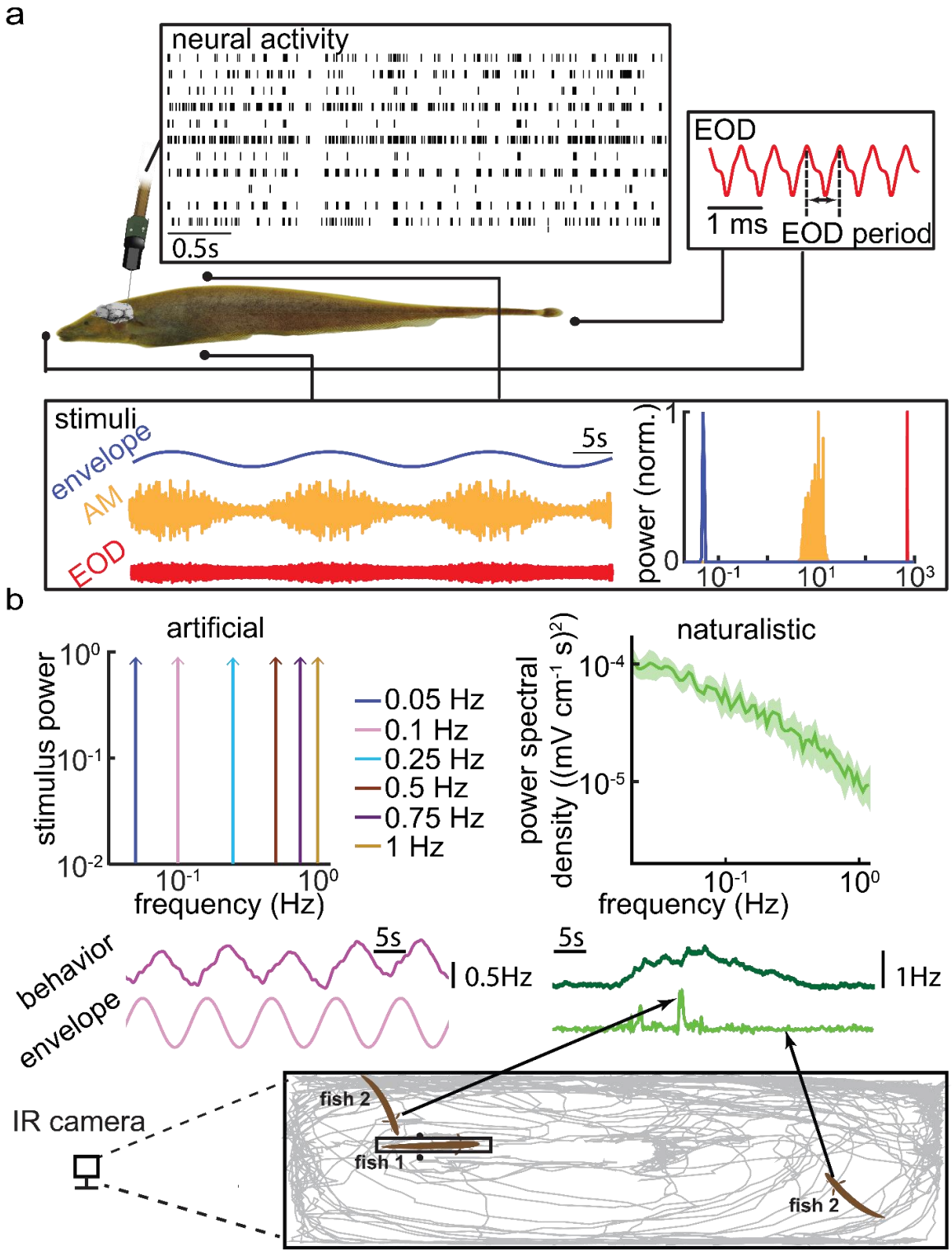
Results

Experimental setup

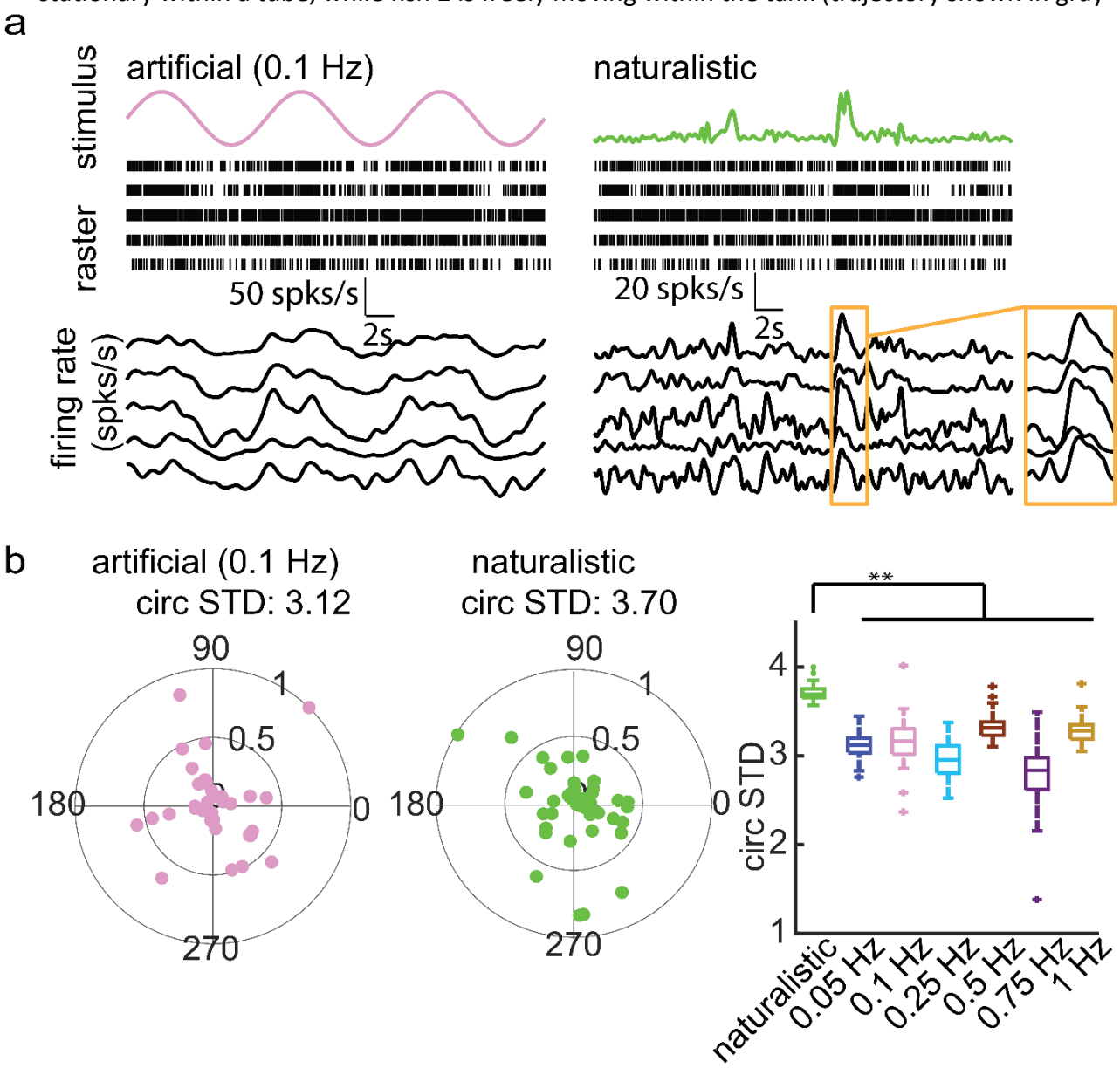
Here we are investigating how populations of neurons respond differently to artificial sinusoidal stimuli and a naturalistic stimulus whose power spectrum decays as a power law exponent of -0.8. We used multi-channel neuropixels probes to record activities of multiple ELL pyramidal cells simultaneously in the hindbrain in awake behaving fish while playing artificial and naturalistic stimuli (Fig. 1a). Both ON and OFF pyramidal cells were analyzed since we did not find significant difference between their responses to different stimuli, consistent with previous

Figure 1. **Experimental set up. a)** Top: Spike train of ELL pyramidal cells recorded using neuropixels probes, and the behavioral (EOD) responses of the fish. Bottom: Schematic showing the stimuli used in the experiments and their normalized power. Shown in the bottom are example AM waveform (orange), its envelope (blue), and the full signal received by the animal (red). **b)** Top: Power spectrum of the artificial sinusoidal envelope stimuli displayed together (left, each color indicates a different envelope frequency) and the naturalistic stimulus (right). Arrow heads indicate that values go up to infinity. Shown below are examples of behavior traces (light purple and dark green) and stimuli waveform (pink and light green). Bottom: schematic of the tank set up while recording fish movement with an infrared (IR) camera. Fish 1 is stationary inside a tube (black rectangle), while fish 2 is freely moving in the tank (trajectories in gray). Two locations of fish 2 are shown, which correspond to two time points of the example naturalistic stimuli (light green). Small dipoles located close to fish 1 record the stimulus (black circles).

results (Huang & Chacron, 2016). We also recorded the animal's behavior responses (i.e., changes in EOD frequency) using electrodes placed at the head and tail of fish. During social interactions, the EODs of two stationary fish interact to give an amplitude modification (AM;



