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Review Article

Serotonergic modulation of visual processing

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Abstract

Neuromodulators are chemicals that alter the activity of neural networks. They can have -immediate or delayed effects on neurons, affecting their properties at both nearby and distant synapses. Neuromodulators can influence neurons in various ways, allowing even small neural Networks generate a diverse range of functional outcomes. This diversity is crucial for the flexibility and adaptability of neural functions, including sensory processing.

Keywords: Neuromodulators ; Serotonergic modulation ; neural functions

Introduction

Neuromodulators are chemicals that alter the activity of neural networks. They can have -immediate or delayed effects on neurons, affecting their properties at both nearby and distant synapses. Neuromodulators can influence neurons in various ways, allowing even small neural Networks generate a diverse range of functional outcomes. This diversity is crucial for the flexibility and adaptability of neural functions, including sensory processing.

Serotonin is a widely conserved signaling molecule that influences various sensory systems across different species(1-3). It plays a crucial role in regulating states such as arousal, mood, and motivation (4-7). Serotonergic neurons, similar to other modulatory neurons, can influence a cell's activity without needing to form a direct synapse with it (8, 9). Sensory systems gather and process environmental information to create a internal representation of external world. Nevertheless, these systems must adapt to changes in the environment and the animal's internal state. This review aims to discuss how serotonin, a specific neuromodulator, influences sensory processing.

Serotonnin as a modulator of sensory systems

Serotonin's effects on sensory systems have been extensively studied across different species and sensory modalities, making it an prime example for illustrating fundamental principles of neuromodulation. The sensory processing can modulated by serotonergic system in various behavioral scenarios. This influence can be complex and specific to particular stimuli(13). The diverse characteristics of serotonergic neurons allow serotonin to modulate sensory processing in a nonuniform and complex manner. This means that serotonin's effects can vary widely depending on the specific neurons and contexts involved.

Moreover, while the specific receptors involved are not fully understood, serotonin has been shown to reduce activity in proprioceptor and mechanosensory networks(14, 15). On the other hand, this neuromodulator also can increase excitability of photoreceptors by stimulation of 5-HT receptors (16-18), and sensitize these sensory afferents more than baseline. The influence of serotonin in V1, possibly via interactions with other neuromodulatory systems (19-23), might therefore aid visual processing during periods of quiet vigilance. This influence works by decreasing the spiking response gain to prevent an obvious orienting reaction in the animal, which is consistent with previously observed effects of serotonin in suppressing the acoustic startle response (24).

In early visual processing of cat, significantly reduced responses were observed after serotonin was applied iontophoretically in the lateral geniculate nucleus (LGN) (10) and V1 area of rat brain (11). In a more recent study involving awake macaques, where serotonin was iontophoretically applied and compared with the effects of pH-matched saline application, an overall reduction in sensory responses due to serotonin was observed (12).

Diversity of serotonergic neurons

DRN neurons have diverse pathways through which they send signals to other parts of the brain. Besides serotonin, these neurons can contain other neurotransmitters. The inherent electrical and chemical properties of these neurons vary. DRN neurons receive inputs from various sources, adding to their diversity. The genes expressed in these neurons differ, contributing to their functional diversity (13). Anatomical projections of Serotonergic system are heterogeneous, and this can reveal various

functional aspects within specific sensory systems. For example, serotonergic neurons do not distribute evenly across the insect visual system; instead, they selectively innervate different layers within each visual neuropil.(25-30).

Likewise, the extent of serotonergic innervation differs both intranuclear and internuclear in rodent auditory nuclei, such as those in the superior olive and the inferior colliculus. (31-33). Collectively, these facts demonstrate the diverse nature of serotonergic projections to networks that involved in sensory processing. This variability precise targeting of different processing layers or stimulus-specific subcircuits. Recent advances in technology have shown that subsets of serotonergic neurons are diverse in their molecular and anatomical characteristics(34-39). To investigate subsequent changes in V1, it is important to consider the extensive topographic organization within the DRN (40). Activation of 5-HT neurons may not only directly affect V1 but also modulate other cortical and subcortical regions that could, in turn, influence V1 activity (41). Moreover, it's important to note that, in addition to 5-HT neurons, some subpopulations of neurons that release glutamate in the raphe nuclei also express ePet. (42, 43).

