Review: ACS Chemical Neuroscience

Serotonin modulation of prefronto-hippocampal rhythms in health and disease

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KEYWORDS: serotonin, prefrontal cortex, hippocampus, neural network activity, oscillation, synchrony, psychiatric disorder, schizophrenia

Abstract

There is mounting evidence that most cognitive functions depend upon the coordinated activity of neuronal networks often located far away in the brain. Ensembles of neurons synchronize their activity generating oscillations at different frequencies that may encode behaviour by allowing an efficient communication between brain areas. The serotonin system, by virtue of the widespread arborisation of serotonergic neurons, is in an excellent position to exert strong modulatory actions on brain rhythms. These include specific oscillatory activities in the prefrontal cortex and the hippocampus, two brain areas essential for many higher-order cognitive functions. Psychiatric patients show abnormal oscillatory activities in these areas, notably patients with schizophrenia who display psychotic symptoms as well as affective and cognitive impairments. A synchronization of neural activity between the prefrontal cortex and the hippocampus seems to be important for cognition and, in fact, reduced prefronto-hippocampal synchrony has been observed in a genetic mouse model of schizophrenia. Here, we review recent advances in the field of neuromodulation of brain rhythms by serotonin, focusing on the actions of serotonin in the prefrontal cortex and the hippocampus. Considering that the serotonergic system plays a crucial role in cognition and mood and is a target of many psychiatric treatments, it is surprising that this field of research is still in its infancy. In that regard, we point to future investigations much needed in this field.

Serotonin (5-hydroxytryptamine, 5-HT) is an evolutionarily ancient neurotransmitter within the central nervous system. It is synthesized by serotonergic neurons of the midbrain raphe nuclei. The axons of serotonergic neurons reach almost every structure in the brain and this widespread innervation allows a powerful modulation of brain activity and function (1,2). 5-HT signalling is crucial for a myriad of brain functions, including sensory processing, cognition, mood, autonomic responses, and motor activity. This potent modulation is accomplished by the release of 5-HT in targeted areas that act via several pre- and post-synaptic receptors. So far, 14 different 5-HT receptor subtypes classified in 7 separate families have been identified. Among these, 5-HT_{1A}, 5-HT_{2A}, and 5-HT_{3A} receptors (5-HT_{1A}R, 5-HT_{2A}R, and 5-HT_{3A}R, respectively) are the most abundantly expressed and, therefore, the ones most thoroughly studied. 5-HT_{1A}R and 5-HT_{3A}R play a role in learning and memory (3–5) whereas 5-HT_{2A}R are involved in cognitive flexibility and behavioural control (6–8).

The prefrontal cortex (PFC) and the hippocampus (HPC) are two major targets of serotonergic neurons and express several 5-HT receptors densely (Figure 1). The PFC is an associational cortical area crucial for the control of important goal-directed behaviours such as working memory, associative learning, cognitive flexibility, decision-making, and behavioural inhibition (9,10). Consistently, frontal cortex damage typically produces profound deficits in these cognitive functions (11,12). Manipulations of 5-HT transmission in the PFC have unravelled a prominent role of PFC 5-HT in cognition. For instance, excessive or insufficient 5-HT in PFC increases impulsivity and cognitive inflexibility and this is mediated by 5-HT_{1A}R and 5-HT_{2A}R (1,12). The HPC, on the other hand, plays a critical role in memory processes, spatial navigation, decision-making, and social relationships. Damage to the HPC and surrounding structures can cause amnesia and abnormal social interactions (13,14). Pharmacological manipulations of 5-HT transmission in the HPC have highlighted a crucial role of HPC 5-HT in learning and memory processes, 5-HT_{1A}R being the receptors more thoroughly investigated (3,4).

The sophisticated cognitive tasks encoded by the PFC and HPC depend upon specific firing patterns and brain rhythms. Neuronal ensembles in PFC and HPC coordinate their activity to form functional neural networks following diverse dynamics during behaviour. As such, their activity oscillates generating small electrical waves that can be easily detected outside the skull via electroencephalography (EEG) on the scalp or intracerebrally via local field potential signals (LFPs). Specific oscillatory activities correlate with specific behaviours (see for review (15)) and may provide a means for regulating neural communication of neuron populations (16). This synchronous firing can more strongly drive downstream neurons, which may be especially important for complex cognitive tasks that require coordination of long-range networks across the brain (17). During wake states, neocortical oscillations in the alpha (8-14 Hz), beta (14-30 Hz), and

