

Effects of Phasic Activation of Locus Ceruleus on Cortical Neural Activity and Auditory Discrimination Behavior

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Although the locus ceruleus (LC) is recognized as a crucial modulator for attention and perception by releasing norepinephrine into various cortical regions, the impact of LC–noradrenergic (LC–NE) modulation on auditory discrimination behavior remains elusive. In this study, we firstly recorded local field potential and single-unit activity in multiple cortical regions associated with auditory–motor processing, including the auditory cortex, posterior parietal cortex, secondary motor cortex, anterior cingulate cortex, prefrontal cortex, and orbitofrontal cortex (OFC), in response to optogenetic activation (40 Hz and 0.5 s) of the LC–NE neurons in awake mice (male). We found that phasic LC stimulation induced a persistent high gamma oscillation (50–80 Hz) in the OFC. Phasic activation of LC–NE neurons also resulted in a corresponding increase in norepinephrine levels in the OFC, accompanied by a pupillary dilation response. Furthermore, when mice were performing a go/no-go auditory discrimination task, we optogenetically activated the neural projections from LC to OFC and revealed a shortened latency in behavioral responses to sound stimuli and an increased false alarm rate. These impulsive behavioral responses may be associated with the gamma neural activity in the OFC. These findings have broadened our understanding of the neural mechanisms involved in the role of LC in auditory–motor processing.

Key words: auditory–motor response; gamma oscillation; neuroelectrophysiology; noradrenergic neuromodulation; optogenetics; prefrontal cortex

Significance Statement

The locus ceruleus (LC) plays a vital role in mediating behaviors related to perception, but the underlying mechanisms remain unclear. Using optogenetic techniques, we selectively activated the neural projections from the norepinephrine (NE) neurons of LC to the orbitofrontal cortex (OFC). We found that phasical activation of LC neurons increased NE levels in the OFC and induced a gamma band neuronal activity while also shortening the reaction latency of mice in auditory discrimination tasks but at the cost of increased false alarm rates. These results reveal a neural mechanism involving the LC in auditory–motor processing, providing a new perspective for understanding attention and perception.

Introduction

The brainstem noradrenergic nucleus locus ceruleus (LC) is a crucial component of the ascending arousal system, with a critical role in mediating several brain functions and behaviors, such as sleep–wake transition, perception, attention, and learning (Berridge et al., 2012; Martins and Froemke, 2015; Schwarz and Luo, 2015; Uematsu et al., 2017; McBurney-Lin et al.,

2019; Hayat et al., 2020). LC circuit malfunction has also been associated with several neurological disorders (Arnsten, 2000; Aston-Jones and Cohen, 2005; Sara, 2009; Sara and Bouret, 2012; Waterhouse and Navarra, 2019; McBurney-Lin et al., 2020). LC neurons typically fire in tonic or phasic mode. Tonic LC activity is associated with shifting away from the present task and exploring alternative behaviors (Aston-Jones and Cohen, 2005). In contrast, phasic LC activity is associated with focused attention and behavioral responses to salient stimuli (Bouret and Sara, 2004; Clayton et al., 2004; Sara and Bouret, 2012). Previous electrophysiological research has shown that LC phasic activation induced an increase of gamma rhythm (30–80 Hz) of neural electrical activity in the prefrontal cortex (PFC), similar to noxious somatosensory stimuli (Marzo et al., 2014; Neves et al., 2018). Gamma rhythm has been consistently linked with high-level cognitive functions such attention (Fries et al., 2001; Gregoriou et al., 2009; Rouhinen et al., 2013; Vinck et al., 2013), memory (Pesaran et al., 2002; Colgin et al., 2009;

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Carr et al., 2012), and perception (Rodriguez et al., 1999; Melloni et al., 2007). Gamma rhythm may play an important role in the cortical processing in binding different attributes of a stimulus (Fries, 2009; Tallon-Baudry, 2009; Uhlhaas et al., 2009). The neocortex is organized in anatomical hierarchies (Felleman and Van Essen, 1991), involved in distinct signal representation, transformation, and transmission processes (Kumar et al., 2010; Gilbert and Li, 2013). Though cortical gamma oscillations have been observed following LC activation, the distribution profile of the evoked gamma oscillation among the neocortex remains unclear.

On the other hand, the roles of the LC-induced gamma oscillations in the behavior responses to sensory stimuli are largely unrevealed. An increase of gamma oscillation power is typically linked with cortical desynchronization (Fries, 2009), which is observed during active behavior in rodents (Niell and Stryker, 2010). Therefore, it is reasonable to presume that LC-induced gamma oscillations could modulate sensory cortex activity and impact behavioral performance in perceptual detection/discrimination tasks. To date, only a limited number of studies have explored this possibility by investigating the influence of LC on perception-related behavior (Escanilla et al., 2010; Martins and Froemke, 2015; Navarra et al., 2017; Rodenkirch et al., 2019; Yang et al., 2021). The majority of these perceptual behavioral studies used visual or somatosensory tasks (McBurney-Lin et al., 2020; Yang et al., 2021). Auditory tasks were less commonly used. To address the question of modality specificity, it is crucial to investigate how LC modulates cortical activities to accommodate auditory perception tasks. Previous research has investigated the effects of LC stimulation on cortical sensory-evoked responses (Snow et al., 1999; Devilbiss and Waterhouse, 2004; Moxon et al., 2007) and has identified that LC stimulation can lead to plastic changes in the response properties of auditory cortical and thalamic neurons to auditory stimuli (Manunta and Edeline, 2004; Edeline et al., 2011; Martins and Froemke, 2015). However, the scope of these studies has been confined to the traditional auditory central system, with a lack of systematic analysis and comparison across broader cortical regions. The methods of LC stimulation have also predominantly utilized electrical stimulation, lacking selective activation of LC–noradrenergic (LC–NE) neurons.

In this study, we first examined the projection of LC–NE neurons to the cortex by locally injecting AAV-EF1 α -DIO-hChR2 (H134R)-EYFP virus into the LC area of male DBH-cre mice (B6.Cg-Dbh^{tm3.2(cre)Pj}/J). We then observed the effect of optogenetic activation of LC–NE neurons on the neural electrophysiological activities in multiple cortical stages associated with auditory–motor processing, including the auditory cortex (AC), posterior parietal cortex (PPC), secondary motor cortex (M2), anterior cingulate cortex (ACC), PFC, and orbitofrontal cortex (OFC). We further used norepinephrine (NE) molecular probes to examine the effect of LC activation on the cortical NE level. Finally, we trained the mice to perform a go/no-go task to discriminate different sounds while simultaneously assessing how activation of LC–OFC projection modulates the behavior performance and neural activities in the mice. Our results broaden our understanding of the neural mechanisms involved in the role of LC phasic activation in auditory–motor processing.

Materials and Methods

Animals. Forty-one adult male DBH-cre mice (033951, The Jackson Laboratory) were used in this study. In our preliminary experiments, we have found that optogenetic activation of LC had a similar effect on the cortical neural activities of male and female mice. Nevertheless, because

male mice have a relatively larger body weight, they are more resistant to surgical procedures and capable of completing a higher number of behavioral trials daily. Therefore, we have selected male mice for our study. Animals had *ad libitum* access to food pellets and water and were group housed in cages under standard ambient conditions (12 h day/light cycle). All animal procedures were performed in compliance with the National Institutes of Health guide for the care and use of laboratory animals (NIH Publications Number 8023, revised 1978) and were approved by the Institutional Animal Care and Use Committee of the China Medical University (Number CMU2019126).

Implantation of metal headpost. Mice were deeply anesthetized with isoflurane (3% with O₂). Body temperature was kept at 37°C throughout the surgery with a heating pad. An ocular ointment was applied over the eyes to prevent them from drying. As local analgesic, a mix of lidocaine and bupivacaine was injected below the scalp before any surgical intervention. A povidone iodine solution was used for skin disinfection. To expose the skull, a part of the scalp was removed with surgical scissors. The periosteal tissue was removed with cotton buds and a scalpel blade. After disinfection with betadine and rinsing with ringer solution, the skull was dried well with cotton buds. A thin layer of super glue (Loctite Super Glue 401, Henkel) was then applied across the dorsal part of the skull, and a custom-made head fixation implant was glued to the right hemisphere. A second thin layer of the glue was applied homogeneously on the left hemisphere. After the glue had dried, the head implant was further secured with dental cement (Super-Bond C&B). For electrophysiological recordings, a chamber was made by building a wall with denture acrylic along the edge of the bone covering the left hemisphere. Mice were returned to their home cages, and carprofen (2 mg, HY-B1227, MedChemExpress) was added to the drinking water for 3 d after surgery.