orange; Fig. 1a, bottom left). When the fish start to move, the amplitude modification is further modified, forming a second order signal, also known as the envelope (blue; Fig. 1a, bottom left). The frequency spectra of EOD, AM and envelope signals can be found in Fig 1a, bottom right. We used both artificial stimuli, consisting of sinusoidal envelopes with six different frequencies (i.e., 0.05 Hz, 0.1Hz, 0.25Hz, 0.5Hz, 0.75Hz and 1Hz), and a naturalistic stimulus (Fig. 1b). Fig. 1b bottom shows a schematic of the tank setup with an infrared (IR) camera where fish 1 is stationary within a tube, while fish 2 is freely moving within the tank (trajectory shown in gray



<u>Figure 2.</u> Neural responses are more heterogeneous to the naturalistic stimulus than to artificial stimuli. a) Waveform (pink and light green) of artificial and naturalistic stimuli, raster plots and filtered firing rate for the same example ELL neurons. The inset on the right shows a blow-up time window of the filter firing rate. Neurons do not respond to naturalistic stimulus with low amplitude. Only high amplitude epochs are selected for further analysis. **b)** Polar plots showing neural sensitivity (spks/s/mV/cm, ρ-axis) as a function of preferred phase (θ-axis) for example artificial (pink) and naturalistic stimuli (light green). Box plots quantify the circular stand deviation (circ STD) and shows that the circ STD of the naturalistic stimulus is significantly higher than all envelope frequencies of the artificial stimuli (compare light green and the rest six colors; Kruskal-Wallis test, $p = 1.45*10^{-46}$, Bonferroni corrected; n=50, bootstrapped).

traces). Two positions of fish 2 are shown to show the relative position of the two fish at different time points of the naturalistic stimulus. The closer fish 1 and fish 2 get, higher the amplitude of the stimuli. The power spectral density of the naturalistic stimulus has a power law exponent of -0.8, which is the average exponent observed under natural conditions (Huang et al., 2019). The changes in EOD frequency (light purple and dark green; Fig. 1b) tracks the stimuli waveform (pink and light green), indicating that the behavior of the animal contains information of the detailed time course for both types of stimuli.