Figure 1: *Anatomical connectivity of the serotonin system with the prefrontal cortex and the hippocampal complex.* Serotonergic neurons in the dorsal and median raphe nuclei (DR and MnR) project to the PFC bilaterally. In turn, PFC sends afferents to both raphe nuclei. All hippocampal regions (CA1, CA3, DG) receive serotonergic fibers mainly from the MnR. Hippocampal CA1 projects to the PFC ipsilaterally. Insets show the known distribution of the main 5-HT receptors within each target area (5-HT_{1A}R in red; 5-HT_{2A}R in green, 5-HT_{3A}R in blue).

gamma (30-80 Hz) frequencies have been associated with attention, learning, memory, and sensory perception (15,18–22). During sleep states, prominent slow (<2 Hz) and spindle (8-12 Hz) oscillations govern cortical activity (23) (Figure 2). In the HPC, a variety of highly ordered spatiotemporal activity patterns are believed to underlie memory formation and consolidation (24) and spatial navigation (25). Theta (~8 Hz) oscillations prevail during exploration (26) together with gamma rhythms, whereas during wake rest episodes sharp wave-ripple complexes (~200 Hz) are associated with memory consolidation (27). Recent evidence has demonstrated functional interactions between the PFC and the HPC in the form of synchronization of oscillatory activity during behaviour (25,28,29). The tight relationship between this synchrony and the behavioural performance suggests an important role of the hippocampal-prefrontal circuit for cognition.

Given the diffuse projection of 5-HT neurons to many brain regions and the remarkable influence of 5-HT on neuronal activity, it is not surprising that the serotonergic system is a major modulator of

brain rhythms, including those in the PFC and HPC. Along these lines, recent investigations have unravelled that 5-HT is a potent modulator of synaptic plasticity and it is crucial for the maintenance of an excitatory-inhibitory balance (see for review (30)), providing a potential cellular mechanism underlying 5-HT generation/modulation of network dynamics. Thus, in the neural circuit discussed here two types of connectivity may be actually relevant for the generation/modulation of network activity and PFC-HPC synchrony: direct connections between the PFC and HPC and the 5-HT innervation of PFC and HPC itself.

Figure 2: Serotonin modulation of neural oscillations in the prefrontal cortex and hippocampus. Recapitulative table showing the effects of 5-HT on specific oscillations present in the PFC and HPC, and the receptors involved. +/=/- indicate an increase, no effect, or reduction in the amplitude of the oscillation. ⊕ and ⊖ indicate a pharmacological activation or inhibition of the serotonin receptor noted. ↑[5-HT] and ↓[5-HT] indicate an increase and decrease in the concentration of extracellular 5-HT, respectively.

Furthermore, due to this anatomical and functional organization, the serotonergic system has become the target of many pharmacological interventions to treat brain disorders. For example, most antidepressants block the 5-HT transporter increasing the concentration of extracellular 5-HT and many antipsychotic and anxiolytic drugs are agonists or antagonists of 5-HT receptors. In this context, understanding the role of 5-HT in the generation and modulation of network activity in the fronto-hippocampal circuit is of major clinical importance. Unfortunately, few laboratories have focused on this field of research. Hence, the main aim of the present review is to revise recent

advances regarding how 5-HT modulates neural network dynamics in the fronto-hippocampal circuit of the intact brain. Moreover, these investigations are analysed in the context of psychiatric disorders and their treatments, mainly schizophrenia and depression where most of the work has been carried out.

Serotonin modulation of neural network activity in the prefrontal cortex

The PFC is densely innervated by serotonergic afferents originating in the dorsal and median raphe nuclei (DR and MnR, respectively) of the midbrain (Figure 1). Excitatory pyramidal neurons can express 5-HT_{1A}R and 5-HT_{2A}R and, in fact, many co-express both receptors (31). In addition, separate subpopulations of inhibitory GABAergic interneurons express 5-HT_{1A}R, 5-HT_{2A}R and 5-HT_{3A}R. Two segregated populations of parvalbumin-expressing fast-spiking interneurons localized in deep cortical layers express 5-HT_{1A}R and 5-HT_{2A}R (32), while 5-HT_{3A}R are mainly expressed by slow-spiking interneurons in superficial layers (33). This complementary distribution of 5-HT receptors along different compartments of the pyramidal tree allows 5-HT to finely tune the excitability of pyramidal neurons providing the 5-HT system with a powerful cellular mechanism to modulate cortical activity (1,2).