Receptor Foundations of serotonergic Modulation

Serotonergic neurons themselves exhibit considerable diversity, and this is mirrored in the variety of serotonin receptors (5-HTRs). These receptors differ in their serotonin affinity, duration of action, and the secondary messenger systems they engage (44). The earliest 5-HTR appeared approximately over 500 million years ago (3), and vertebrates have seven primary 5-HTR families (5-HT1–7), while invertebrates possess at least three families (5-HT1, 2, and 7)(45).

Types of serotonin synapses and receptors involved in sensory modulation

Serotonergic projections to primary sensory areas are characterized by small, varicose axons that are broadly extented (46).The number of synaptic specializations, which are typically asymmetric, is minimal (47), indicating that serotonin primarily operates through bolus transmission from these varicosities. Although, there is ongoing debate regarding the reliance of neuromodulatory systems on "wired" transmission—highly localized and typically synaptic—or "volume" transmission, which is more spatially diffuse(48-51).

In the mammalian brain, seven serotonin receptor families, each with multiple subtypes, have been identified, contributing to the functional diversity of serotonin(52). While a comprehensive review of all receptors is beyond this scope, a few key receptors are worth noting. The 5-HT1A receptor is found on pyramidal neurons of cortex (53). In the primary visual cortex of macaques, the 5-HT1B and 5-HT2A receptors are most densely expressed, particularly in layer 4 (54), The 5-HT1B receptor is also highly expressed in the LGN but shows weak expression in other cortical regions, such as the auditory and somatosensory cortices (54).

In mice, GABAergic neurons that have the 5-HT3A receptor do not express the calcium-binding proteins parvalbumin or somatostatin, suggesting they may form a unique group of inhibitory interneurons (55). In anesthetized macaques, when examining the impact of the two most prominently expressed receptors in primary visual area, 5-HT1B and 5-HT2A, using receptor-specific ligands, researchers observed various pattern of reciprocal modulation for these receptors (54). In one study researchers found that when 5-HT was iontophoretically applied to the visual cortical area of wakeful primates, it primarily reduced the gain of evoked responses at the population level while leaving ongoing activity unchanged.(12).

This distinct effect of 5-HT on gain response has been linked to the selective activation of 5-HT2A receptors (56) through several approaches, such as the subcutaneous injection of a hallucinogenic 5-HT2A receptor agonist in mice (57). The findings suggest that 5-HT induces separate inhibition of evoked and ongoing activity, influencing the gain of both in a divisive manner. simultaneous iontophoretic application of specific antagonists for 5-HT1A and 5-HT2A receptors (58-62) suggests that these receptors play distinct roles in regulating inhibition rate of ongoing and evoked network activity, respectively (63).

The findings demonstrates that activation of the serotonergic system influences two aspects of network activity in the visual cortex (V1): ongoing and evoked responses, with both being affected in a distinct and divisive manner. Each component is modulated through separate inhibitory effects of the 5-HT1A and 5-HT2A receptors, respectively. many studies in primary visual cortex, which used specific agonists for 5-HT1B and 5-HT2A receptors in combination with single-unit recordings in anesthetized monkeys, found bi-directional modulation depending on instantaneous firing rates. When a 5-HT2A agonist was applied, neurons with strong responses were suppressed, while those with weaker responses were facilitated, whereas the opposite occurred with the application of a 5-HT1B receptor agonist(54, 64).

Oppositely, the divisive scaling of stimulus driven responses is likely due to the dominant activation of excitatory 5-HT2A receptors, as inhibiting these receptors significantly lessened the inhibition of the evoked component. Furthermore, 5-HT2A receptors are linked to the Gq/11 signaling pathway (65), which typically increases neuronal firing rather than reducing it. This reduction in activity may be mediated by GABAergic neurons, which in turn decrease the activity of pyramidal neurons (66).

