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Research Paper

Investigating the Serotonergic Modulation of Orientation Tuning of Neurons in Primary Visual Cortex of Anesthetized Mice

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ABSTRACT

Introduction: Sensory processing is profoundly regulated by brain neuromodulatory systems. One of the main neuromodulators is serotonin which influences higher cognitive functions, such as different aspects of perceptual processing. Accordingly, malfunction in the serotonergic system may lead to visual illusion in psychiatric disorders, such as autism and schizophrenia. This study aims to investigate the serotonergic modulation of visual responses of neurons to stimulus orientation in the primary visual cortex.

Methods: Eight-week-old naive mice were anesthetized and a craniotomy was done on the region of interest in the primary visual cortex. Spontaneous and visual-evoked activities of neurons were recorded before and during the electrical stimulation of the dorsal raphe nucleus using in vivo whole-cell patch-clamp recording. The square-wave grating of 12 orientations was presented. The data were analyzed and the Wilcoxon signed-rank test was used to compare the data of two conditions that belong to the same neurons, with or without electrical stimulation.

Results: The serotonergic system changed the orientation tuning of nearly 60% of recorded neurons by decreasing the mean firing rate in two independent visual response components, namely gain and baseline response. It also increased the mean firing rate in a small number of neurons (about 20%). Additionally, it left the preferred orientation and sensitivity of neurons unchanged.

Conclusion: Serotonergic modulation showed a bidirectional effect. It causes predominately divisive and subtractive decreases in the visual responses of the neurons in the primary visual cortex that can modify the balance between internal and external sensory signals and result in disorders.

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Highlights

- The serotonergic system predominantly decreased the mean firing rate of neurons in the primary visual cortex.
- The serotonergic system decreased responses of visual cortical neurons by subtractive and divisive changes of orientation tuning.
- The serotonergic system leaves the spontaneous activity of visual cortical neurons unchanged.

Plain Language Summary

Serotonin is one of the well-known neuromodulators involved in many physiological functions of the brain, such as sensory processing. It can play an essential role in producing perceptual psychotic episodes following the use of psychedelic drugs. Neural mechanisms of changes in cortical processing by the serotonergic system are not elucidated enough. In this study, we showed the electrical stimulation of the dorsal raphe nucleus as the main resource for projecting serotonergic neurons to the visual cortex, causing to decrease in visual-evoked responses of neurons in the primary visual cortex without changing the spontaneous activity. This effect may lead to an imbalance between the brain's intrinsic and stimulus-evoked activity and result in various kinds of psychiatric disorders, such as visual hallucinogenic experiences in schizophrenia and autism. Accordingly, it is crucial to understand the mechanisms by which serotonin affects the rapid and long-term activity of neocortical circuits. Such studies can be helpful in the diagnosis and treatment of disorders related to the neuromodulatory roles of the serotonergic system by providing new methods for rebalancing these intricate components.

1. Introduction

In the early steps of sensory processing, the brain's internal states modulate the neuronal representation of external stimuli (Harris & Thiele, 2011; Aston-Jones & Cohen, 2005). The processing of information in the sensory system is highly tuned by the neuromodulatory networks that are differently active in various states, which project to specific layers and regions of cortical and large areas of subcortical structures and exert feedforward and feedback effects on signaling in the sensory system by different mechanisms (Cumming & Nienborg, 2016; Jacob & Nienborg, 2018).

Serotonin is one of the major neuromodulators of the sensory systems. Serotonergic neurons in the midbrain medial and dorsal raphe nuclei frequently project to the forebrain through the medial frontal bundles (Calizo et al., 2011; Dahlström & Fuxe, 1964; Hornung et al., 1990). Similar to some other neuromodulatory systems, these nuclei consist of different cell types, including GABAergic, glutamatergic, and peptidergic neurons (Calizo et al., 2011; Waselus et al., 2006; Carcea & Froemke, 2013). The well-known serotonergic system is implicated in many basic functions, such as controlling blood pressure, appetite and nutrition, sleep, body temperature, pain perception, anxiety, aggression, sexual behaviors, reward, mood and emotions, social cognition, learning and memory, motor control, and sensory processing (Muller & Cunningham, 2020; Pollak Dorocic, 2016; Curzon, 1988; Peroutka, 1991; Lucki, 1992; Tseng & Atzori, 2007). The system is also involved in different kinds of psychiatric disorders, including schizophrenia, attention deficit hyperactivity disorder, depression, autism, drug addiction, obsessive-compulsive disorder, stress, eating disorders, aggression, and anxiety disorders; in addition, the malfunction of this system is the basis for the effects of the hallucinogenic drugs (Lucki, 1998). Serotonin and its receptors can play an essential role in the production of perceptual psychotic episodes following the use of psychedelic drugs as well as in schizophrenia (González-Maeso et al., 2008; Lesch & Waider, 2012). Therefore, it is crucial to understand the mechanisms by which serotonin affects neocortical circuits' rapid and long-term activity.