Neural responses are more heterogeneous to the naturalistic stimulus than to artificial stimuli

First, we analyzed ELL pyramidal neural responses to artificial and naturalistic stimuli. The filtered firing rate and the raster plots show that neural responses are more heterogeneous (i.e., the responses are more different from each other) to the naturalistic stimulus than to artificial stimuli (Fig. 2a). The inset in Fig. 2a, right highlights the phase differences of the neural responses, as the peak rises at different time points. Since the filtered rates follow the stimulus's time course for both types of stimuli, linear systems identification techniques were used to compute neuronal gain and phase. The polar plots show the neural sensitivity as a function of preferred phase of the neural responses. The data points were more spread out for

naturalistic responses, indicating again that the response is more heterogeneous to the naturalistic stimulus (Fig. 2b, left). This is quantified by calculating the circ STD of the responses, as shown in the box plot (Fig 2b, right). The circ STD for naturalistic stimulus is significantly higher than artificial stimuli of all envelope frequencies (Kruskal-Wallis test, df = 6, $p = 1.45*10^{-46}$, Bonferroni corrected). The circ STD is the standard deviation of a wrapped normal distribution. The higher the circ STD, the data points are more spread out. In this case, high cic STD means that neural responses are very different from each other. Putting this all together, our results show that neural responses to the naturalistic stimulus are more heterogeneous.

A decoding scheme recovers more information for the naturalistic stimulus than artificial stimuli with low envelope frequencies

Next, we quantified the information carried by ELL pyramidal cell neural responses about the detailed time course of the stimuli (Fig. 1b). Therefore, we used an optimal linear decoding scheme to reconstruct stimuli using neural responses (Rieke et al., 1996) (see methods). Each spike train is convolved with a unique kernel to account for heterogeneity in the responses, and these contributions from each neuron are then summed to reconstruct the original stimuli (Fig. 3a). The kernels were chosen to minimize the mean square error between the reconstructed and the original stimuli. The reconstructed stimuli obtained for each neuron (black traces; Fig. 3b) sum up to reconstruct the original stimuli (light purple and dark green traces). The reconstructed naturalistic stimulus followed the original stimulus more closely than the 0.1 Hz artificial stimulus (compare light green and dark green traces versus pink and light purple