In fact, divisive modulation of responses in visual cortex has been shown to significantly depend on the activation of soma-targeting parvalbumin-expressing interneurons ((67), although other studies suggest differing roles (68, 69) for neurons that predominantly express 5-HT2A receptors (70, 71).

Activation of 5-HT2A receptors may also induce depolarizing currents in pyramidal neurons, leading to shunting inhibition, which increases conductance and affects both the gain and time constant of neuronal responses (72).

In two studies, selective activation of 5-HT2A receptors consistently produced a strong suppressive effect on the gain of visually evoked population responses (57, 73), despite cell-type and layer-specific differences across single cells (57). These findings support our current observations that DRN-triggered scaling of evoked responses is mediated by cortical 5-HT2A receptors at the population level. They also suggest that the distribution of a single neurotransmitter receptor type, or "receptome," can account for a distinct function in sensory processing (74-79). While 5-HT2A receptors regulate response gain, the scaling of ongoing V1 activity triggered by the DRN appears to be primarily controlled by 5-HT1A receptors (11).

Bidirectional interactions between serotonergic systems and sensory systems

Serotonergic neurons both influence sensory circuits and receive inputs from them. This bidirectional interaction allows the impact of serotonin on sensory processing to be modulated according to the sensory inputs the animal encounters.(45). This reciprocal interaction enables sensory networks to adjust to varying stimulus state. Fr example, some studies demonstrate that signal-to-noise ratio can altered by serotonin (11, 80, 81), which helps maintain stable stimulus representation even in a noisy environment. Sensory input to serotonergic neurons can lead to specific modifications in serotonin release. This means that the release of serotonin can be tailored to the specific sensory stimuli being experienced. In certain instances, first sensory neurons and serotonergic cells are identical, enabling the sensory field to directly trigger releasing of serotonin (11, 80-87).

Sensory Stimulus-Driven Serotonin Release

Many serotonergic neurons, in addition to projecting to both sensory and nonsensory regions (36, 37, 88), also receive inputs from sensory systems. In certain cases, these neurons can acquire sensory input locally within the very networks they modulate. For example, in Drosophila and moths, CSDn activity is affected by odors (89-92) through direct synaptic connections with antennal lobe principal neurons (91, 93-95). The pattern of local input to a single neuron can differ across sensory networks, as CSDns can be both stimulated and suppressed by the same odor due to local synaptic inputs targeting various neuronal compartments. (90).

Serotonergic neurons in the DRN and MRN also receive inputs from various cortical and subcortical sensory areas, such as the inferior and superior colliculi and brainstem sensory nuclei (96, 97). Morevere, these neurons are responsive to stimuli across various sensory modalities (98-102). Although the strongest sensory responses are often found in nonserotonergic raphe neurons, serotonergic neurons themselves have been shown to be responsive to sensory inputs (103-105), and nonserotonergic DRN neurons may relay indirect sensory input to serotonergic neurons. Furthermore, some sensory responses in serotonergic DRN neurons exhibit very short latencies, suggesting input from early stages of sensory processing (103). Consequently, whether they are confined to a single network or span multiple networks, serotonergic neurons, by having close access to the history of network activity, can adjust their modulatory effects based on the current stimulus or circuit state (106).

Serotonergic Neurons Adjust Based on Behavioral State and Context

The circumstances surrounding serotonin release are multifaceted, encompassing both dependent and independent stimulus state. Researches shows that serotonergic neurons react to sensory stimuli but are also affected by factors like internal states, movement, and the importance of sensory events in relation to past experiences. This implies that serotonin helps transmit information to sensory systems regarding both the external environment and the internal conditions in which sensory events happen (45).

By using varying stimulus intensities, the normalization of visual responses was identified. In anesthetized animals, the ongoing activity contributed to response normalization by acting as a subtractive factor. However, in the awake state, normalization was governed by the gain of the evoked response and was independent of any concurrent suppression of ongoing activity.