Overall, both *in vitro* and in anesthetized rodents the actions of endogenous 5-HT on PFC neuronal activity are overwhelmingly inhibitory. The suppression of activity affects individual pyramidal neurons as well as fast-spiking interneurons and it is mediated by 5-HT_{1A}R (31,32,34–36). The predominance of 5-HT_{1A}R-mediated inhibitory responses may be due to the localization of these receptors on the somata and axon initial segment of pyramidal neurons, locations that maximize their ability to suppress the generation of action potentials. In addition, smaller proportions of pyramidal neurons and fast-spiking interneurons respond to endogenous 5-HT with slow (long-latency) excitations that are mediated by 5-HT_{2A}R, whereas slow-spiking interneurons do so with fast (short-latency) 5-HT_{3A}R-mediated excitations (for a detailed review see (1)). Thus, not only is the distribution of 5-HT_{2A}R and 5-HT_{3A}R in cortical interneurons complementary but the timing of the 5-HT activation they mediate is finely tuned as well. It is important to note that the PFC is reciprocally connected with the raphe nuclei and sends direct projections to both the DR and MnR and that DR and MnR are also interconnected (2,37) (Figure 1). Descending excitatory fibers from the PFC exert complex functional regulation of 5-HT neuron activity, with an overall inhibitory effect mediated by 5-HT_{1A}R autoreceptors and feedforward inhibition (38). Thus, the actions of 5-HT in PFC should always be interpreted in the context of this anatomical and functional PFC-raphe loop.

Indeed, this sophisticated organization of PFC-raphe circuits may provide some explanation to the fact that the inhibitory actions of 5-HT on cortical neural activity do not correspond with its

excitatory effects on neural network dynamics, at least in the anesthetized preparation. The serotonergic system plays a key role in the regulation of brain states, most 5-HT neurons show increased activity during waking states and less activity during sleep, while they are almost silent during paradoxical sleep (39). During natural sleep and under anesthesia, networks of neurons in the cortex fire synchronously generating slow oscillations that alternate between epochs of activation (UP states) and silence (DOWN states). Endogenous 5-HT modulates the frequency and amplitude of these oscillations by promoting rapid initiation of UP states (32). Since UP states are generated by the synchronous depolarization of large ensembles of cortical neurons, 5-HT may have a net excitatory effect on cortical networks *in vivo*. Pharmacological manipulations suggest that these 5-HT-mediated excitatory actions occur via the activation of 5-HT_{2A}R, and not via 5-HT_{1A}R or 5-HT_{2C}R. Moreover, during UP states spindle and gamma oscillations emerge (23,40). 5-HT seems to modulate gamma oscillations via both 5-HT_{1A}R and 5-HT_{2A}R, perhaps by regulating the activity of 5-HT_{1A}R- and 5-HT_{2A}R-expressing fast-spiking interneurons (32) without affecting spindle waves (2) (Figure 2).

During wakefulness, and especially under heavy cognitive demand, other types of oscillations emerge in the PFC. For example, alpha rhythms play a role in attention by helping to suppress unattended information (15,41–44). Moreover, beta rhythms are consistently observed in learning and memory tasks (45–47), and gamma rhythms correlate with attention, movement, and sensory perception (22,48). However, to our knowledge, a direct evidence for the influence of 5-HT on the generation and modulation of these brain oscillations during behaviour is missing. Some indirect evidence arises from the correlations observed between increased alpha oscillations in the PFC and augmented levels of 5-HT in whole blood in human subjects during exercise and attention (49,50).

Serotonin modulation of neural network activity in the hippocampus

The HPC is a principal target of serotonergic afferents along with all the limbic system (51,52). Interestingly, the dorsal HPC is innervated predominantly by the MnR and receives only afferents from a handful of 5-HT neurons in the DR (see for review (51)). All the major 5-HT receptor subtypes (5-HT_{1A}R, 5-HT_{2A}R, and 5-HT_{3A}R) are expressed in the three regions of the HPC (53–56). Similar to the pattern of expression in cortical areas, 5-HT_{1A}R are expressed on the somata of pyramidal neurons, 5-HT_{2A}R on the body and apical dendrite of pyramidal neurons as well as on the majority GABAergic interneurons, and 5-HT_{3A}R in non-parvalbumin cholecystokinin-expressing interneurons (30,54–56) (Figure 1).