The serotonergic system has projected mainly to the primary sensory regions. It has an important effect in tuning sensory inputs from the early stages in the primary sensory areas and thalamic relay nuclei (Jacob & Nienborg, 2018). Serotonin is also implicated in the functional and structural regeneration of circuits in the cortex. Serotonergic neurons affect areas of the cortex that are involved in processing sensory information, in addition to somatic sensation and vision. Their response

properties can be changed by neuromodulators following long-term changes in sensory input activity, specifically in early postnatal life (Gu, 2003; Gu, 2002). In vivo and in vitro evaluation of serotonin function on cortical neurons has shown complicated patterns. The literature demonstrates that the effect of serotonin in the cerebral cortex is to regulate cortical neurons' excitability during sensory gating, determining the threshold for synaptic changes related to activity and increasing the signal-to-noise ratio (Tseng & Atzori, 2007). Despite the diversity of serotonergic modulation research on sensory processing, the more common effect is to reduce the gain of neuronal responses (Jacob & Nienborg, 2018).

There are serotonergic receptors, including an inotropic receptor (5-HT3A), and different types of metabotropic receptors on inhibitory interneurons and pyramidal neurons in the cortex. Metabotropic receptors of serotonin can regulate potassium channel activity and intracellular calcium levels and interact directly or indirectly with glutamate metabotropic receptors, thereby controlling synaptic transmission, neuronal excitability, and excitation-inhibition balance in the network (Bockaert et al., 2010; William Moreau et al., 2010; Ögren et al., 2008; Yuen et al., 2005). Receptor 5-HT3A is the main marker of the one kind of 3 types of inhibitory interneurons, indicating that serotonin's modulatory role in controlling inhibition of cortical neural networks would be a specific function.

The visual cortex's functional status is mainly regulated by non-visual input systems, which are neuromodulatory inputs from subcortical areas and can modify responses of visual input to overcome the threshold of anatomical and physiological changes related to the activity (Tseng & Atzori, 2007). In the visual cortex, serotonin neurotransmission is assumed one of the non-visual inputs that might partly involve in the neurochemical basis of motivation, attention and excitation, and influence them. One of the functions of the serotonergic system in the cortical processing of vision is to change the response of neurons to visual sensory input. The stimulation of dorsal raphe nucleus electrically and in vivo direct serotonin application on the cortical neurons demonstrate neuronal activity suppression or facilitation (Waterhouse et al., 1990; Reader, 1978; Krnjević & Phillis, 1963). While non-visual inputs to the visual cortical areas are essential modulators of plasticity in the visual cortex (Gu, 2002; Gu, 2003), serotonin's involvement in cortical plasticity has also been confirmed in vivo and in vitro.

Previous studies have shown that serotonin can affect GABAergic interneurons directly in the visual cortical areas through its receptors. For example, 5-HT3 receptor activity reduces the size and pattern of excitation in the ferret visual cortex (Roerig & Katz, 1997) because of an increase in GABAergic synaptic activity (Xiang & Prince, 2003) fast-spiking (FS).

Considering the complexity of the serotonergic system function in neuronal networks, and given that most works on the effect of serotonin in visual processing have been done using an extracellular recording, this study aims to investigate the supra-threshold and sub-threshold responses of neurons to stimulus orientation in the primary visual cortex of anesthetized mice.

2. Materials and Methods

Study animal and craniotomy

Eight-week-old naive mice weighing 20 to 30 g of either sex were used in this study. The animals were anesthetized by intraperitoneal urethane injection (1.5-2 mg/g body weight). After cutting the hair of the head and mustache, the animal was placed inside the stereotaxic device, and the head was kept fixed. Part of the skin and muscles were removed in the parietal area. A craniotomy of 1.5×2 mm (AP: 2.5-4 mm and L: 2-4 mm) was done on the left hemisphere's primary visual cortex area (area 17). A metal head plate was planted on the skull with superglue and dental acrylic. After thinning the skull, part of it as well as the dura matter was removed from the primary visual cortex to allow access to the cortex. The temperature of the animal's body was sustained at 36°C-36.5°C with a rectal thermal probe (ATC-402, Unique Medical).

Visual stimulation

The visual stimulus includes a drifting grating stimulus using the spatial frequency of 0.04 cycles/degree, a contrast of 100%, and a temporal frequency of 1 Hz. The square-wave gratings of 12 orientations in 30-degree (0-360°) steps were moved on an LCD monitor (Flexscan L788, 19-inch, Eizo Nanao). The visual stimuli of 12 orientation patterns (2 s before, 3 s during, and 2 s after the presentation of each stimulus, respectively) were presented in shuffled random order 3 times. The LCD monitor was located at a distance of 28 cm from the eyes of the animal and included an 80×50 degrees field of vision.