Inhibition tends to dominate activity in the awake cortex (107), possibly alongside elevated 5-HT levels (108, 109). Consequently, since the inhibition of baseline activity depends on initial baseline levels, the additional impact of the spontaneous part on normalization in the anesthetized condition could be due to significant fluctuations in its amplitude, which are less common during wakefulness (107). As a result, the extent of serotonin-regulated integration of sensory input and Baseline activity dependent to cortical condition and baseline levels of serotonin, and this seems to be predominantly controlled by 5-HT1A receptors (110).

In summary, the interplay between 5-HT1A and 5-HT2A receptors leads to a notable and significant adjustment in both spontaneous and evoked components of population activity in V1. One key observation is that the inhibition of gain modulation induced by 5-HT is more pronounced in the anesthetized condition compared to the awake state. This suggests that, while awake, response normalization depends less on spontaneous activity and is less affected by internal cortical signals.

Given that spontaneous activity reflects top-down expectations, whereas Neural responses to stimuli provide bottom-up sensory information, any imbalance in the activation of these receptors—whether due to specific agonist application or irregular receptor expression—can disrupt the integration of these components and thus affect cortical information processing. Such an imbalance could lead to an excessive focus on internally generated expectations(111, 112) at the expense of sensory input, or the reverse (113).

Serotonergic Modulation of Sensory Computations

Sensory systems use various strategies to dynamically adjust the range of individual stimulus features they encode. Given the widespread presence of serotonergic systems, it's unsurprising that serotonin either modulates or directly participates in these processes. For example, as animals move through their environment, they encounter fluctuations in stimulus intensity. In situations where sensory input is intense (such as bright light or strong odors), neurons may struggle to properly encode the stimulus due to saturation. On the other hand, when stimuli are at low intensities, such as the faint scent of a predator, animals may fail to detect them. To address these challenges, sensory systems typically employ a range of computations, including "gain control" (72), which adaptively adjusts the input-to-output ratio of a network. Across different sensory modalities, 5-HT receptors (5-HTRs) expressed by sensory afferents enable direct serotonergic modulation of sensory input gain(45).

Serotonin can decrease the signal-to-noise ratio by reducing evoked activity more than spontaneous activity (11) The concept of serotonergic modulation of population codes is relatively recent, and further research in this area could help bridge the gap between the effects of monoamines on neural codes and sensory-related behaviors (114). This modulation involves a reduction in retinotectal transmission mediated by 5HT1B receptors selectively expressed by optic afferents, though postsynaptic 5HT1A receptors may also contribute to a decline in responsiveness (115).

In macaque V1, gain changes are the most frequently reported modulatory effect. Both acetylcholine (ACh) and serotonin (and likely norepinephrine, NA) modify gain in some way; however, studies vary (and possibly the systems themselves) in terms of how many neurons are suppressed versus enhanced. Other reviews have presented studies on ACh and serotonin (12, 54), that report conflicting findings regarding the

dominance of enhancement versus suppression across neurons. Notably, serotonin does not alter rate variability or noise correlations in macaque V1 (12).

The reported effects of serotonin on sensory processing have been inconsistent(11, 54, 113, 114, 116) making it difficult to develop a straightforward computational explanation. However, studies showed that across the neuronal population in V1 and across different stimulus dimensions, serotonergic modulation is surprisingly simple: serotonin primarily reduces the gain of visual responses, with minimal impact on tuning properties. Results suggest that serotonin is well-suited to controlling the response gain of neurons in V1, potentially complementing existing gain control mechanisms.

Across various visual stimulus dimensions, serotonergic modulation was uniformly characterized by a reduction in response gain, a slight slowing of response dynamics, and no systematic changes in neuronal variability, co-variability, or stimulus selectivity.

These effects could be captured by a model in which serotonin induces a simple additive change in the threshold-linear spiking nonlinearity. Overall, the observed modulation was homogeneous, resulting in a straightforward decrease in response gain across the neural population (12). Such gain modulation is an essential aspect of cortical computation (117) allowing responses to be modulated without altering receptive field properties, and making it well-suited to adjust responses according to the animal's internal state, influenced by the context's valence (118).