Also in line with 5-HT modulation of neural activity in PFC, activation of 5-HT_{1A}R reduces the firing rate of CA1 pyramidal neurons *in vitro* and *in vivo*, both in anesthetized and awake rats (57–59), and similar results have been obtained in pyramidal neurons of CA3 and dentate gyrus (60–63). The activation of HPC 5-HT_{3A}R by endogenous 5-HT from the MnR generates fast excitations of hippocampal interneurons *in vivo*. Interestingly, this fast synaptic activation of hippocampal interneurons by MnR afferents is accomplished via glutamate/serotonin co-transmission (64). Unlike 5-HT_{1A}R and 5-HT_{3A}R, the *in vivo* actions of 5-HT₂R on hippocampal neural activity remain unexplored. *In vitro*, 5-HT₂R modulate 5-HT-induced outward currents in hippocampal pyramidal neurons and facilitate GABAergic transmission (62,63,65).

Serotonin exerts a strong influence on oscillatory activities of the HPC, mostly on theta and gamma oscillations (Figure 2). Early studies showed that 5-HT neurons of the MnR are critically involved in the control of the hippocampal EEG. In anaesthetized rats, activation and inhibition of MnR 5-HT neurons desynchronized and enhanced, respectively, hippocampal theta, the oscillatory pattern associated with acquisition of information and memory formation (66–69). Consistently, selective depletion of 5-HT in the HPC increases hippocampal theta and facilitates spatial learning and memory (70). More recently, it has been shown that a subpopulation of 5-HT neurons discharge action potentials phase-locked to theta cycles (71). 5-HT modulates hippocampal theta oscillations via 5-HT_{1A}R, 5-HT_{2C}R, and 5-HT₆R (Figure 2). *In vivo*, the pharmacological activation of these receptors reduces theta (72–75) and causes marked alterations in the sleep-wake cycle (73,76). This indicates that the ascending serotonergic system is involved in complex information processing as well as the regulation of state transitions. 5-HT_{3A}R also seem to be involved in the regulation of hippocampal theta. Pharmacological blockade of 5-HT_{3A}R increases the frequency of theta oscillations in freely-moving rats and, interestingly, also facilitates memory, possibly via enhancement of long-term potentiation (LTP) (77). 5-HT has also significant influence on hippocampal gamma oscillations *in vitro*. In rat hippocampal slices, carbachol-induced gamma oscillations are reduced by 5-HT both in CA1 and CA3. This suppression is mimicked by stimulation of 5-HT_{1A}R and 5-HT_{3A}R (this latter via desynchronization of PV-containing interneurons), while 5-HT₂R agonists produce the opposite effect (60,78–80) (Figure 2). However, whether 5-HT plays a role in modulating hippocampal gamma oscillations *in vivo* awaits future elucidation.

Neuromodulation of prefronto-hippocampal synchrony

The PFC and the HPC are anatomically and functionally connected. Some regions of the PFC receive direct projections from hippocampal CA1, while prefrontal inputs enter the HPC via the entorhinal cortex (81,82). Lesion studies have demonstrated that this connectivity is unilateral,

hippocampal axons innervate primarily the ipsilateral PFC. These disconnection studies have also highlighted a crucial role of the prefronto-hippocampal circuit in spatial working memory (83,84). Indeed, the PFC and the HPC are also functionally connected such that neural activity in both areas synchronize (28). Many PFC neurons fire phase-locked to hippocampal theta oscillations and their spikes follow (rather than lead) theta cycles, in accord with the unilateral anatomical projections (26,29). This PFC unit phase-locking to hippocampal theta is enhanced during learning and working memory tasks along with an increase in theta-frequency coherence between the two brain areas (25,85,86). More importantly, the strength of this PFC-HPC theta coherence correlates with performance of laboratory animals in working memory tasks (85). Theta oscillations may be particularly privileged to facilitate PFC-HPC interactions, since synchrony at other frequency ranges does not correlate with task performance (28). Interestingly, prefronto-hippocampal synchrony in the theta-frequency range can be modulated by dopamine. Theta coherence between the HPC and the PFC increases with learning and this is mimicked by local injections of dopamine in the PFC of anesthetized rats (18,86). Surprisingly, whether 5-HT modulates prefronto-hippocampal synchrony is virtually unknown. In fact, the overall actions of 5-HT on the synchrony of neural activity have been scarcely investigated (a Medline search for “*Serotonin and synchrony*” yields only 43 results). Due to the direct interconnections between the PFC, the HPC, and the raphe nuclei (Figure 1), some contribution of 5-HT to PFC-HPC synchrony is to be expected. As a matter of fact, whether the widespread innervation of PFC and HPC by 5-HT fibers plays a role in the actual synchronization of activity should also be considered. This could be directly tested *in vivo* by a selective inactivation/stimulation of 5-HT terminals locally in PFC and HPC. Such contribution of the 5-HT system to the regulation of PFC-HPC network dynamics could originate in the slow metronome-like rhythmic activity exhibited by many 5-HT neurons that synchronize with nearby neurons (71,87). Serotonin and dopamine comodulation of PFC and HPC rhythms and synchrony is also plausible. In that regard, a mathematical model that incorporates available experimental findings suggests that 5-HT and dopamine cooperate to regulate beta and gamma oscillations in the PFC via complex cellular mechanisms that involve several of their receptors (88).