Sound stimulus delivering. Click-trains were trains of rectangular pulses of a 0.2 ms duration each, which repeated at a rate of 40 or 2 cycles/s and continued for a total duration of 0.5 s. In one session, 60–120 trials of click-train were presented at a random interval between 4 and 8 s. The waveform of sound stimulus was generated digitally with a 100 kHz sampling rate using a custom-built program and transferred to an analog signal by a D/A board (PCI-6052E, National Instruments) and then played through an open-field loudspeaker (K701, AKG) placed at 50 cm apart from the ear of the animal. The intensity of the sound stimulus was adjusted to be at 55 dB SPL and measured at the location of animal's ear (Bruel & Kjaer type 2238 sound level meter).

Electrophysiological recording. After recovery from surgery, animals were trained daily to tolerate head fixation until all signs of stress during head fixation disappeared (e.g., teeth chattering, porphyrin staining, vocalization, and physically resisting fixation) at which point we began collecting recordings of local field potential (LFP) and single-unit activity (SUA) in response to optogenetic LC activation and sound stimuli. The recordings were performed in a light and sound attenuation chamber. LFPs and SUAs were recorded using single-shank silicon probes with 16 contacts (ASSY-1-16-3-3 mm, Lotus Biochips, Creation Technologies) covering 750 μ m of the cortical depth. The shank length is 3 mm, and the interval between adjacent recording sites is 50 μ m. Each dimension of the recording site is 11 $\times$ 15 μ m. The impedance of each recording sites is $\sim$ 0.033 M Ω . In each session, one probe was inserted in one of the brain targets acutely. Probes were coated with Dil-dye (HY-D0083, MedChemExpress) for post hoc recovery of the recording location (see below). The neural data were filtered between 0.3 Hz and 7.5 kHz and amplified using a multichannel preamplifier (PBX Preamplifier; Plexon). The amplified signal was transferred to a digital multichannel acquisition processor (Plexon) and stored on an internal HDD of the host PC for off-line analysis. Spike sorting of single units was performed using the commercially available software (Offline Sorter, Plexon). Only large (amplitude superior to the baseline mean plus three times the standard), easily isolatable units with a minimum refractory period >1 ms and a stable waveform throughout the entire recording were used.

Optoelectrode recording of the LC. The optoelectrode was constructed according to the previously outlined procedures (Ono et al., 2018). We made glass pipettes by pulling borosilicate glass capillaries (Sutter Instrument) with an electrode puller (P-97 Flaming/Brown, Sutter Instrument). The tip diameter ranged from 2 to 3 μm , and the resistance ranged from 4 to 6 M Ω when filled with 10 mM phosphate-buffered saline (PBS). An insulation-coated silver wire (785500, A-M Systems) was inserted into the pipette. The optoelectrode assembly was encased within a hollow plastic sleeve designed to accommodate both the optical fiber and the silver wire, thereby facilitating their passage. The silver wire was connected to the headstage of the recording amplifier, and the optical fiber was connected to the laser driver (BT-Aurora-300–470, Newdoon Technology). During the experiment, the optoelectrode was inserted into the LC under the control of a manipulator (MO-10, Narishige). Once the desired depth was reached, we searched for and isolated single-unit spikes by adjusting the depth in 2–5 μm steps. After isolating a single unit, we collected spontaneous firing of LC neurons for 10–20 min, then delivered the laser pulses, and recorded their response to optogenetic stimulation. Optogenetic stimuli were generated by a laser driver and delivered to the brain through a 200- μm -diameter optical fiber. The intensity of the laser stimulus was measured using an optical power meter (Newdoon Technology) and calibrated to 0.83–3.33 mW/mm² at the fiber tip. Laser stimuli (470 nm wavelength, 10 mW, 5 ms pulse length, 0.5 s duration) at 2, 4, 10, 20, 30, and 40 Hz were randomly present with 30 repetitions.

Optogenetic LC activation. For optogenetic LC activation, during the initial aseptic surgery, AAV-EF1a-DIO-hChR2(H134R)-EYFP virus (titer, $\sim 9.35 \times 10^{12}$ vg/ml, BrainVTA) was injected through a pulled glass pipette using a picoinjector (Pump 11 Elite, Harvard Apparatus, 20 nl/min, 300 nl at each site) into the LC (AP, -5.4 mm; ML, ± 0.9 mm; DV, -3.3 mm) according to the stereotaxic coordinates. Four weeks following the initial injection, a second surgery was performed during which a fiber-optic cannula (200 μm diameter, 0.37 NA) was positioned targeting the LC and fixed using dental cement and bone screws anchored around the perimeter of the skull. This transfection and fiber-optic cannula implantation allowed us to activate the LC using blue light stimulation (470 nm wavelength, 20 mW, pulse length 5 ms, 40 Hz repetition rate, 0.5 s duration).

NE probe injection and optical fiber recording. The DBH-cre mice were anesthetized with isoflurane (3% in oxygen) and secured on the stereotaxic apparatus. AAV-hSyn-GRAB-NE2m (3.1) probe virus (300 nl; titer, $\sim 2.0 \times 10^{12}$ vg/ml; BrainVTA) was injected into the OFC (AP, $+2.5$ mm; ML, $+1.5$ mm; DV, -2.5 mm) at a rate of 20 nl/min. The AAV-EF1a-DIO-hChR2(H134R)-EYFP virus was injected into the LC using identical infusion parameters. Fiber-optic cannulas (200 μm diameter, 0.37 NA) were implanted into the OFC and LC. The cannulas were affixed to the skull with dental cement and two stainless steel screws. After 10 min to solidify, a black pigment was applied to prevent light interference. After allowing the mice to recover from surgery, we conducted optogenetic activation of the LC using blue light (470 nm wavelength, 20 mW, pulse length 5 ms, 40 Hz repetition rate, 0.5 s duration) and simultaneously monitored the release of NE within the OFC.

The recording optical fiber was connected to a fiber photometry system (R710, RWD Life Science) to capture and analyze the fluorescence signal changes ($\Delta F/F$) induced by the GRAB-NE2m (3.1) fluorescent probe. A fiber-coupled laser source was meticulously employed to sequentially illuminate the implanted optical fiber with 470 and 410 nm excitation light. The 470 nm wavelength was deliberately selected to achieve optimal excitation of the GRAB-NE2m (3.1) probe, while the 410 nm wavelength functioned as an isosbestic point, instrumental in mitigating photobleaching effects and movement-induced signal artifacts. The emitted fluorescence was adeptly collected by the same optical fiber and directed toward a spectrophotometer for precise quantification of fluorescence intensity. The acquired fluorescence signals were sampled at a rate of 15 Hz and subsequently subjected to a dual-emission wavelength processing approach, adeptly isolating the NE-specific signal.

Pupil size measurement. We employed an infrared camera (SF-3056DX, Shenzhen Safer Science and Technology) for the precise quantification of murine pupillary diameter. The data were acquired at a sampling frequency of 30 Hz.

Behavior paradigm. We trained head-fixed mice on a go/no-go auditory task (Fig. 6A). The sound waves of click-train were generated with a computer and presented through the speaker (K701, AKG) controlled by A/D converter board (PCI-6052E, National Instruments). The speakers were calibrated to ensure that the target and nontarget sounds had the same intensity of 55 dB. Mice were water restricted and ordinarily had access to water only during training. However, additional water was given if necessary to ensure that their body weight (monitored daily) did not drop below 85% of the starting value.