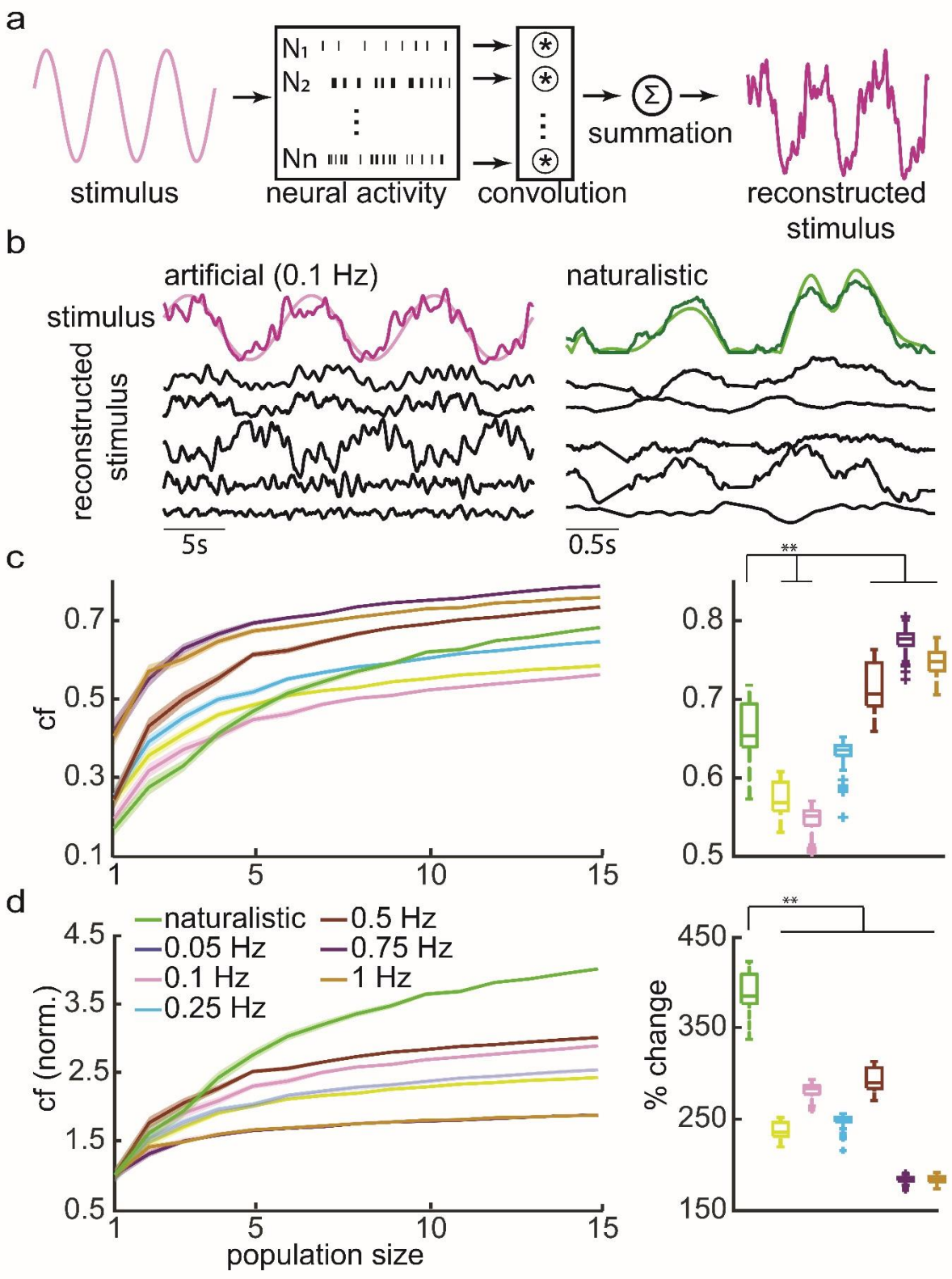

a
N1
N2
Nn
Σ
summation
stimulus
neural activity
convolution
reconstructed stimulus
b
artificial (0.1 Hz)
naturalistic
stimulus
reconstructed stimulus
5s
0.5s
c
cf
0.7
0.5
0.3
0.1
1
5
10
15
**
0.8
0.7
0.6
0.5
d
naturalistic
0.05 Hz
0.1 Hz
0.25 Hz
0.5 Hz
0.75 Hz
1 Hz
cf (norm.)
4.5
3.5
2.5
1.5
0.5
population size
% change
450
350
250
150

***Figure 3*. An optimal linear decoding scheme recovers more information for the naturalistic stimulus than for low frequency artificial stimuli. a)** Schematic describing the optimal linear decoding scheme for which each neural activity is convolved with a different kernel to minimize the mean square error between the original and reconstructed stimuli. Filtered neural activity is summed to reconstruct the original stimuli. **b)** Waveform (pink and light green) of artificial and naturalistic stimuli, the reconstructed stimulus of the network (light purple and dark green) and reconstructed stimulus from five example ELL neurons (black traces) Same ELL neurons were selected for the reconstruction of both the artificial and the naturalistic stimuli. **c)** Left: Coding fraction as a function of population size for different stimuli (error is stand error; n=50, bootstrapped). Right: Coding fraction at the maximum population size for naturalistic stimulus is significantly larger than artificial stimuli with low envelope frequencies, and significantly bigger smaller than high envelope frequencies (compare light green and the rest six colors; Kruskal-Wallis test, df = 6, p = 6.17*10-135, Bonferroni corrected; n=50, bootstrapped). **d)** Left: Normalized coding fraction as a function of population size (normalized to n=1; error is standard error; n=50, bootstrapped). Right: Coding fraction percentage change between maximum population size (n=15) and minimum population size (n=1) is the highest for naturalistic stimulus (compare light green and the rest six colors; Kruskal-Wallis test, df = 6, p = 1.43*10-138, Bonferroni corrected; n=50, bootstrapped).

races). The quality of the reconstruction was quantified using cf, which represents the fraction of stimulus that is correctly reconstructed. Coding fraction ranges from 0 to 1, and the closer the value to 1, the better the reconstruction. Coding fraction as a function of population size showed that adding more ELL pyramidal neurons recovers more information of the stimulus (Fig. 3c, left). The information contained in single neurons was limited. The quality of reconstruction at maximum population size (n=15) was significantly higher for naturalistic stimulus than artificial stimuli with low envelope frequencies (0.05 Hz and 0.1 Hz, Kruskal-Wallis test, df = 6; $p = 6.17*10^{-135}$, Bonferroni corrected). Also, the coding fraction for naturalistic responses is significantly lower than artificial stimuli with high envelope frequencies (0.5 Hz, 0.75Hz and 1Hz; Kruskal-Wallis test, df = 6; $p = 6.17*10^{-135}$, Bonferroni corrected; Fig. 3c, right). Coding fraction normalized to the first data point for n=1 showed the changes of the quality of reconstruction as population size increases (Fig 3d, left). The percentage change was quantified

at the maximum population size (n=15). Neural responses to naturalistic stimulus change significantly more than all other artificial stimuli (Kruskal-Wallis test, df = 6, $p = 1.43*10^{-138}$, Bonferroni corrected; Fig. 3d, right). Thus, our results so far demonstrate that ELL pyramidal cells respond more heterogeneously to naturalistic stimulus than artificial envelope stimuli, and they provide more information about the detailed time course of the naturalistic stimulus than low frequency artificial envelope stimuli. This latter result is important as naturalistic stimuli primarily contain lower frequencies (see Fig. 1b. right).