Action of serotonin drugs on neural network activity: Relevance for psychiatric disorders

Brain rhythms are abnormal in numerous psychiatric disorders such as schizophrenia, major depression, and bipolar disorder (89–92). However, a direct causal relationship between altered 5-HT transmission and aberrant neural network dynamics has yet to be established. In schizophrenia patients, cortical oscillatory activities in the slow and gamma frequency bands are abnormal (92–95). Considering the cognitive impairments suffered by many of these patients and the fact that new generation atypical antipsychotic drugs preferentially target the serotonergic system vs. the

dopaminergic system (96), the study of 5-HT modulation of neural network dynamics is of high clinical interest. In that regard, animal models of schizophrenia are starting to shed new light into the cellular imbalances of network activity observed in the disorder and the compensation produced by antipsychotic medication. First, acute administration of hallucinogens acting on 5-HT_{1A}R and 5-HT_{2A}R receptors reduces slow oscillations in the PFC of anesthetized rats. These include DOI, activating preferentially 5-HT_{2A}R, and 5-MeO-DMT, activating both 5-HT_{1A}R and 5-HT_{2A}R. Interestingly, DOI's effects were reversed more by the atypical antipsychotic clozapine (preferential antagonist of 5-HT_{2A}R) than the typical haloperidol (preferential antagonist of dopamine D2 receptors), although both agents reversed 5-MeO-DMT's effects in a similar way (97,98). So far, the actions of hallucinogens and antipsychotic medication on hippocampal network activity *in vivo* have not been described, however some work has been carried out *in vitro*. In hippocampal slices, both typical and atypical antipsychotic drugs suppress gamma oscillations, haloperidol and clozapine having the highest inhibitory effects mediated by dopamine D3 and 5-HT_{3A} receptors, respectively (99). Nonetheless, how antipsychotic drugs acting on the 5-HT system affect network dynamics in the HPC is poorly understood, an important issue that needs further investigation.

Other psychotomimetic drugs that induce schizophrenia-like symptoms in healthy individuals and exacerbate pre-existing symptoms in patients with schizophrenia are the NMDA receptor antagonists ketamine and phencyclidine (PCP). In laboratory animals, administration of ketamine or PCP induces cognitive deficits and behavioural phenotypes relevant to psychosis. In this context, acute administration of ketamine to awake behaving rats increases cortical gamma oscillations and this can be prevented by chronic administration of both haloperidol and clozapine (100). PCP consistently induces learning and memory deficits that can be reversed by antipsychotic drugs, especially those targeting 5-HT_{1A}R and 5-HT_{2A}R (101–104). Under general anesthesia, acute PCP reduces delta oscillatory activity in the PFC of rats, and clozapine reverses its effects via 5-HT_{1A}R activation (105,106). Interestingly, in freely moving rats, systemic PCP produces long-lasting activation of PFC neurons together with augmentation of locomotor activity and behavioural stereotypies, and this effect depends on excitatory projections to PFC from the ventral HPC (107). So, an abnormal communication between PFC and HPC may mediate PCP-induced psychosis. Thus, it is plausible that a dysfunction in the prefronto-hippocampal system is responsible for some alterations observed in schizophrenia (108) and, indeed, a reduced PFC – HPC synchrony has been observed in a genetic mouse model of schizophrenia (85). To sort this out, a thorough investigation of the actions of psychotomimetic drugs, including those acting on the 5-HT system, on prefronto-hippocampal synchrony is urgently needed.