For behavioral training, the head of the mouse was tightly fixed through the screw fit into a metal post. The animal was allowed to run freely on a flat plate rotating smoothly around its center. After an initial ~ 7 d of habituation, response shaping, and conditioning, the mice were moved to the auditory discrimination task. The auditory stimulus was presented after the mice kept still for 2 s with a duration of 0.5 s. Licking during the period of stimulus presentation had no consequence, and the following 1.5 s period was set as response window. Licking during the response window of a go trial (presentation of the 40 Hz click-train) was counted as a hit, while no licking was counted as a miss. In no-go trials (4 Hz click-train), licking was counted as a false alarm (FA) and no licking as a correct rejection. The first lick during the response window triggered either reward or punishment: in go trials, licking triggered a water reward (~ 4 μl), and in no-go trials licking triggered a 5 s time-out period. The intertrial interval was 3 s, with an extra 2 s for reward consumption after hit trials. For behavioral data analysis, the hit rate was defined as # hits / (# hits + # misses) and the FA rate as # FAs / (# FAs + # correct rejections). Behavioral performance was measured by percent correct = (# hits + # correct rejections) / # trials. Individual behavioral session generally consisted of 100 trials with 1:1 ratio of 40 and 4 Hz click-train. Each day mice could complete 2–3 sessions.

Mice were trained daily until reaching criterion performance, defined as $>70\%$ correct trials for at least 3 consecutive days or $>75\%$ correct for 2 consecutive days. Once the mice reached these criteria, we started performing optogenetic experiments, in which phasic stimulation of LC (470 nm light pulse, 5 ms pulse width, 40 Hz repetition rate, 0.5 s duration) was randomly present at 1 s before sound presentation in half trials. Electrophysiological recording experiments were conducted in a part of mice ($n = 9$) after ~ 7 d break for chamber implantation (see below). No additional shaping procedures were required after the surgery for electrodes implantation, since there was no noticeable drop in performance caused by the procedure.

Histology and localization of electrode/optical fiber tracks. At the end of experiments, recording sites, AAV injection, and fiber implant placements were confirmed using immunohistochemistry on collected brain tissue sections. Mice were perfused with PBS followed by 4% paraformaldehyde in PBS. The brain was postfixed overnight at room temperature. Expression of EYFP and track of electrode was observed by epifluorescence microscope in serial 20 μm coronal sections cut by a cryostat microtome (FS800, RWD).

Analysis of electrophysiological data. To extract SUA from broadband extracellular potentials, we bandpass filtered data between 300 and 5,000 Hz and applied a threshold at 3 standard deviations. We computed the instantaneous firing rate from each SUA, which was used to construct peristimulus time histograms (PSTHs) and raster plots during the analysis window. PSTH for each neuron and each condition was computed by using the start times of each trial to extract spike times and then convert these to 1 ms bin size histograms smoothed with Gaussian kernel. Then, trials from a given condition were averaged together to produce the average PSTH. LFPs were obtained by low-pass filtering broadband extracellular potentials at 300 Hz in both the forward and reverse direction to avoid phase shifts (fourth-order Butterworth filter). LFPs were then downsampled to a sample rate of 1 kHz.

The trial-based spectra of LFPs were analyzed using a wavelet-based analysis algorithm, implemented in custom-written code using the eeglab toolbox (<https://sccn.ucsd.edu/eeglab/index.php>). The LFP power in the spectral–temporal domain was averaged across the LC stimulation or nonstimulation trials from one session. For the data recorded from one session, the LFP power was computed utilizing the multitaper method available in eeglab to derive a spectral–temporal function. The results presented as a relative estimation of the ratio between the values after the stimulus onset and baseline value (stimulus/prestimulus).

Statistics. Data are represented as mean $\pm$ SEM unless otherwise noted. The statistical tests used and numbers are reported explicitly in the main text or figure legends. *p* values are corrected for multiple comparisons, and methods are indicated in figure legends.

Data availability. Electrophysiological data, as well as code that was used to perform outlined analyses, can be made available from the corresponding author upon reasonable request.

Results

Phasic activation of LC neurons in response to optogenetic stimuli

To investigate the reactivity of LC–NE neurons to optogenetic control, we stereotactically injected an adeno-associated virus (AAV) encoding the blue light-sensitive channelrhodopsin-2 (ChR2) variant H134R under the EF1 α promoter (AAV-EF1 α -DIO-hChR2(H134R)-EYFP) into the LC of DBH-cre mice 3 weeks prior to the experiments (Fig. 1A). Figure 1B demonstrates that EYFP expression is colocalized with tyrosine hydroxylase (TH) in the LC, confirming the specific expression of ChR2 within NE neurons. Additionally, we detected the presence of EYFP-positive fiber terminals across a broad spectrum of cortical regions, including the OFC, PFC, ACC, M2, PPC, and AC, with a denser distribution in the more anterior sectors of the OFC (Fig. 1C).

We used a train of 470 nm light pulse (with a 5 ms pulse width, 0.5 s duration, and 10 mW) to photostimulate the LC neurons and simultaneously recorded the SUA of awake head-restrained mice (Fig. 1D–F). Figure 1D depicts the trajectory (in red) of the recording electrode as it traverses through the area where LC–NE neurons (in green) are clustered. The waveform shapes, interspike intervals (ISI) and spontaneous firing rates of a representative LC single unit are present in Figure 1E. A light pulse could elicit a burst of spikes that increased proportionally with an increase in pulse repetition rate (Fig. 1F). Consistent with previous studies (Carter et al., 2010; Hayat et al., 2020), a train of light pulse at a 40 Hz repetition rate was more efficient to phasically elicit the LC neuron. The latency of evoked response (the first peak of PSTH) was 4.1 ms in this representative SUA. The averaged latency of all the recorded LC units ($n = 37$) was 4.0 ± 1.3 ms.

Phasic activation of LC induced different LFP responses in the cortices

We then investigated the effects of phasic activation of LC on the cortical activities by recording the LFP and SUA in one of the cortical regions (AC, PPC, M2, ACC, PFC, or OFC) in head-fixed awake mice in response to 40 Hz photostimulation on the ipsilateral LC (Fig. 2A). For each recording, the traces were averaged over all electrode contacts; the baseline window was selected -0.5 – 0 s from the onset of photostimulation. The group average of LFPs recorded in different cortical regions are illustrated in Figure 2B, revealing that optogenetic activation of LC using 40 Hz light pulse trains evoked a periodic fluctuation of the LFPs, in which the amplitude of fluctuation decreased along

the posterior–anterior axis (LC–AC–PPC–M2–ACC–PFC–OFC), with LC exhibiting the highest fluctuation and OFC generating the lowest. We conducted time–frequency spectrum analysis on LFPs, comparing the light-on and light-off periods, and found an increase in power in the 40 Hz frequency band during the light-on period (Fig. 2C,D). The 40 Hz response in LC, AC, and PPC was constant during the period of LC activation, while the duration of response decreased as the recording site moved toward M2, ACC, PFC, and OFC. Plotting the averaged power ~ 40 Hz during the light-on period revealed a decreasing gradient of power along the posterior–anterior axis, as illustrated in Figure 2E ($F_{\text{region}(6,96)} = 114$; $p < 0.001$; $F_{\text{photostimulation}(1,16)} = 590.6$; $p < 0.001$; $F_{\text{region} \times \text{photostimulation}(6,96)} = 197.4$; $p < 0.001$; two-way ANOVA).

Another noticeable observation is that an increase of gamma band power following the cessation of photostimulation (0.85–1.55 s from the onset of photostimulation) to the LC occurred in anterior brain regions, including OFC, PFC, and ACC (Fig. 2D, dashed box). These later gamma oscillations occurred in a frequency range between 50 and 80 Hz, which was higher than the frequency of photostimulation (40 Hz) used for the LC. Moreover, the power of these later gamma oscillations presented an increasing gradient along the posterior–anterior axis, as illustrated in Figure 2F ($F_{\text{region}(6,144)} = 202.1$; $p < 0.001$; $F_{\text{photostimulation}(1,24)} = 161.8$; $p < 0.001$; $F_{\text{region} \times \text{photostimulation}(6,144)} = 1127$; $p < 0.001$; two-way ANOVA). The temporal and spectral distinctions between these later gamma oscillations and LC photostimulation may imply that the effects of LC activation are more extensive and persistent in the anterior cortical areas. We employed 10 Hz light stimulation to the LC, yet no distinct gamma oscillation was observed across the various brain regions (data not shown). Hence, the observed gamma response is specific to 40 Hz photostimulation.