Differences in coding fraction to different stimuli are primarily due to response heterogeneities

How does the differences in coding fraction arise? Does the correlation of the ELL pyramidal cells also play a role on the dissimilarity of the quality of reconstruction observed? To answer these questions, we calculated the correlation between pairs of ELL pyramidal cells. There are two kinds of correlation: signal correlation, the correlation between the mean responses of two neurons to a given stimulus, and noise correlation, the correlation between the trial-to-trial variabilities of neural responses to the presentation of repeated stimulus (Fig 4. a). Both signal and noise correlation of responses to 0.1 Hz envelope stimulus are higher than that of the naturalistic stimulus (Fig. 4b). This trend is also observed for the 0.05 Hz envelope stimulus, but not for all the other envelope frequencies. Specifically, signal correlation of responses to naturalistic stimulus is significantly different from stimuli with low envelope frequencies (0.05Hz, 0.1Hz and 0.25Hz; Kruskal-Wallis test, df = 6, $p = 3.39*10^{-9}$, Bonferroni corrected; Fig. 4c). Noise correlation of responses to naturalistic stimulus is significantly different from stimuli

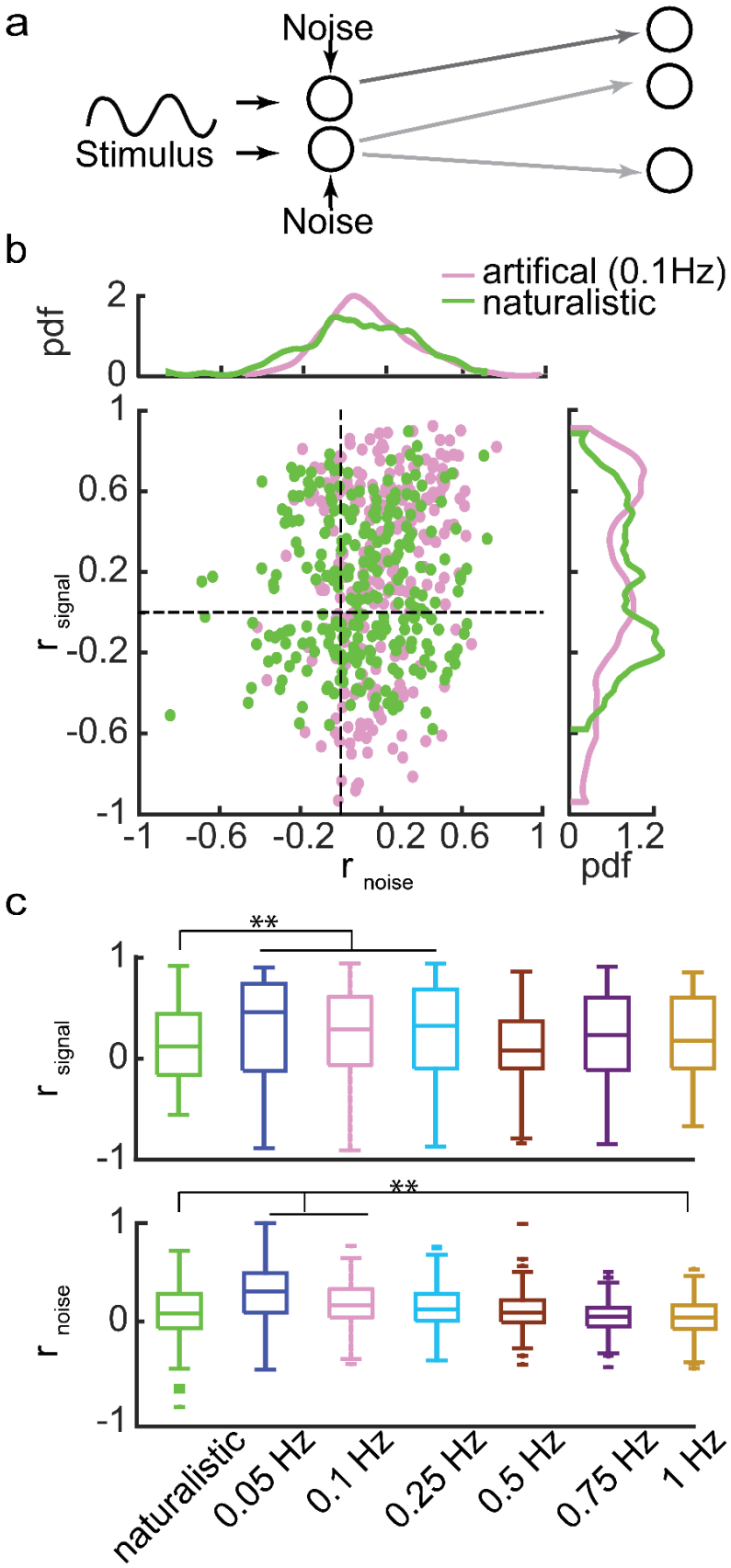


Figure 4. **Correlation structure of the neural responses. a)** Schematics of signal and noise correlations. Signal correlation arises from similar responses to a given stimulus (light grey and dark grey); noise correlation arises from shared noisy synaptic input (light grey). **b)** Example correlation structure for neural responses to artificial (0.1 Hz) and naturalistic stimuli and the probability density functions of signal and noise correlations. **c)** Boxplot of signal and noise correlation shows that signal correlation for naturalistic stimuli is significantly smaller than artificial stimuli with low envelope frequencies (compare light green and the rest six colors; Kruskal-Wallis test, $p = 3.39*10^{-9}$, Bonferroni corrected). Noise correlation of naturalistic stimuli is significantly different from 0.05, 0.1 and 1Hz envelope frequencies (compare light green and the rest six colors; Kruskal-Wallis test, $p = 1.33*10^{-39}$, Bonferroni corrected).

with envelope frequencies of 0.05Hz, 0.1Hz and 1 Hz; Kruskal-Wallis test, df = 6, $p = 1.33*10^{-39}$, Bonferroni corrected).