Some patients with major depression also show abnormal oscillatory activities. More specifically, depressive patients that respond to selective serotonin reuptake inhibitors (SSRIs) have greater alpha oscillations in some cortical areas compared with non-responders and healthy control subjects (109). This is consistent with the correlations between increased alpha oscillations and blood 5-HT levels mentioned above, suggesting that the 5-HT has some influence on the alpha band. Moreover, a genetic mouse model of 5-HT deficiency exhibits hypersynchronized PFC-amygdala neural network activity. Mice genetically engineered to express a rare naturally occurring variant of the tryptophan hydroxylase-2 enzyme (involved in the synthesis of brain 5-HT) present in human subjects with major depression exhibit deficient baseline and evoked extracellular 5-HT levels (110). These mice display increased local synchrony of both delta and beta oscillations within the PFC and the basal amygdala, and exacerbated amygdala-PFC synchrony in the delta band. Interestingly, treatment with the SSRI and antidepressant fluoxetine tended to reduce such aberrant hypersynchronization in the PFC. These results help establish a functional link between hyposerotonergia and abnormal PFC-amygdala neural network dynamics (111). By contrast, genetically engineered mice with deficient 5-HT transporter function, a mouse model of emotional dysregulation where extracellular 5-HT levels are elevated, exhibit impaired fear conditioning responses accompanied by increased theta synchronization between the lateral amygdala and the PFC (112). Although collectively these studies suggest that 5-HT transmission is relevant for inter-regional synchrony, we are far from understanding how an impaired serotonergic system may contribute to the emergence of the aberrant oscillatory activities observed in psychiatric disorders.

Conclusions

Sophisticated cognitive functions depend upon a dynamic communication between brain areas often located far away in the brain. Two of these areas are the PFC and the HPC, both heavily involved in encoding higher-order cognitive tasks. Serotonin neurons' widespread axonal arborisation reaches almost every brain structure, allowing the serotonergic system to exert profound influences on neural network dynamics. 5-HT neurons from the DR and the MnR innervate massively the PFC where 5-HT modulates oscillatory activities in the slow-, alpha-, and gamma-frequency bands. Similarly, 5-HT neurons originating in the MnR innervate the HPC where 5-HT regulates theta and gamma oscillations. However, a direct evidence for the involvement of 5-HT in the modulation of other important neural oscillations (e.g. cortical alpha and beta, hippocampal ripple waves) is missing. Overall, 5-HT seems to decrease spiking activity of pyramidal neurons via 5-HT_{1A}R and to increase spiking of GABAergic interneurons via 5-HT_{2A}R and 5-HT_{3A}R, both in PFC and HPC. Despite these complementary actions on neuronal activity, locally elevated 5-HT systematically desynchronizes neural oscillations (with the exception of cortical spindles), and this is also region independent. This suggests that the levels of 5-HT are

finely regulated and deviations from these normal concentrations markedly affect the synchronization of neural networks. The cellular mechanisms (including the receptors involved) of 5-HT modulation of neural oscillations are complex and much work is needed for their full elucidation.

Importantly, neural activity in the PFC and HPC synchronize during behaviour. PFC-unit phase-locking to hippocampal theta is enhanced during learning and working memory tasks along with an increase in theta-frequency coherence between the two brain areas. Surprisingly, whether 5-HT modulates this PFC-HPC synchronization of activity has not been investigated. The fact that dopamine can influence this synchrony strongly suggests that 5-HT may also do so. From the clinical perspective, resolving this issue may be of high importance since recent investigations have suggested that an impaired prefronto-hippocampal synchrony may underlie the psychotic symptoms in schizophrenia. Furthermore, a series of studies carried out in animal models of schizophrenia (PCP models) have demonstrated that antipsychotic medication that target the serotonergic system can restore the observed network imbalances, at least in the PFC. In closing, and more generally, many brain rhythms are abnormal in psychiatric disorders that are treated with serotonergic medication. As a result, it is urgent to make progress in our understanding of the cellular mechanisms underlying the actions of serotonin on neural oscillations and synchrony.

Conflict of interest disclosure

The authors declare no conflict of interest.

Acknowledgements

We thank M. Alemany for helpful comments about the manuscript. MV Puig is recipient of a Ramón y Cajal award from the Spanish Ministry of Economy and Competitiveness (MICINN) (RyC-2012-10042) and a 2013 NARSAD Young Investigator Grant from the Brain & Behavior Research Foundation.

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