Phasic activation of LC modulated the SUAs in the cortices

Next, we examined the influence of LC activation on SUAs in the cortices. As exemplified in Fig. 3, some SUAs exhibited enhancement during the light-on period (Fig. 3A), which persisted for 0–0.8 s after the light stimulation was turned off. Other SUAs demonstrated an increase in the fire rate during the light-on period, which could not extend beyond the end of light stimulation (Fig. 3B). We counted the firing rate of SUAs during the period of 0.85–1.55 s after light-on (0.35–1.05 s after light-off), subtracted by those without LC activation. Then, we examined the correlation between the firing rate induced by LC activation and the power in the gamma frequency band during the same light-off time window (Fig. 3C). The number of SUAs, in which the firing rate was enhanced by LC activation, gradually decreased in the following order: prefrontal cortices (OFC, PFC, and ACC) > secondary motor cortices (M2 and PPC) > primary sensory (AC). Furthermore, there was a positive correlation between the induced firing rate and gamma power, and the correlation was the highest in the OFC and then gradually decreased, reaching the lowest levels in the AC.

Effects of photostimulation of LC–OFC projection on the level of NE and arousal state

Furthermore, we utilized an in vivo fiber-optic recording technique to evaluate the effects of phasic LC activation on local NE levels within the OFC. To do this, we stereotactically injected a AAV-Ef1 α -DIO-hChR2(H134R)-EYFP virus into the LC of DBH-cre mice. Subsequently, we injected an AAV-hSyn-GRAB-NE2m (3.1) fluorescent probe into the OFC. Following this, we

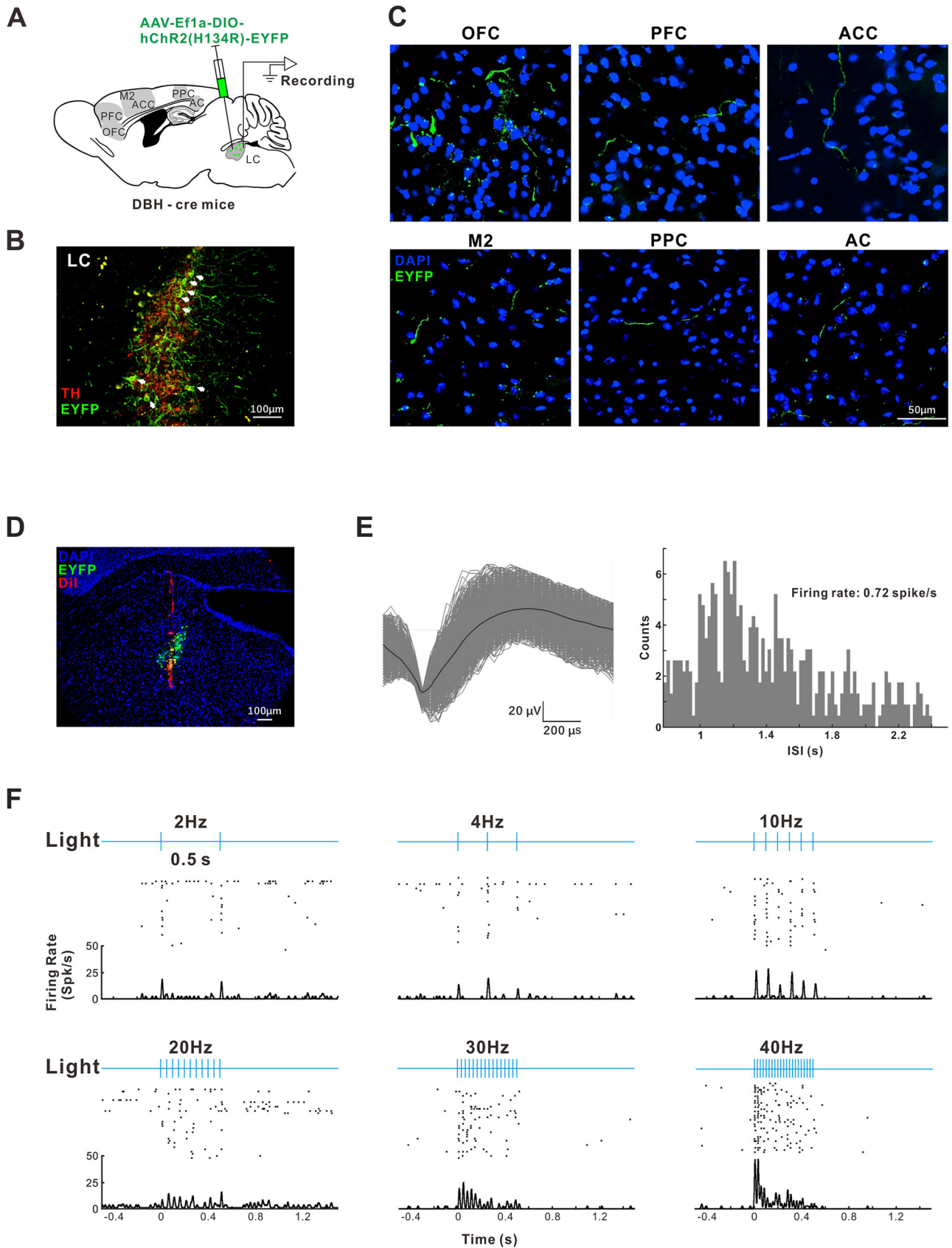


Figure 1. Distribution of LC projection among the brain regions and neuronal responses of LC elicited by optogenetic stimuli in DBH-cre mice. **A**, Schematic diagram showing the experimental setup for virus injection and electrophysiological recording. **B**, Immunofluorescence staining of TH (red) and EYFP (green) in the LC. White arrows indicate EYFP expression is colocalized with TH. **C**, Main distributions of LC projection terminals in various brain regions. **D**, The trajectory (red) of the recording electrode of LC-NE neurons (green); nuclei are stained with DAPI (blue). **E**, A representative LC SUA. Left, The waveform shapes of SUA. Right, ISIs and spontaneous firing rates. **F**, A raster plot showing the firing activities induced by light pulses at varying repetition rates, represented by the ticks at the top.