Pairs of neurons could represent stimuli and direct behavior in a redundant manner, meaning that they jointly convey less information, thus reducing information transmission (Averbeck & Lee, 2006). Since correlation could introduce redundancy, the question to ask is whether the observed differences in coding fraction are due to signal or noise correlation of the ELL pyramidal cells. Therefore, we reconstructed the stimulus after removing the noise correlation of the neural responses by shuffling epochs of the binary sequences. The quality of reconstruction mimics those of neural responses with noise correlation (compare Fig. 3c&d and Fig. 5). Specifically, coding fraction at maximum population size of responses to naturalistic stimulus without noise correlation is significantly higher than artificial stimuli with low envelope frequencies (0.05 Hz and 0.1 Hz), and lower than artificial stimuli with high envelope frequencies (0.5 Hz, 0.75Hz and 1Hz; Kruskal-Wallis test, df = 6, $p = 8.74*10^{-138}$, Bonferroni corrected; Fig. 5a, right;). The percentage change of neural responses to naturalistic stimulus without noise correlation is significantly higher than all artificial stimuli (Kruskal-Wallis test, df = 6, p = 2.43*10-140, Bonferroni corrected; Fig. 5b right). Noise correlation does not affect stimulus reconstruction. Therefore, our results showed that the differences in coding fraction to different stimuli are primarily if not exclusively due to response heterogeneities. Putting all results together, our results showed that ELL pyramidal cell populations transmitted more information under naturalistic stimulation due to higher level of neural response heterogeneity, suggesting that these neural populations have adapted to the statistics of natural stimuli to better encode these.