The serotonergic system activation by electrical stimulation of dorsal raphe nucleus

To stimulate the serotonergic projections of the dorsal raphe nucleus (DRN) to the primary visual cortex in the anesthetized animal, we used DRN electrical stimula-

tion. We implanted a bipolar tungsten electrode in the brain using a micromanipulator and a stereotaxic atlas of the mouse brain (AP: 4.3 mm, L: 0, and DV: 3 mm). The histological validation was done to confirm the exact location of the electrode insert by destroying the area and then cutting it into slices and observing it under a microscope. The DRN was stimulated electrically at 400-700 μA and the pulse frequency was 20 Hz (Mokler et al., 1998) including vigilance state, changes. The amount of 5-HT released was found to be frequency dependent with higher frequencies (20 Hz 3 times during visual stimulation.

In vivo whole-cell patch-clamp recording

Whole-cell patch-clamp recording of excitatory and inhibitory neurons of layer I at a depth of 20 to 90 μm and layer II/III at a depth of 200 to 300 μm was blindly performed. The electrodes for recording were made from borosilicate glass capillary with filaments (an inner diameter of 0.86 mm and an outer diameter of 1.5 mm), filled by a pre-prepared internal solution. The internal solution had an osmolarity of 280-290 mOsm and adjusted its pH with KOH to 7.2 to 7.4, which is equivalent to the intracellular environment, and its compounds were (in mM) as follows: $CaCl_2$, 0.1; MgATP, 4; K-Gluconate, 130; Na_3GTP, 0.3; HEPES, 10; EGTA, 1; Na-Phosphocreatine, 10 and $MgCl_2$, 2 (Safari et al., 2017; Ghaderi et al., 2018). The resistance of these electrodes with the internal solution was 6-8 MΩ. We recorded neuronal membrane potentials in current-clamp mode using the Axopatch 200B amplifier. The sampling rate was 20 kHz, filtered at 2 to 5 kHz, digitized at 10 kHz, and transmitted to a computer with a NI-DAQ board (PCI-MIO-16E-4, National Instruments). The data were then acquired using custom-made LabVIEW software. The block diagram of our method is mentioned in Figure 1.

Even though the intracellular recording technique was blindly done in anesthetized animals and most of the neurons were recorded in superficial layers of the visual cortex, as reported in previous studies, in such circumstances, we are much more likely to have recorded regular-spiking putative pyramidal neurons (Liu et al., 2009; Adesnik, 2017). Although the reported data is a mixture of different types of neurons, they are mainly obtained by pyramidal excitatory neurons, abundant in layers II/III.

Computational data analysis

We calculated the mean firing rate for every orientation of stimulus (0-360 degrees in steps of 30 degrees) and constructed the orientation tuning curve of every neuron before (control condition) and during electrical stimulation of DRN (deep brain stimulation [DBS] condition), separately. We use DBS to state the DRN electrical stimulation condition. In the first step, we wanted to know whether there was an effect of DRN stimulation on each recorded neuron's orientation responses. We examined statistically significant changes in the mean firing rate for all trials between control and DBS conditions. According to this, recorded neurons were classified as unaffected cells, inhibited cells (decreased mean firing rate in the DBS condition compared to the control condition), and facilitated cells (increased mean firing rate in the DBS condition compared to the control condition). In the second step, to test how DRN stimulation affected the orientation tuning of neurons, we fitted the orientation tuning curve of neurons to the Gaussian function model using the Equation 1:

$$1.R(\theta)=Ae-(\frac{\theta-\theta 0}{\sigma})^{2}+R_{0}$$

Where "" is the neuronal response for each oriented stimulus, "A" is amplitude or gain, indicating response size at the preferred orientation relative to baseline response, "" is the preferred orientation (the orientation in which the neuron shows the maximum response), "σ" is the bandwidth that reflects the tuning width and also the selectivity of a neuron related to preferred orientation, and "R0" is the offset, indicating the baseline response of the neuron.

Afterward, the statistical significance of the changes in these 4 parameters extracted from the model was investigated in the cell groups to determine by what mechanism the serotonergic system has affected the changes in the orientation tuning curve.

Statistical analysis

The values were given as Mean±SEM; otherwise, they were noted. We used the Kolmogorov–Smirnov test to statistically assess the normality of data distribution. Non-parametric analysis method, the Wilcoxon signed-rank test, was used to compare the data of two conditions that belong to the same neurons, with or without DRN stimulation.