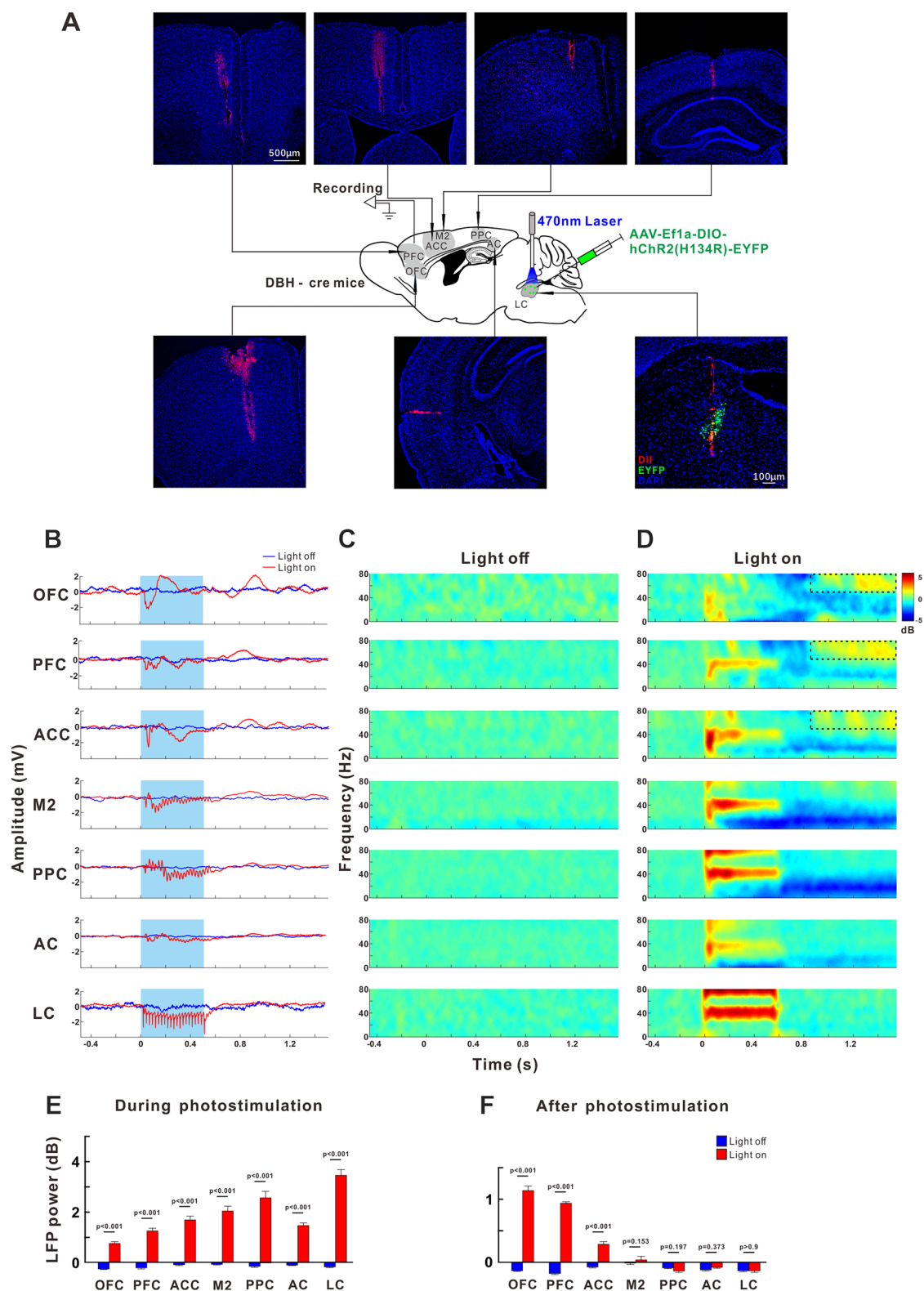


Figure 2. Effects of photostimulation of LC on LFPs across different cortical regions. **A**, A schematic diagram showing the experimental setup and brain sections showing the track of electrode probe. **B**, Representative of the group average of LFPs recordings showing a fluctuation during photostimulation of LC (blue stripe) recorded in different cortical regions. **C**, **D**, Time–frequency spectrum of LFP signals without and with photostimulation of LC, respectively. Dashed rectangle marks the gamma band power appeared after the cease of photostimulation. **E**, **F**, Bar plots showing the mean and SEM of LFP power calculated during the time–frequency windows of 0–0.5 s/35–45 Hz and 0.85–1.55 s/50–80 Hz, respectively. LC, locus ceruleus; AC, auditory cortex; PPC, posterior parietal cortex; M2, secondary motor cortex; ACC, anterior cingulate cortex; PFC, prefrontal cortex; OFC, orbitofrontal cortex. Data are shown as mean $\pm$ SEM. $n = 16$.

implanted optical fibers for subsequent measurements. After a 3 week recovery period, we stimulated the LC with blue light pulses of varying frequencies, recording the fluorescence signals of NE

release in the ipsilateral OFC and simultaneously monitoring changes in mouse pupil diameter (Fig. 4A). The results, as depicted in Figure 4B, indicate that optogenetic activation of

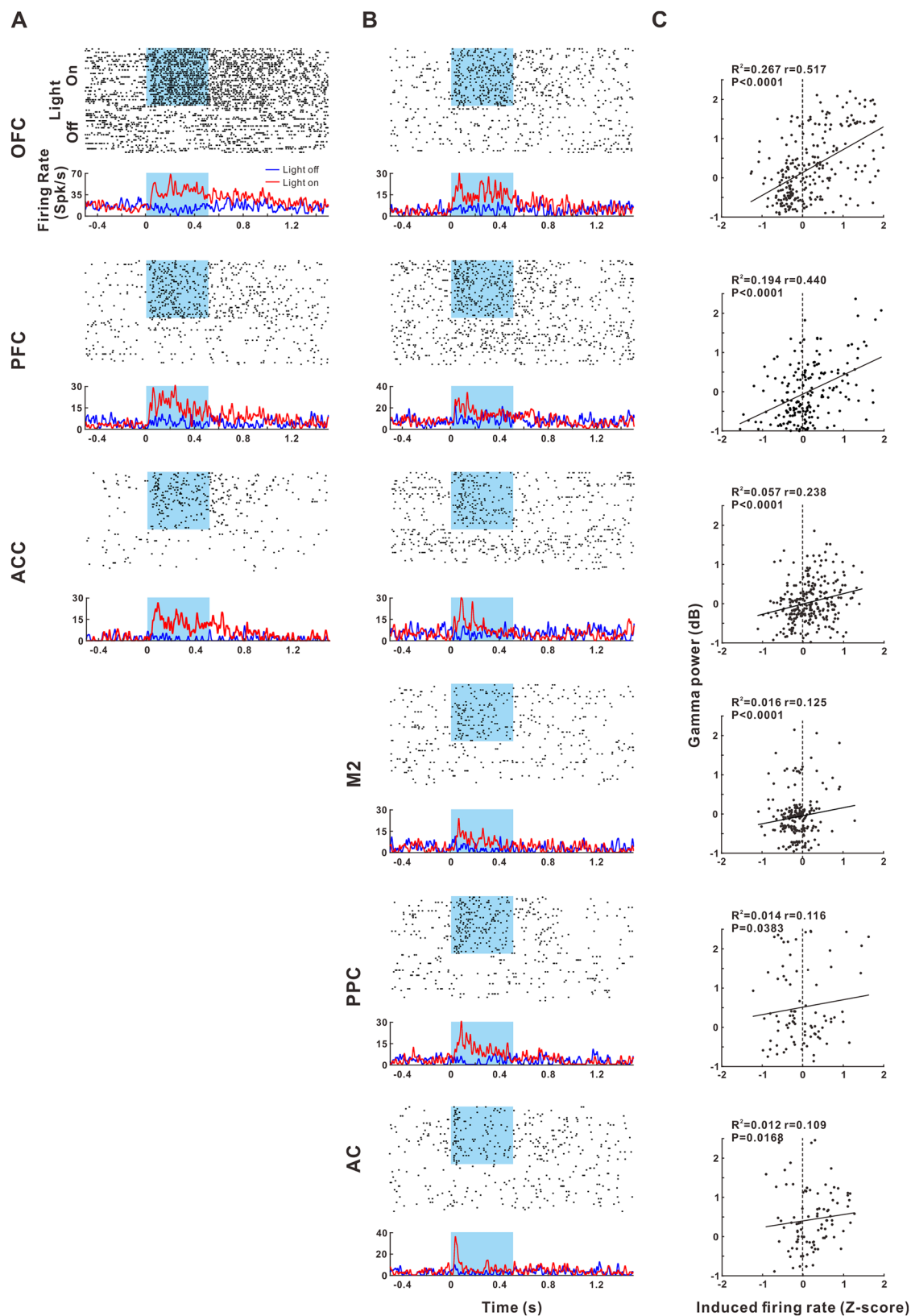


Figure 3. Effects of photostimulation of LC on the SUAs across different cortical regions. **A**, Spike raster (top) and the firing rate (bottom) of SUA examples. These examples show an increase in the firing rate during the light-on (blue stripe) and light-off period of photostimulation of the LC-OFC projection. **B**, SUA examples depicting an increase in the firing rate only during the light-on period of photostimulation. **C**, Correlation between the induced firing rate and gamma power. Each dot represents a SUA. All the data collected from 16 mice.