The inhibitory effect of serotonin was the predominant pattern observed across the large neuronal population. This reduction was mainly attributed to a multiplicative change (gain change) in the neuronal tuning curves (119). Behaviorally, a recent study that administered a serotonin-reuptake inhibitor to enhance serotonin's effect during a color discrimination task in macaques found that reaction times slowed and perceptual performance deteriorated (120), consistent with the expected outcome of reduced visual responses.

On the other hand, a reduction in the gain of spontaneous responses (113), aligns with an increased signal-to-noise ratio (SNR), or a reduction in the gain of tuning curves (116).

The mechanisms and nature of how specific populations of neuromodulatory inputs influence sensory processing content remain largely unclear.

Studies shown that Serotonin can modulate the transmission of early visual information within critical regions, such as the dorsolateral geniculate nucleus (dLGN) (121, 122), the suprachiasmatic nucleus (123, 124), and the superior colliculus (115), in addition to its effects on early olfactory and auditory information (116, 125).

Serotonergic modulation of retinal processing

Specifically, in vitro pharmacological administering high dosage of serotonin or it's agonists has been shown to reduce retinal axon stimulation-evoked glutamate release via presynaptically expressed 5-HT1B receptors (121-123). However, it remains uncertain whether "endogenous" serotonin release significantly modulates the activity of mouse retinal axonal boutons in vivo, and if this modulation is selective for particular retinal axons.

An Study indicates that serotonin preferentially suppresses retinal ganglion cell (RGC) axonal boutons with high baseline activity that respond to full-field stimuli. This selective suppression by serotonin may alter the tuning of the postsynaptic cell toward smaller, more localized stimuli, similar to what has been observed in zebrafish(126).

In fact, electrical stimulation of the dorsal raphe nucleus (DRN) selectively diminishes evoked activity in thalamocortical neurons with large receptive fields (127), which aligns with observations of stronger suppression of full-field boutons. Also slow fluctuations in serotonin release within the dLGN, a small fraction of which could be attributed to a weak anti-correlation with arousal levels (128). The behavioral contexts that drive these serotonin fluctuations are still largely unknown, as are the roles of serotonergic suppression of retinothalamic transmission in shaping downstream visual processing and behavior (128). However, while serotonin preferentially suppresses RGC axons that are strongly responsive to full-field luminance changes, arousal more selectively suppresses boutons that are more responsive to localized stimuli. This suggests the intriguing possibility that serotonergic axons and other modulatory inputs may implement multiple, complementary, state-dependent selective filters for specific visual information channels at a critical bottleneck in the pathway, before these channels reach thalamocortical neurons and are further relayed and amplified in brain regions responsible for guiding behavior and learning (128).

Serotonergic modulation of visual processing by various receptors

The 5-HT1B receptor has been shown to influence neurotransmission in various pathways, including the retinocollicular (129) retino-suprachiasmic nuclear (123), and thalamocortical (130) pathways. Given the increased expression of 5-HT1B and 5-HT2A receptor genes in V1, it is plausible that these two receptors play significant roles in modulating neurotransmission in this region (54).

Activity-dependent expression of 5-HT1B receptor mRNA has also been observed in the LGN. To determine the time needed for monocular inactivation to take effect, shorter durations of monocular inactivation (1 day, 6 hours, and 3 hours) were examined. The downregulation of 5-HT1B and 5-HT2A receptor mRNAs in V1 was detected even after just 3 hours of monocular inactivation. These findings suggest that the specific expression patterns of 5-HT1B and 5-HT2A receptor mRNAs in V1 are maintained by ongoing visual activity. Consequently, it is speculated that 5-HT1B agonist (CP93129) mainly facilitated visual responses in V1 neurons, although it tended to suppress neurons with low firing rates. This example illustrates that activation of 5-HT1B receptors enhances responses to high-contrast (>30%) stimulation but is either suppressive or ineffective for low-contrast stimuli. The results indicate that the effect of the 5-HT1B receptor agonist is contingent on each neuron's response level and that it improves the signal-to-noise ratio of visual input from the LGN to the cortex (54).