3. Results

We recorded 63 neurons in layers I and II/III of the primary visual cortex using in vivo whole-cell patch-clamp recording before and during electrical stimulation of DRN. Then, each neuron's orientation tuning curve was constructed in control and DBS conditions, and their

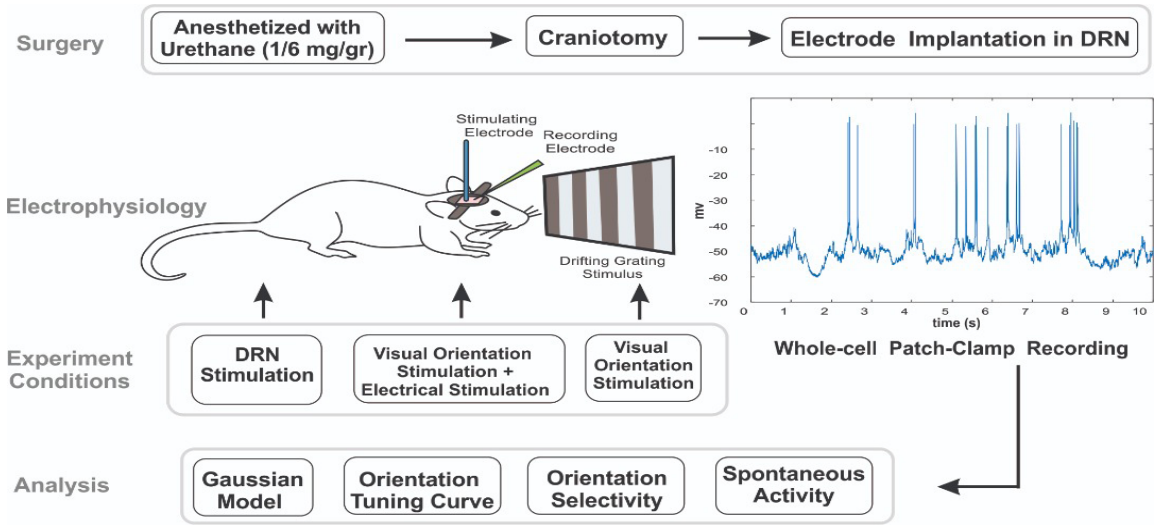

Figure 1. Schematic representation of stereotaxic surgery and whole-cell patch-clamp recording of neurons from the superficial layer of V1 while electrical stimulation of dorsal raphe nucleus in anesthetized mice presenting drifting grating stimulus

orientation selectivity was examined. A total of 32 out of 63 neurons showed orientation selectivity and the others were excluded from the analysis. As mentioned in previous studies, unlike what is observed in monkeys and cats where most neurons show orientation selectivity, more than 50% of neurons do not show this phenomenon in mice (Jeyabalaratnam et al., 2013). A total of 25 neurons showed a significant effect of DRN electrical stimulation on the mean firing rate. Meanwhile, 19 out of 25 neurons (59.4%) were inhibited and 6 out of 25 neurons (18.8%) were facilitated by DRN stimulation. There was not any meaningful change in the mean firing rate between control and DBS conditions in 7 of 32 neurons (21.8%). Accordingly, we called them unaffected cells. Therefore, the dominant effect of serotonergic system modulation on recorded neurons' visual response was suppression. The mean firing rate and mean membrane potential (average across the orientation tuning curve) were compared in control and DBS conditions (Figure 2). At the population level of inhibited cells, DRN stimulation significantly reduced the mean firing rate in the DBS condition (P=0.04, Wilcoxon signed-rank test). Still, there was no meaningful difference in mean membrane potential between the two conditions (P=0.12, Wilcoxon signed-rank test).

After fitting the orientation tuning curve of neurons to the Gaussian function model, it is possible to have 4 dif-

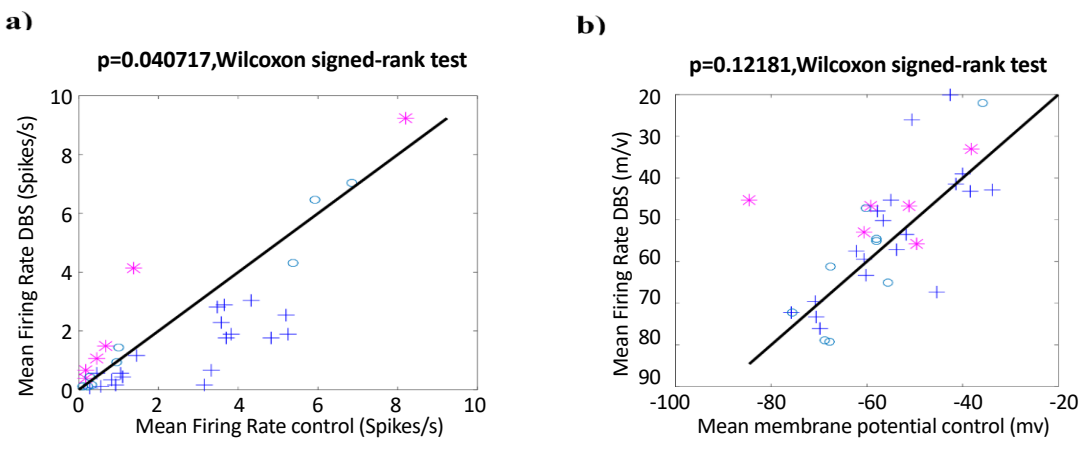

Figure 2. The comparison of visual evoked activity of recorded neurons before and during electrical stimulation of dorsal raphe nucleus

a) Mean firing rate, b) Mean membrane potential of neurons in control and DBS conditions. '+' '*' 'o' represent inhibited, facilitated, and unaffected cells, respectively.