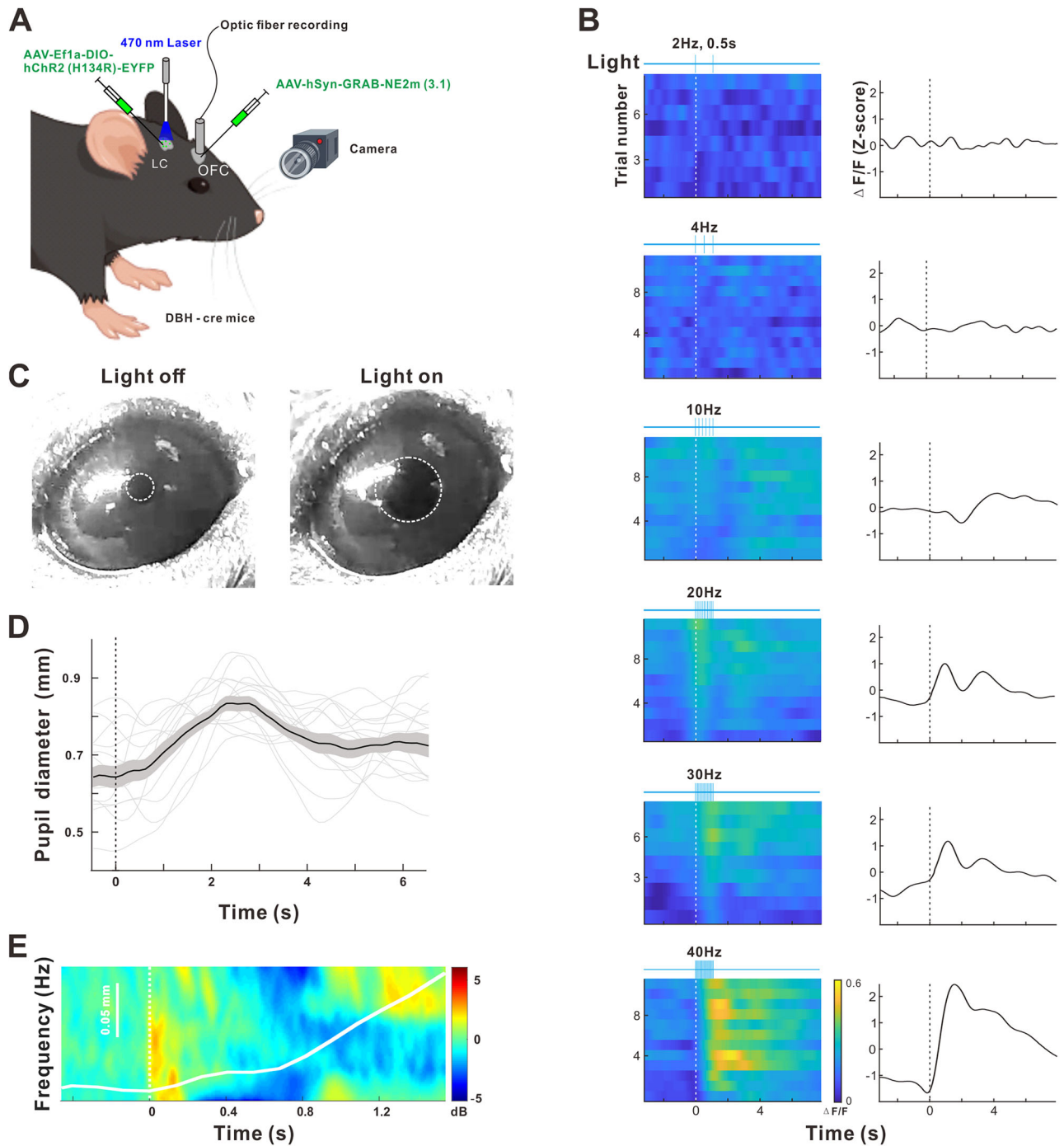


Figure 4. Effects of phasic activation of LC projection on NE release and pupillary response. **A**, A schematic diagram showing the experimental setup of fiber-optic recording and pupillometry. **B**, The dynamic changes of NE in the OFC. Left, The temporal dynamics of GRAB-NE2m fluorescence signal intensity following each optogenetic stimulation of the LC. Right, Normalized mean NE fluorescent signals in the OFC. Blue line, The different frequencies of light stimulation modes. Dashed line, The start of optogenetic stimulation. **C**, Representative image showing the pupil diameters before and after optogenetic activation of LC. The dashed line represents the range of the pupil. **D**, Pupil diameter changes in mice ($n = 3$). Light gray line, The change in pupil diameter following a single blue light stimulation of the LC. Black line, The average change in pupil diameter across all stimulations; the dark gray-shaded area represents SEM. Time 0 marks the start of light stimulation. **E**, Pupil dilation response following LC activation correlates with the gamma oscillations in the OFC. The curve of pupil diameter against time (white solid line) was plotted on the time–frequency spectrum of LFP recorded in the OFC. White dashed line, The start of light stimulation.

LC–NE neurons leads to a transient increase in the fluorescence signal of NE in the OFC, accompanied by a pupillary dilation response (Fig. 4C,D), with the most pronounced changes observed upon 40 Hz light stimulation. We also found that the timing of the pupillary dilation response coincided with the emergence of gamma oscillations in the OFC (Fig. 4E). These findings suggest that the 40 Hz optogenetic

stimulation of the LC induces a phasic release of NE in the OFC, thereby enhancing the arousal level of mice.

Effects of photostimulation of LC–OFC projection on the performance of auditory discrimination task

To investigate the effect of LC activation on auditory perception, we trained head-fixed mice on a go/no-go auditory

discrimination task (Fig. 5A; see Experimental Procedures). Mice were trained to report the presence of a target from nontarget sound (40 vs 4 Hz click-train). Licking after a grace period of 1.5 s in response to target sound (hit) was rewarded with water, while licking in response to nontarget sound (FA) was punished with 5 s time-out. After 2–3 weeks of training, all mice performed consistently above chance, indicated by a high probability of licking at the end of target sound (Fig. 5B–D).

Next, we used the above optogenetic paradigm to photostimulate LC–OFC projections at 1.5 s before sound presentation in randomly alternating light-on and light-off trials within one test session (Fig. 5E). We found that activation of the LC–OFC projection enhances the reactivity of mice to auditory stimuli. Upon hearing the 40 Hz target sound stimulus, the mice rapidly exhibited a lick response, often before the auditory stimulus stopped, resulting in a significantly reduced licking latency compared with when the LC was not activated (Fig. 5F,G). Conversely, when the 4 Hz nontarget sound was presented, the mice also responded with a lick, leading to an increased FA rate. We further employed light stimulation at varying frequencies (2, 4, 10, 20, 30, and 40 Hz) to activate the LC and found that light stimulation at frequencies above 20 Hz consistently resulted in significant reductions in lick latency and increases in FA rates (Fig. 5H). When we reversed the task rules, designating the 4 Hz sound as the target stimulus and the 40 Hz sound as the nontarget stimulus, optogenetic activation of the LC–OFC projection still induced similar behavioral changes (Fig. 5I,J). These results suggest that activation of the LC–OFC projection can induce impulsivity in mice, prompting them to make behavioral response decisions more readily and with less patience for anticipation. Furthermore, we also attempted direct optogenetic activation of the LC and observed no significant alteration in the mice's behavioral responses. This may be attributed to the broad neural projections of the LC to various brain regions, where the direct activation of the LC results in countervailing effects that collectively yield an inconspicuous integrated outcome.

Effects of photostimulation of LC–OFC projection on the neural activity during the auditory discrimination task

To examine the association between changes in neural activity and behavioral outcomes, we recorded LFPs and SUAs in the OFC of mice while performing the auditory discrimination task. Under normal physiological conditions, the LFPs and SUAs in the OFC exhibited similar patterns of response to the onset of 4 and 40 Hz click-train sounds (Fig. 6A,D). However, the responses to the 40 Hz target sound persisted longer than those to the 4 Hz nontarget sound, indicating that the later OFC neural response is related to the decision-making process in the mice's behavioral responses. When the projection from the LC was optogenetically activated, the OFC displayed LFP fluctuations that were in tune with the frequency of the light stimulation. After the cessation of photostimulation, the OFC exhibited a continuous gamma band oscillation that was integrated with subsequent sound-evoked LFP responses, and the difference of SUA responses to the target and nontarget sound stimuli was also masked by the responses induced by the responses evoked by photostimulation (Fig. 6B,E). Correspondingly, the mice showed a reduced licking latency in response to the 40 Hz target sound and an increased FA rate in response to the 4 Hz nontarget sound (Fig. 6C,F). These results suggest that activation of the LC–OFC projection modulates behavioral choice by inducing gamma band neural activities.