In vivo electrophysiological experiments demonstrated that 5-HT1B and 5-HT2A agonists modulate V1 neuron responses in macaque monkeys. This analysis revealed that 5-HT2 agonist (DOI) facilitates visual responses in neurons with low firing rates but suppresses those with high firing rates (54) .

They conclude that 5-HT2A receptors exhibit response-dependent modulatory effects, but their effects are opposite to those of 5-HT1B receptors. Then, they indicate that the laminar distributions of the effects of 5-HT1B agonist (CP93129), DOI, and 5-HT2A antagonist (ketanserin). This contrasts with the highly layer-specific distribution of 5-HT1B and 5-HT2A receptor mRNAs (54).

Seeburg et al.(122) shown that each receptor can exert both suppressive and facilitative effects depending on the firing rate of the recorded neurons. Regarding the 5-HT1B receptor, similar context-dependent bidirectional modulation has been observed in vitro using brain slices containing the optic tract and LGN (122) or the ventral posterior medial nucleus of the thalamus and somatosensory cortex (130). For instance, Seeburg et al. in 2004 (122) found that 5-HT1B receptor-mediated serotonergic modulation of LGN neuron responses to optic tract stimulation depends on the stimulus's temporal frequency.

The 5-HT1 receptor agonist suppresses retinogeniculate transmission for low-frequency inputs but is either ineffective or facilitative for high-frequency inputs. The authors suggested that alleviation of synaptic depression due to high-frequency stimulation might underlie these effects of the 5-HT1B receptors.

On the other hand, activation of 5-HT2A receptors is known to exert direct facilitatory actions on pyramidal neurons and interneurons (131, 132), indirectly inhibiting neighboring pyramidal neurons (133-135). Thus, serotonin likely has complex effects by regulating the relative activity of excitatory and inhibitory neurons within local circuits through 5-HT1B and 5-HT2A receptors (54).

Serotonin release in V1 could be locally regulated by 5-HT1B autoreceptors on the presynaptic terminals of raphe neurons that project to V1 or potentially by prefrontal cortex activity (136). Therefore, serotonin's cortical effects likely depend on the dynamic regulation of its levels and receptors. Although the enhanced expression of 5-HT1B receptor mRNA in the LGN and V1 suggests its primary role in the visual system, it is also widely expressed in the thalamus. In a study, it was demonstrated that activating 5-HT1B receptors in V1 generally enhances visual responses but tends to suppress weak responses. This suggests that, in geniculocortical transmission, non-synchronized spontaneous activity (noise) from LGN neurons is reduced by 5-HT1B receptor-mediated suppression, while visually evoked synchronized signals are preserved or efficiently transmitted to V1, thereby enhancing the signal-to-noise ratio in the input-output relationship.

Conversely, neurons in V1's input layers, which express the 5-HT2A receptor abundantly, may act as gain controllers by enhancing weak signal responses and suppressing excessive responses. Therefore, we suggest that serotonin release in V1 exerts coordinated modulatory effects through 5-HT1B and 5-HT2A receptors on V1 neurons. It is thus possible that the serotonin system has contributed to the evolution of the primate visual system's sophisticated function (54).

In a study, it was investigated visual processing and experience-dependent learning in SERT-deficient mice. They did not find significant alterations in orientation, spatial frequency, and contrast tuning in naive mice, consistent with a previous operant conditioning study that found intact learning in visual discrimination tasks in SERT-deficient mice (137). Additionally, compensatory mechanisms may partially correct for the lack of functional SERT to maintain cortical development (138). However, they observed a lack of bias toward cardinal orientations in V1 of SERT-deficient mice before visual experience, which partially recovered in SERT heterozygous mice after perceptual experience but not in knockout animals. Observations of prolonged oscillatory activity following perceptual experience in SERT-deficient mice further support the hypothesis that 5-HT may play a role in cortical plasticity. They also found decreased orientation selectivity and broadened orientation tuning in SERT knockout mice. Interestingly, these changes resemble those seen in Fmr1 knockout mice, which are known to result from hypoactivation of parvalbumin-positive fast-spiking interneurons and corresponding circuit alterations (139, 140).