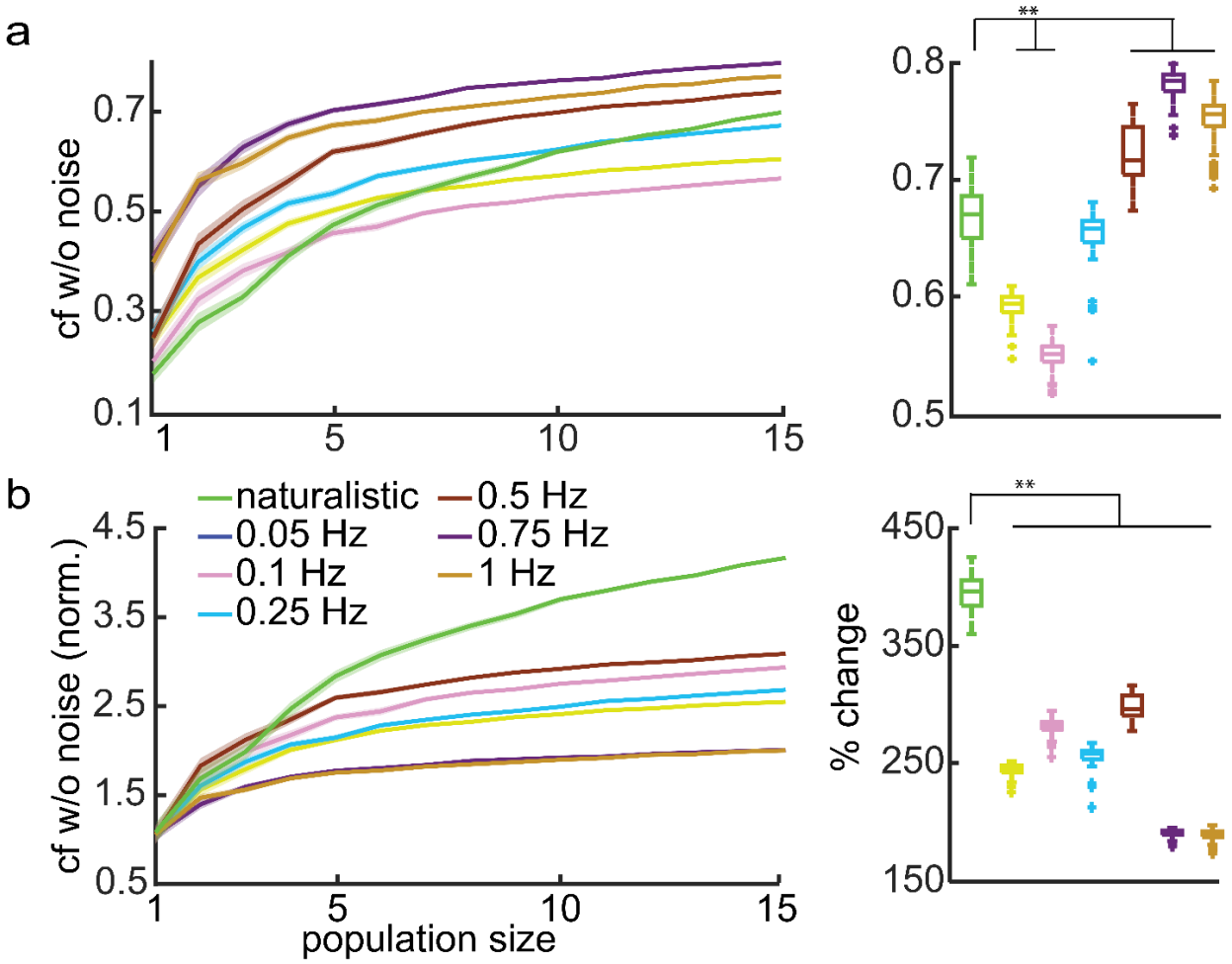


Figure 5. **A decoding scheme recovers more information for naturalistic stimulus than artificial stimuli when noise correlation is removed. a)** Left: Coding fraction as a function of population size for different stimuli (error is stand error; n=50, bootstrapped) when noise correlation is removed. Right: Coding fraction without noise correlation at the maximum population size for naturalistic stimulus is significantly larger than artificial stimuli with low envelope frequencies, and significantly smaller than high envelope frequencies (compare light green and the rest six colors; Kruskal-Wallis test, $p = 8.74*10^{-138}$, Bonferroni corrected; n=50, bootstrapped). **b)** Left: Normalized coding fraction as a function of population size without noise correlation (normalized to n=1; error is standard error; n=50, bootstrapped). Right: coding fraction without noise correlation percentage change between maximum population size (n=15) and minimum population size (n=1) is the highest for naturalistic stimulus (compare light green and the rest six colors; Kruskal-Wallis test, $p = 2.43*10^{-140}$, Bonferroni corrected; n=50, bootstrapped).

Discussion

Summary

We performed multiunit recording in the electrosensory lateral line lobe of weakly electric fish *Apteronotus leptorhynchus* while stimulating the fish with naturalistic and artificial envelope stimuli. We qualified the information transmitted by neural populations by evaluating reconstruction of stimuli presented to the fish using neural responses and found that neurons carried more information about naturalistic stimuli than artificial stimuli of equivalent frequency content. This was true both with and without noise correlation. Also, during naturalistic stimulation, neural responses were more heterogeneous and signal correlation between neurons was lower. These results suggested that neural populations have adapted to the statistics of natural envelopes to better encode them than artificial stimuli. Therefore, our results supported the use of naturalistic stimuli in future research. In addition, we were able to use Neuropixels probes to record population of neurons (n=15 & n=18) simultaneously and successfully identified pyramidal cells using Kilosort (Steinmetz et al., 2021) and Phy 2 (https://github.com/cortex-lab/phy).

Population coding by ELL pyramidal cells

Our results show that ELL pyramidal cell populations encode naturalistic vs. artificial envelope stimuli in fundamentally different manners. This is because neural responses were more heterogeneous during naturalistic stimulation, which effectively reduced redundancy and increased information transmission by reducing signal correlation magnitude. In general, population coding is influenced by the relationship between signal and noise correlations (Averbeck et al., 2006; Averbeck & Lee, 2006; Ecker et al., 2010; Franke et al., 2016; Kohn et al.,

2016; Lin et al., 2015; Moreno-Bote et al., 2014; Zylberberg et al., 2016). Understanding the effect of noise correlations on information transmission has been further complicated by the fact that they depend on various factors (see (Doiron et al., 2016) for review) such as the animal's behavioral state (Ecker et al., 2014; Erisken et al., 2014; Poulet & Petersen, 2008; Vinck et al., 2015), attention (Cohen & Maunsell, 2009; Steinmetz et al., 2000), and stimulus attributes (Franke et al., 2016; Gutnisky & Dragoi, 2008; Snyder et al., 2014; Tan et al., 2014; Zylberberg et al., 2016). Previous studies have shown that noise correlations between the responses of ELL pyramidal cells greatly vary depending on the spatial extent of the stimulus when comparing prey vs. conspecific-like stimulation (Chacron & Bastian, 2008; Simmonds & Chacron, 2015). Specifically, noise correlations during conspecific-like stimulation were lower in magnitude than during prey stimulation, thereby reducing redundancy during conspecific-like stimulation (Hofmann & Chacron, 2018). Further studies have shown that such changes were mediated by descending input (Litwin-Kumar et al., 2012; Simmonds & Chacron, 2015). However, as such descending input also reduced responses to conspecific-like stimuli, it was hypothesized that its function was to effectively cancel out responses to conspecific-like stimulation at the single neuron level and reduce noise correlations at the population level in order to better enhance the detection of prey stimuli (Bol et al., 2011; Litwin-Kumar et al., 2012; Mejias et al., 2013). A qualitatively different picture emerges when one instead considers the coding of natural electrocommunication stimuli. While studies based on single neuron recordings have extensively characterized how electrosensory neurons respond to these (Aumentado-Armstrong et al., 2015; Benda et al., 2005, 2006; Marsat & Maler, 2010; Marsat et al., 2009; Metzen & Chacron, 2017; Metzen, Hofmann, et al., 2016; Metzen et al., 2020; Sproule

& Chacron, 2017; Vonderschen & Chacron, 2011; Walz et al., 2014), recent studies conducted at the population level have shown that noise correlations have no detrimental effects and can actually benefit population coding for these stimuli (Metzen & Chacron, 2021; Wang & Chacron, 2021).

When the coding of envelope stimuli is instead considered, our results show that noise correlations were mostly independent of stimulus attributes and had a detrimental effect on information transmission (i.e., reduced by 11.76 %). Such "detrimental noise correlations" have been observed ubiquitously across systems and species (Cohen & Kohn, 2011) and can be actually enhanced during a perceptual task (Cohen & Newsome, 2008), which suggests that they serve a beneficial function rather than limiting information transmission through increased redundancy. A recent modeling study predicts that such noise correlations are beneficial by increasing the learning rate and robustness (Nassar et al., 2021). As such, we propose that the "detrimental noise correlations" observed during envelope stimulation might serve to help the electrosensory system adapt to changes in the statistics of natural envelope stimuli. A previous study has shown that such statistics change depending on the level of activity of the animal and that the response properties of single ELL pyramidal cells can adapt such as to optimally encode these (Huang et al., 2019). As such, we propose that noise correlations in ELL pyramidal cell population serve to increase the rate and robustness of adaptation to changes in natural envelope statistics. Further studies are needed to test this prediction.