Discussion

Our present study is the first to investigate how phasic activation of the LC affects auditory perception at both electrophysiological and behavioral levels. Our principal findings indicate that (1) LFP recordings from a broad range of cortical areas, including the AC, PPC, M2, ACC, PFC, and OFC, showed an oscillation synchronized to the frequency of optogenetic stimulation on the LC–NE neurons, and the amplitude of oscillation decreased along the posterior–anterior axis. Meanwhile, later gamma oscillations appeared in the ACC, PFC, and OFC after light-off of LC stimulation. (2) The percentage of SUAs that were modulated during or after LC stimulation period increased along the posterior–anterior axis, with the OFC exhibiting the highest ratio of modulated neurons. (3) Phasic activation of the LC–NE neurons can result in elevated NE levels within the OFC and is also associated with a pupillary dilation response. (4) Photostimulation of the LC–OFC projection led to a decrease of licking latency in response to a target sound and an increase of FA response to a nontarget sound, due to the interference of gamma oscillations with sound-evoked responses in the OFC. Overall, our results reveal the neural mechanism of the LC regulating cortical activities involved in sensory–motor processing.

Effects of LC phasic activation on cortical activities

The LC is the largest cluster of NE neurons in the mammalian brain (Swanson and Hartman, 1975; Jones and Yang, 1985), which exhibit tonic and phasic discharge patterns associated with different behavioral states (Berridge and Waterhouse, 2003). Tonic LC discharge is characterized by stochastic firing at slow rates (0.1–5.0 Hz) and is essential for maintaining wakefulness and vigilance (Aston-Jones et al., 1991; Carter et al., 2010; Gompf et al., 2010; Vazey and Aston-Jones, 2014). Phasic LC firing is typically driven by salient stimuli and plays a specific role in attention (Corbetta et al., 2008), facilitating the orienting reflex (Sara and Bouret, 2012) or generating the P300 target-related cortical-evoked potential (Nieuwenhuis et al., 2005). Prior studies have reported that phasic LC activation induces an increase in gamma power in the PFC, which mediate sensory information along an ascending noxious somatosensory pathway (Neves et al., 2018). In this study, we phasically stimulated the LC and recorded LFP and SUA in the multiple cortical regions associated with encoding auditory information for perception. We found that synchronized responses of LFP and SUA to LC activation decrease along the posterior–anterior axis: AC–PPC–M2–ACC–PFC–OFC. However, the proportion of SUA modulated by LC activation increased along the same direction. Our histological results also suggest that direct neural projections from LC distribute more densely in the OFC than in the AC and PPC. Furthermore, high-order cortical stages, including ACC, PFC, and OFC, exhibited persistent gamma oscillation and neural firing after the cessation of LC stimulation, which may be caused by recurrent activation within local neural circuits. Employing an *in vivo* NE fluorescence probe detection approach, we verified that activation of the LC leads to an increase in local NE release in OFC, accompanied by a pupillary dilation response in mice, indicative of an elevated state of arousal. This result is consistent with the previous suggestion that LC neuronal firing shifts the cortex to a desynchronized state within a distributed network of brain regions (Berridge and Foote, 1991; Marzo et al., 2014; España et al., 2016). Our present study provides electrophysiological evidence indicating a bias of LC modulation toward anterior cortical regions, such as OFC.

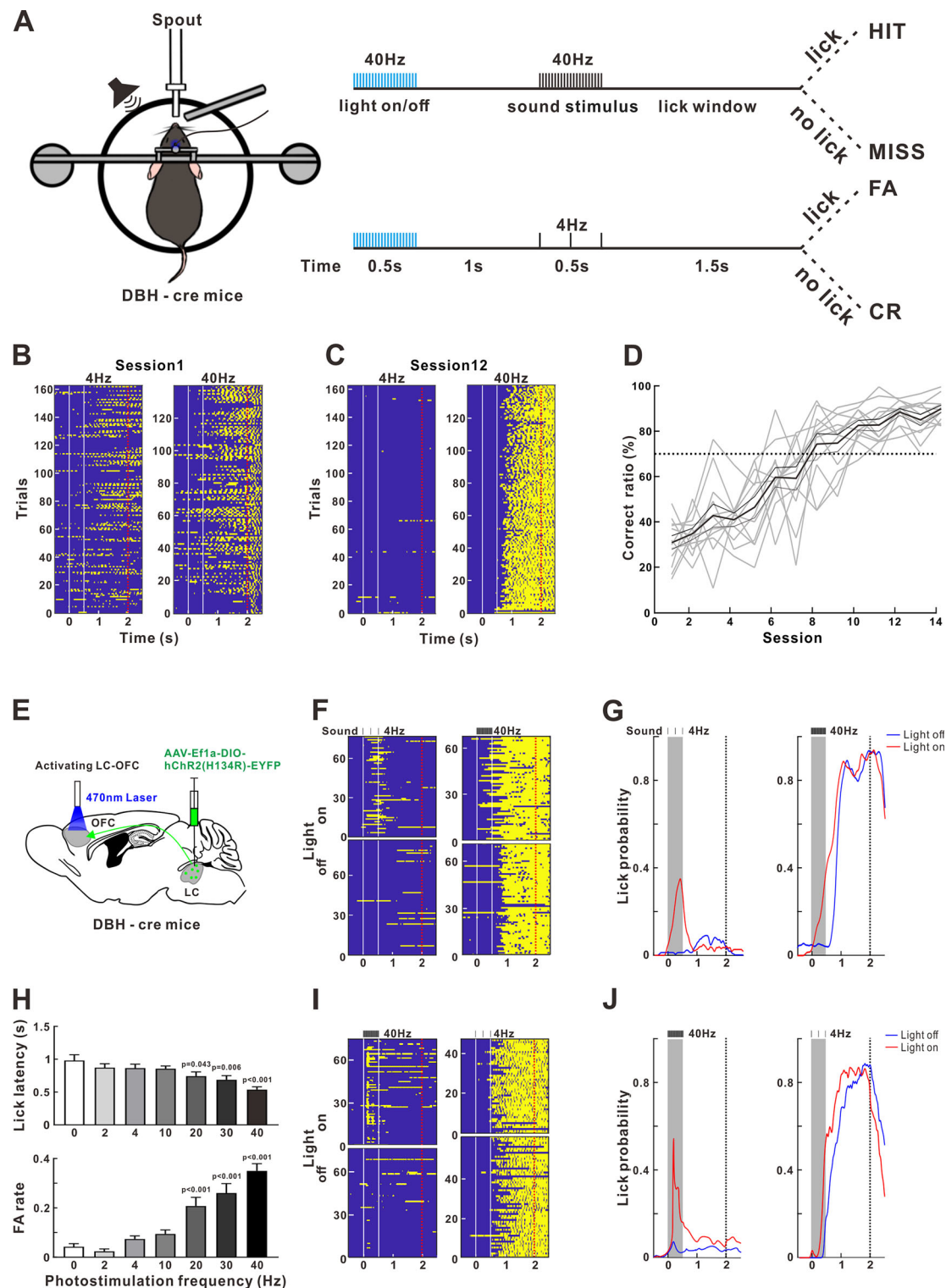


Figure 5. Effects of LC-OFC projection activation on the behavioral of mouse performing a go/no-go auditory task. **A**, Behavioral apparatus for the head-fixed go/no-go sound discrimination task and summary of the trial sequence and its trial outcomes. FA, false alarm; CR, correct rejection. **B**, **C**, Example behavioral sessions at the start and end of training, respectively. Yellow dot, lick; white line, onset and offset of sound presentation; red line, time of reward. **D**, Function of behavioral performance against training session. **E**, A schematic diagram of the optogenetic stimulation paradigm in DBH-cre mice. **F**, Lick responses to four nontarget and 40 Hz target sounds with or without photostimulation of LC-OFC projection. **G**, Time course of the mean lick rate. Gray stripe, sound presentation; dashed line, time of reward. **H**, Effect of different photostimulation frequencies on mouse lick latency and FA rate; data are shown as mean $\pm$ SEM, one-way ANOVA. **I**, Lick responses to 40 nontarget and 4 Hz target sounds with or without photostimulation of LC-OFC projection after the reversal discrimination. **J**, Time course of the mean lick rate after the reversal discrimination.