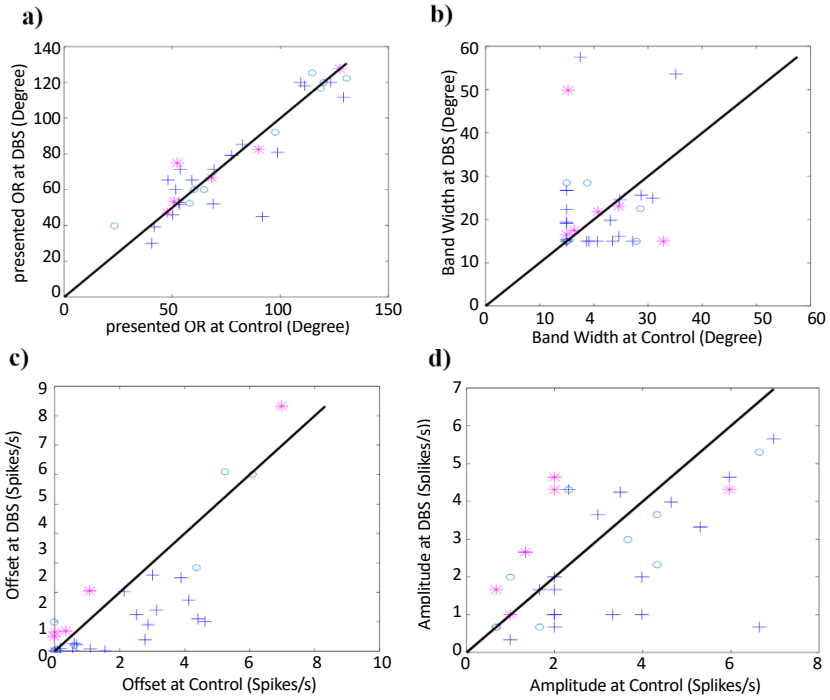

Figure 3. Schematic presentation of the gaussian function model and four predicted curves

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a) The orientation tuning curve was presented as a Gaussian function, and parameters were explained before. b) The mechanism by which selectivity measures changes. c) The mechanism by which preferred orientation changes and there is a shift in the tuning curve. d) The mechanism by which baseline response changes, an increase and decrease in baseline response lead to additive and subtractive effects, respectively. e) The mechanism by which amplitude changes. Increase and decrease in amplitude lead to multiplicative and divisive effects, respectively. The black curve is the control, the pink curve is the increase, and the blue curve is the decrease in response (see arrows).

ferent mechanisms according to changes in 4 parameters of the model (Figure 3a) as follows:

Changes in selectivity measure can cause the sharpening or broadening of the orientation tuning curve; it is correlated to the change in bandwidth (Figure 3b). Changes in preferred orientation (Figure 3c).

Changes in baseline response; it is correlated to the change in offset which can be as an additive (increase in baseline response) or subtractive effect (decrease in baseline response) (Figure 3d).

Changes in gain; it is correlated to the change in amplitude, which can be a multiplicative (increase in amplitude) or divisive effect (decrease in amplitude) (Wilson et al., 2012; Zinke et al., 2006) (Figure 3e).

In our study, the main effect of DRN stimulation on neurons' visual response was suppression; therefore, we focused on inhibited cells. Investigating 4 parameters showed no remarkable change occurred in the preferred orientation during the electrical stimulation of DRN (P=0.74, Wilcoxon signed-rank test) (Figure 4a). We did not find a statistically meaningful difference in bandwidth between control and DBS conditions (P=0.87, Wilcoxon signed-rank test) (Figure 4b). Moreover, the offset parameter decreased in all inhibited cells that it was statistically significant. So, the subtractive effect of DRN stimulation was observed on neurons' visual response (P=0.0001, Wilcoxon signed-rank test) (Figure 4c). In Figure 4d, the scatter plot of amplitude changes has been shown in control and DBS conditions. Amplitude increased in 3 of 19 inhibited cells, and it did not change in 2 of 19 inhibited cells and showed a decrease in the rest of the cells. At the population level of inhibited cells, DRN stimulation statistically decreased the gain of the visual response of neurons in divisive effect (P=0.02, Wilcoxon signed-rank test).