Finally, we note that, in order to be functionally relevant, information transmitted by neural population ultimately has to be decoded by downstream neurons. While the fact that weakly electric fish display behavioral responses that follow the detailed time course of envelope

stimuli (Metzen & Chacron, 2014; Stamper, Madhav, et al., 2012; Thomas et al., 2018) demonstrates that information about these stimuli transmitted by ELL neural populations is decoded by downstream brain areas, the exact mechanisms by which this occurs remain unknown. Further studies are needed to elucidate the nature of these mechanisms.

Mechanisms mediating ELL pyramidal cell response heterogeneities

Previous studies have shown that ELL pyramidal cells are highly heterogeneous in terms of both cell morphology (Bastian & Nguyenkim, 2001) as well as firing properties (see (Maler, 2009) for review). Heterogeneities are also seen in response to a variety of stimuli arising during different behavioral contexts including EOD amplitude modulations occurring as a result of interaction with a conspecific (Avila-Akerberg et al., 2010; Chacron, 2006; Chacron et al., 2005b; Krahe et al., 2008), electrocommunication (Marsat & Maler, 2010; Marsat et al., 2009), as well as the envelope stimuli considered here (Huang & Chacron, 2016)(see (Huang & Chacron, 2017; Huang et al., 2019) for review). Some of the observed response heterogeneities observed *in vivo* to sensory stimulation are also observed *in vitro* to current injection (Mehaffey et al., 2008), indicating that they are intrinsic in origin and are most likely due to differences in the expression of ion channels. For example, expression of small conductance calcium-activated potassium (SK) channels varies widely across ELL pyramidal cells and can actively alter the frequency tuning of ELL pyramidal cells (Ellis et al., 2008; Ellis et al., 2007; Huang et al., 2016). However, network level mechanisms also cause response heterogeneities in ELL pyramidal cells. Specifically, ELL pyramidal cells receive large amounts of descending input (i.e., feedback) from higher brain regions both directly and indirectly (Berman & Maler, 1999; Sas & Maler, 1983). Such feedback can strongly alter the frequency tuning of ELL pyramidal cells to both amplitude

modulation (Chacron, 2006; Chacron et al., 2003; Chacron et al., 2005b) as well as envelope (Hofmann & Chacron, 2019; Huang et al., 2018, 2019) stimuli. It is thus very likely that the differences in response heterogeneities seen during naturalistic vs. artificial stimulation are due to both intrinsic as well as network mechanisms.

For example, previous studies have shown that, at the single neuron level, SK channels contribute to optimally encode naturalistic envelope stimuli via temporal whitening (Huang et al., 2016). Specifically, SK channels contribute to generating a high-pass tuning curve that "opposes" the decaying power spectrum of natural envelope stimuli, such that the response power spectrum is independent of frequency (i.e., "temporally whitened"). While such temporal whitening optimizes information transmission at the single neuron level (Atick & Redlich, 1990; Rieke et al., 1996), it does not necessarily optimize information transmission at the population level because noise correlations are not taken into account. As mentioned above, our results showing that noise correlations do not vary significantly when naturalistic vs. artificial envelope stimuli are presented imply that they cannot contribute to the observed differences in coding during naturalistic vs. artificial envelope stimulation. Thus, we hypothesize that the increased response heterogeneities seen during naturalistic envelope stimulation are due to differences in feedback input that potentially regulate the expression of SK channels in order to effectively better decorrelate neural activities during stimulation. While the fact that previous studies have shown that optimized coding at the single neuron is highly adaptive to changes in envelope stimulus statistics and requires feedback input from the forebrain supports our prediction (Huang et al., 2019), further studies are needed to confirm this interesting hypothesis.

Implications for other systems

Previous studies have highlighted similarities between the electrosensory and other systems (Clarke et al., 2015). In particular, recent work has shown remarkable similarities in processing strategies between ELL pyramidal cells and central vestibular neurons in macaque monkeys. Specifically, neurons in both systems are adapted to the statistics of natural stimuli such as to optimally encode them via temporal whitening (Huang et al., 2016; Mackrous et al., 2020; Mitchell et al., 2018). While growing evidence shows that the brain's coding strategies are adapted to the statistics of natural sensory input (Carriot et al., 2022; Laughlin, 1981; Rieke et al., 1995; Schneider et al., 2015; Sharpee et al., 2014; Sharpee et al., 2006; Wark et al., 2007), the nature of the underlying mechanisms remains largely unknown. While theoretical studies have posited that optimized information can be achieved through redundancy reduction (Barlow, 2001; Barlow, 1961), current evidence including our own results showing that noise correlations contribute to increased redundancy suggests that this is not the strategy employed in general. Rather, our results show that increasing neural heterogeneities during naturalistic stimulation can effectively increase information transmission. Previous theoretical and experimental studies have shown that heterogeneities in neural populations are beneficial for information transmission, as a heterogeneous population can encode a greater range of stimulus features than a homogeneous one but did not explicitly consider natural vs. artificial stimuli (Berry et al., 2019; Hunsberger et al., 2014; Marsat & Maler, 2010; Mejias & Longtin, 2012; Montijn et al., 2015; Osborne et al., 2008; Perez-Nieves et al., 2021; Tripathy et al., 2013; Zeldenrust et al., 2021). It is thus likely that increased information transmission for natural

stimulation relying on increased response heterogeneities as reported here for the electrosensory system will also be seen in other systems.

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