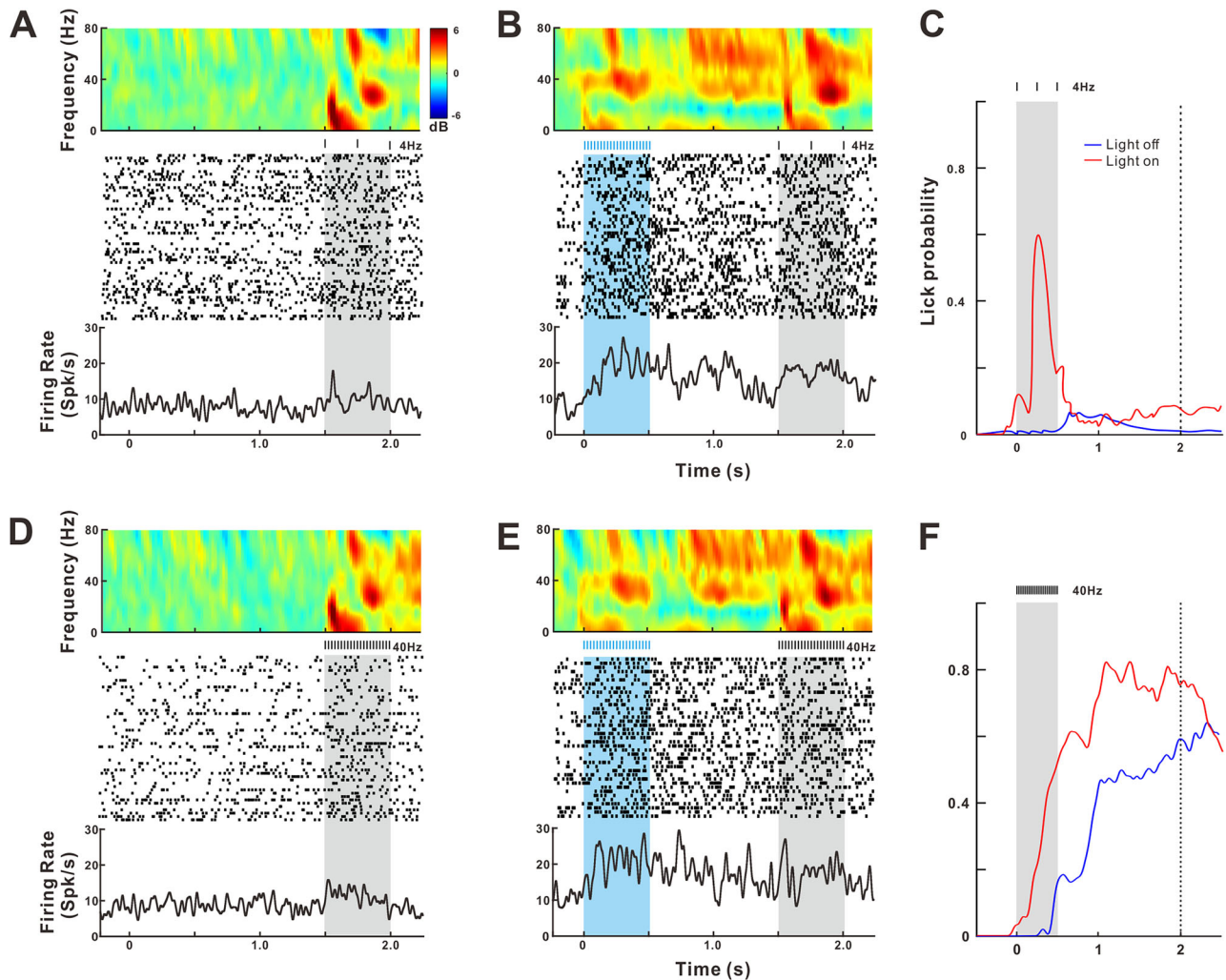


Figure 6. LFPs and SUAs recorded in the OFC as the mice were performing the auditory discrimination task. **A, B**, Time–frequency spectrum of LFPs (top), spike raster (middle), and firing rate (bottom) of SUA in the OFC in response to 4 Hz target sound with or without photostimulation of LC–OFC projection. Gray stripe, period of sound presentation; blue stripe, period of photostimulation. **C**, Time course of the lick rate. Gray stripe, sound presentation; dashed line, time of reward. **D–F**, Results of 40 Hz target sound showing in the same format.

Effects of phasic LC activation on sensory-evoked neural responses

The neural representation of sensory information is known to be dependent on the cortical state, characterized by synchronized and desynchronized states (Castro-Alamancos, 2004; Hasenstaub et al., 2007; Marguet and Harris, 2011). Synchronized states involve strong low-frequency fluctuations in cortical activity, typically observed during slow-wave sleep (Chauvette et al., 2011), whereas desynchronized states are characterized by increased neuronal coherence at high (gamma) frequencies (Munk et al., 1996; Niell and Stryker, 2010). Therefore, the cortical gamma oscillations observed in our experiments may reflect a desynchronized state evoked by LC activation. We found that the LFP response to sound stimuli was masked in the OFC, consistent with previous studies showing that the initial cortical response (up to ~50 ms) to a punctuate stimulus is smaller in desynchronized states than in synchronized states (Castro-Alamancos, 2004; Atiani et al., 2009; Otazu et al., 2009). Similarly, studies have reported that LC modulates sensory neuron responses to external stimuli (Devilbiss and Waterhouse, 2004; Manella et al., 2017; Navarra et al., 2017).

Effects of LC activation on sensory perception

Our behavioral experiments demonstrated that phasic activation of LC–OFC projection impaired performance in the go/no-go task to discriminate 4 and 40 Hz click-trains. This was indicated by an increase in the FA rate and a decrease of response latency to the target sound. Such behavioral changes might be also attributed to the rebounding response after behavioral arrest. Because our LC photostimulation was conducted at 1 s before sound stimulation, the rebounding of behavioral arrest should occur immediately after light-off rather than subsequent to the later auditory stimulus. Consequently, the potential effect of behavioral arrest might be slight in our experiment setting. Several recent studies have reported that LC activation enhances perceptual sensitivity in animals performing tactile discrimination tasks (Rodenkirch et al., 2019; McBurney-Lin et al., 2020), and pharmacologically upregulating NE levels in human subjects increases accuracy in visual tasks (Gelbard-Sagiv et al., 2018). The conflict between our results and previous findings may be due to differences in the stimulation method. The previous studies used a tonic pattern of optogenetic stimulation or drug application, while we used a phasic stimulus pattern delivered before the sound stimulus. LC's phasic activity has been found to

correlate with unexpected stimuli or outcomes and modulate behavioral execution through reward expectation (Bouret and Sara, 2004; Takeuchi et al., 2016; Uematsu et al., 2017; Breton-Provencher and Sur, 2019; Kaufman et al., 2020). Our results showed that phasic LC activation reduced the patience of the behavioral response in the auditory task, which was linked to the gamma band neural response in the OFC. Previous investigations have demonstrated that frontal cortex activity reflects the value of choices, decision-making process, and the value of the course of action pursued (Rushworth et al., 2011; Cai and Padoa-Schioppa, 2014; Rudebeck and Murray, 2014; Soltani and Koehlin, 2022). Therefore, phasic LC activation may induce hyperactivity of the prefrontal neurons, perturbing perceptual signal processing and motor decision. Whether LC activation impairs or improves task performance may depend on the temporal pattern of LC neural activity. Tonic activation of LC has been linked with an elevation of arousal or attention levels, which may help improve task performance. On the other hand, phasic activation of LC is generally evoked by a valiant external stimulus and causes an alert or startle response, which may disturb sensory-motor processing.

In conclusion, our study demonstrates that phasic activation of LC has differential effects on neural activities at various cortical regions, with a preferential modulation of the anterior cortices such as OFC. Activation of the LC can lead to the induction of gamma band neural activity within the OFC, which correlates with the manifestation of impulsive-like behavioral responses during performance of an auditory discrimination task. These findings provide a deeper understanding of the significance of LC regulation systems for executive function in cognitive behavior.

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