Examples of different effects of DRN stimulation on orientation tuning curves of inhibited neurons have been shown in Figure 5. Figure 5a is a sample for an inhibited cell whose electrical stimulation of DRN caused decreased baseline response in orientation tuning; therefore, DRN stimulation decreased neurons' visual response in the subtractive effect in the DBS condition compared to the control. An example of the inhibited cell

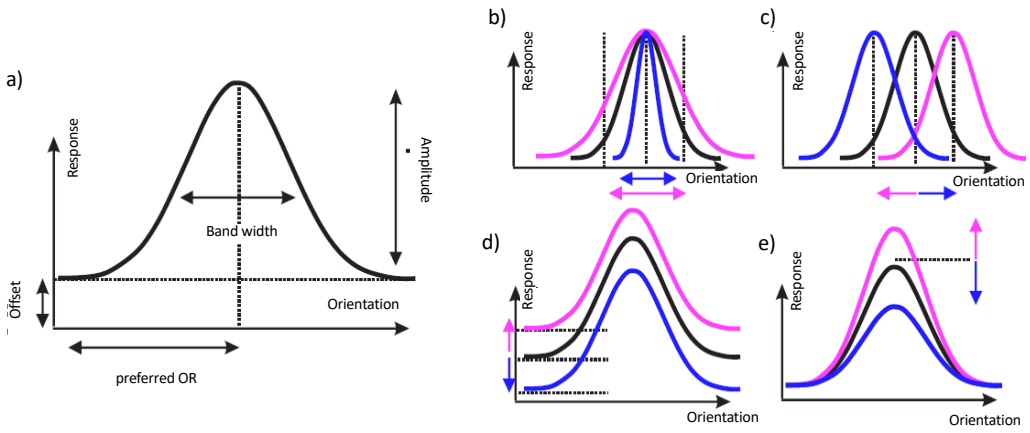

Figure 4. The scatter plots of four extracted parameters from the model

a) Preferred orientation (P=0.74, Wilcoxon signed-rank test). b) Bandwidth (P=0.87, Wilcoxon signed-rank test). c) Offset, most data points related to inhibited cells drop below the diagonal line, presenting that baseline response was decreased by DRN stimulation (P=0.0001, Wilcoxon signed-rank test). d) Amplitude in control and deep brain stimulation conditions, most data points of inhibited cells drop below the diagonal line, presenting which dorsal raphe nucleus stimulation significantly decreased amplitude in most neurons (P=0.02, Wilcoxon signed-rank test).

Diagonal lines present a 1 to 1 ratio. '+' '*' 'o' represent inhibited, facilitated, and unaffected cells, respectively.

has been shown in Figure 5b. The electrical stimulation of DRN led to a decrease in the gain of the visual response of cortical neurons in the divisive effect in DBS condition compared to control.

In facilitated neurons by DRN stimulation, statistically significant changes in model parameters were limited to offset parameters only (P=0.03, Wilcoxon signed-rank test). Because the number of cells in this group was small, more studies are needed.

Finally, this study aimed to understand whether DRN stimulation affected spontaneous activity or not. For this question, we experimented with a blank stimulus again, and the response of neurons was recorded before and during the electrical stimulation of DRN. We investigated mean membrane potential changes and the mean firing rate of recorded cells (n=32). We did not observe any statistically meaningful differences between control and DBS conditions (Figure 6).

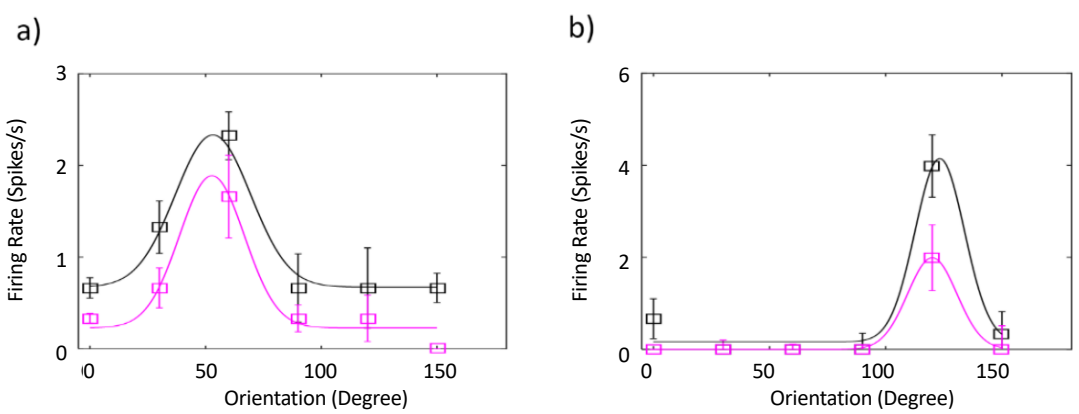

Figure 5. Cell examples of orientation tuning curve before and during electrical stimulation of dorsal raphe nucleus

a) An inhibited neuron by dorsal raphe nucleus stimulation that its baseline response was decreased in DBS condition compared to control and it shows subtractive effect. b) An inhibited neuron by dorsal raphe nucleus stimulation that its amplitude was decreased in deep brain stimulation condition compared to control and it shows divisive effect. The black curve is control; the pink curve is deep brain stimulation condition.