Heterogenous actions of serotonin on interneurons in visual cortex

It is interesting that serotonergic modulation of inhibitory neurons is cell-type specific. Xiang and Prince (141) suggest that serotonergic activation exerts complex influences on cortical inhibitory networks, potentially leading to alterations in cortical information processing (141). The impact of serotonin (5-HT) on the excitability of two cortical interneuron subtypes, fast-spiking (FS) and low-threshold spiking (LTS) cells, as well as on spontaneous inhibitory postsynaptic currents (sIPSCs) in layer V pyramidal cells, was examined in rat visual cortical slices using whole-cell recording methods (141). It was observed that the application of 5-HT induced excitation in half of the FS cells and a small portion of LTS cells, while it caused inhibition in roughly half of the FS cells and the majority of LTS cells. In a few FS and LTS cells, serotonin application triggered excitation followed by inhibition (141).

Serotonergic modulation of spatial attention and receptive field

Patel et al. (142) explore the effects of serotonergic modulation on local network processing in the primary visual cortex (V1) of awake macaques. Their research provides valuable insights into how serotonin influences sensory processing, drawing parallels with the effects of spatial attention. The authors highlight that serotonin application leads to a reduction in local field potential (LFP) power and spike-field coherence, indicating decreased functional connectivity within the local network.

This reduction in synchronization is thought to enhance the signal-to-noise ratio, thereby improving the efficiency of sensory processing. Interestingly, these effects mirror those observed with spatial attention, suggesting that serotonin may play a similar role in modulating sensory inputs.

Patel et al.(142) propose that serotonin's modulation of V1 contributes to a state of "quiet vigilance," where the brain remains alert but less reactive to distracting stimuli. This state is beneficial for maintaining focus on relevant visual inputs while minimizing the impact of irrelevant stimuli that this mechanism allows for a more stable and focused perception, which is crucial for tasks requiring sustained attention. The study also discusses the broader implications of serotonergic modulation across different sensory modalities.

The authors speculate that the effects observed in V1 might extend to other sensory systems, highlighting serotonin's role in fine-tuning sensory processing and maintaining perceptual stability. This cross-modal influence underscores the importance of serotonin in optimizing sensory perception and attention. Their study provides valuable evidence that serotonin, much like spatial attention, can shape sensory experiences by modulating local network dynamics. This insight is crucial for our understanding of how neuromodulators influence sensory modalities, particularly vision.

Serotonin (5-HT) generally diminished the effectiveness of synaptically mediated excitation and inhibition, resulting in a reduction or complete loss of neuronal responsiveness to visual stimuli. Regarding the effects of 5-HT on receptive field characteristics, a simple difference in threshold versus subthreshold synaptic inputs appears insufficient to explain cases where the area of the visual field that could activate a cell significantly

changed during 5-HT application. The reduction in evoked response magnitude observed in many instances could be attributed to the suppressive influence of 5-HT. However, the observed shift in the receptive field within visual space, likely involves a more intricate reconfiguration of synaptic balances that establish receptive field boundaries (11). Serotonin (5-HT) inhibits stimulus-evoked neuronal firing in the sensory regions of the cerebral cortex (11, 143, 144), while having a lesser impact on the background activity of these neurons. Additionally, 5-HT reversibly modifies the receptive fields of visual cortical neurons, causing a shift in the visual field towards the temporal zone(11).

Future directions:

Serotonergic system seems to be one of complicated brain modulatory systems. Different kind of serotonin receptors, difference in serotonergic neurons properties and non-homogenous projection to different sensory areas, are some of the complex aspects of this system. Considering role of before mentioned factors in various time points of visual processing in a cell-type and layer/area specific manner in multiple aspects of vision are necessary. These studies would be possible by more advanced neuroscience techniques with micro/nano meter spatial resolution and micro/nano second temporal reolution of recording of activities of many neurons, in multiple areas of animal brain, in vivo.

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