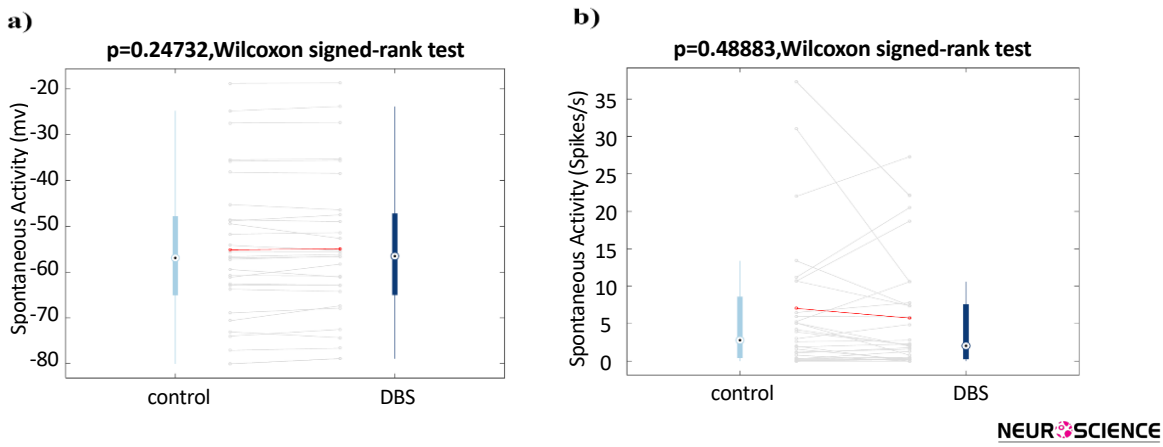

Figure 6. The comparison of spontaneous activity in recorded neurons before and during electrical stimulation of dorsal raphe nucleus

a) Mean membrane potential. b) Mean firing rate of neurons in control and deep brain stimulation conditions (n=32).

4. Discussion

The main goal of this research was to investigate the serotonergic modulation of the neural responses to the stimulus orientation in layers I and II/III of the primary visual cortex using the whole-cell patch-clamp recording technique in anesthetized mice. Given that DRN is the main source of serotonergic neuromodulatory neurons in the brain projecting to the visual cortex, we used its electrical stimulation to increase cortical projecting serotonergic neurons' activity. Although the electrical stimulation of DRN is not precisely similar to the specific activation of serotonergic neurons, they like other neuromodulator neurons, show highly synchronous locked-in stimulus firing activity (Lottem et al., 2016; Berkes et al., 2011) and can be used as a model for serotoninergic system activation.

Our findings showed that the serotonergic system might significantly decrease the mean firing rate by nearly 60% of the recorded neurons compared to the control condition and increased it in a small number of neurons (about 20%); however, the serotonergic system showed a bidirectional effect; its dominant effect was suppression. Accordingly, it decreased the visual response of neurons, which is consistent with other studies (Waterhouse et al., 1990, Petzold et al., 2009; Watakabe et al., 2009; Seillier et al., 2017; Azimi et al., 2020; Michaiel et al., 2019). The investigation of the mechanism by which the serotoninergic system decreased visual response revealed that the serotonergic system significantly reduced the baseline response in all inhibited neurons, indicating a subtractive effect. On the other hand, the serotonergic system decreased the gain of visual response through the divisive mechanism in most inhibited neurons. In line with our results, Azimi et al. in 2020, using wide-field calcium imaging, multi-unit recording, and optogenetic stimulation of DRN reported serotonergic modulation caused two independent inhibitory components, including the effect on decreasing gain or amplitude called divisive suppression and the effect on decreasing baseline response called subtractive suppression, each mediated by a specific type of serotonergic receptors.

There was no statistically significant difference in preferred orientation and bandwidth between control and DBS conditions; therefore, the serotonergic system did not change the preferred orientation and selectivity of the recorded neurons. In 2017, a study by Seillier et al. (2017) used an extracellular recording technique and serotonin iontophoresis in the primary visual cortex of the awaking macaque, serotonergic system decreased visual response gain without changing tuning characteristics of neurons including preferred orientation and selectivity.

In our study, there were no meaningful changes in mean membrane potential and mean firing rate of neurons' spontaneous activity before and during electrical stimulation of DRN, which is in line with some previous studies (Michaiel et al., 2019). In contrast, some studies reported decreased spontaneous activity in neuronal response by serotonin modulation (Lottem et al., 2016; Seillier et al., 2017; Azimi et al., 2020; Azimi et al., 2018). As Lottem et al. reported in 2016, serotonin reduced neurons' spontaneous activity in the olfactory cortex without altering stimulus-evoked activity. Serotonin changed the weight of two aspects of recorded signals in the sensory cortex, including spontaneous and stimulus-evoked activities (Azimi et al., 2020; Azimi et al., 2018). It was suggested that decreasing gain might decrease the priority of a sensory stimulus (Seillier et al., 2017) an important neuromodulator in the brain, is implicated

in affective and cognitive functions. However, its role even for basic cortical processes is controversial. For example, in the mammalian primary visual cortex (V1). Otherwise, suppose it only influences the spontaneous response but does not affect the evoked responses (Lottem et al., 2016). In that case, it may enhance the signal-to-noise ratio of a neuron and consequently increase the stimulus's priority effectively.

As there are many subtypes of serotonin receptors in the cortex, some of these diverse effects of serotonin depend on the postsynaptic compounds of the serotonin receptor subtypes on different neurons in various layers of the cortex (Tseng & Atzori, 2007). Among the subtypes of serotonin receptors, the 5-HT1 receptors activation leads to an enhancement in potassium ions' conduction throughout the cell membrane, followed by a reduction in the excitability of neurons (McCormick et al., 1993). In contrast, 5-HT2 and 5-HT4 receptors enhance the spiking activity and excitability of neurons by reducing potassium ions' rest conductance and depolarizing the cell membrane (Andrade, 1991; Panicker et al., 1991; Bockaert et al., 2010; Bockaert et al., 2011). Both 5-HT1A and 5-HT2A receptors are major factors in the function of serotonin in the cortical neurons. Studies done by in situ hybridization techniques have shown the simultaneous existence of 5-HT2A and 5-HT1A receptor mRNAs in most pyramidal cells (about 80%) in the cortex. Serotonin can hyperpolarize pyramidal neurons by activating 5-HT1A receptors due to the opening of G protein-coupled inwardly-rectifying potassium channel. This hyperpolarization reduces the spiking activity of excitatory neurons. Serotonin can simultaneously depolarize the same cells via 5-HT2A receptors activation and enhance their excitation. Although there are several hypotheses, it is unclear which elements define the inhibitory or excitatory response to serotonin in a target population of excitatory neurons. In the same way, the effect of these two receptors in modulating the role of the GABAergic interneuron is unclear. Studies of anatomical bases show a major percentage of interneurons in layers II-VI that have either 5-HT2A receptors or 5-HT1A receptors (Tseng & Atzori, 2007).

Moreover, 5-HT3 receptors are implicated in controlling the function of GABAergic interneurons. The 5-HT_3 receptors expressing interneurons are located mostly in superficial layers, which play an essential effect in regulating the sensory inputs to the upper parts and tufts of pyramidal neurons' apical dendrites. The function of 5-HT3 receptors mediates rapid synaptic transmission (Roerig et al., 1997; Férézou et al., 2002). The 5-HT3 receptors activation reduces the size of spike and excitation properties in the ferret visual cortex, possibly due to increased GABAergic synaptic activity (Roerig & Katz, 1997). Also, the 5-HT1B receptors activation by serotonin has presynaptic modulation of glutamatergic and GABAergic inputs to pyramidal neurons (Tseng & Atzori, 2007; Xiang & Prince, 2003).

There is a large topographic organization in the dorsal raphe nucleus (Fiser et al., 2010); therefore, other brain's cortical and subcortical areas are also modulated by serotonergic neuromodulatory neurons, affecting activity in the primary visual cortex (Azimi et al., 2018). Moreover, as some serotonergic neurons may also use glutamate co-transmission (Ranade & Mainen, 2009; Muzerelle et al., 2016; Gilbert & Li, 2013), it can be expected that part of the various effects of serotonin depends on the indirect activity of other circuits (non-serotonin) and cross-talk between the serotonergic system and other neurotransmitters (Tseng & Atzori, 2007).

5. Conclusion

The modulatory effect of the serotonergic system on visual sensory processing was a decrease in neural response that can modify the balance between internal and external sensory signals. Perception and sensory cognition is the result of integrating two components (Michaiel et al., 2019). Accordingly, serotonergic system function may modulate cortical states and influence higher cognition functions, such as decision and perception, and long-term dysfunction of the serotonergic system that may lead to psychiatric disorders, including schizophrenia, depression, and stress disorder (Azimi et al., 2018). Such studies can be helpful in diagnosis and treatment by providing new methods for rebalancing these components.

Ethical Considerations

Compliance with ethical guidelines

All ethical standards were conducted under the declaration of Helsinki.

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Authors' contributions

All authors equally contributed to preparing this article.

Conflict of interest

The authors declared no conflict of interest.

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