ACS Chemical Neuroscience

Review

pubs.acs.org/chemneuro

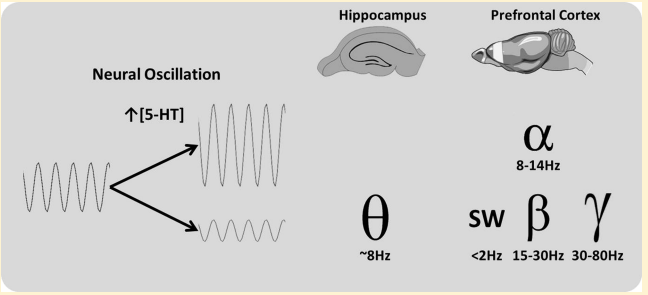
Serotonin Modulation of Prefronto-Hippocampal Rhythms in Health and Disease

M. Victoria Puig[†] and Thomas Gener[†,‡]

[†]Neuroscience Programme, Hospital del Mar Medical Research Institute (IMIM), Barcelona Biomedical Research Park (PRBB), Barcelona, Spain

[‡]Systems Biology Program, Centre for Genomic Regulation (CRG), Barcelona Biomedical Research Park (PRBB), Barcelona, Spain

ABSTRACT: There is mounting evidence that most cognitive functions depend upon the coordinated activity of neuronal networks often located far from each other in the brain. Ensembles of neurons synchronize their activity, generating oscillations at different frequencies that may encode behavior 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. 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 that are much needed in this field.



KEYWORDS: *Serotonin, prefrontal cortex, hippocampus, neural network activity, oscillation, synchrony, psychiatric disorder, schizophrenia, major depression*

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 for powerful modulation of brain activity and function.[1,2] 5-HT signaling 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 postsynaptic receptors. To date, 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 behavioral control.[6−8]

The prefrontal cortex (PFC) and the hippocampus (HPC) are two major targets of serotonergic neurons and densely express several 5-HT receptors (Figure 1). The PFC is an associational cortical area crucial for the control of important goal-directed behaviors, such as working memory, associative learning, cognitive flexibility, decision-making, and behavioral 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 with 5-HT_{1A}R being the receptor more thoroughly investigated.[3,4]

The sophisticated cognitive tasks encoded by the PFC and HPC depend upon specific firing patterns and brain rhythms.

Special Issue: Serotonin Research

Received: December 20, 2014
Accepted: March 23, 2015
Published: March 23, 2015

DOI: 10.1021/cn500350e
ACS Chem. Neurosci. 2015, 6, 1017−1025

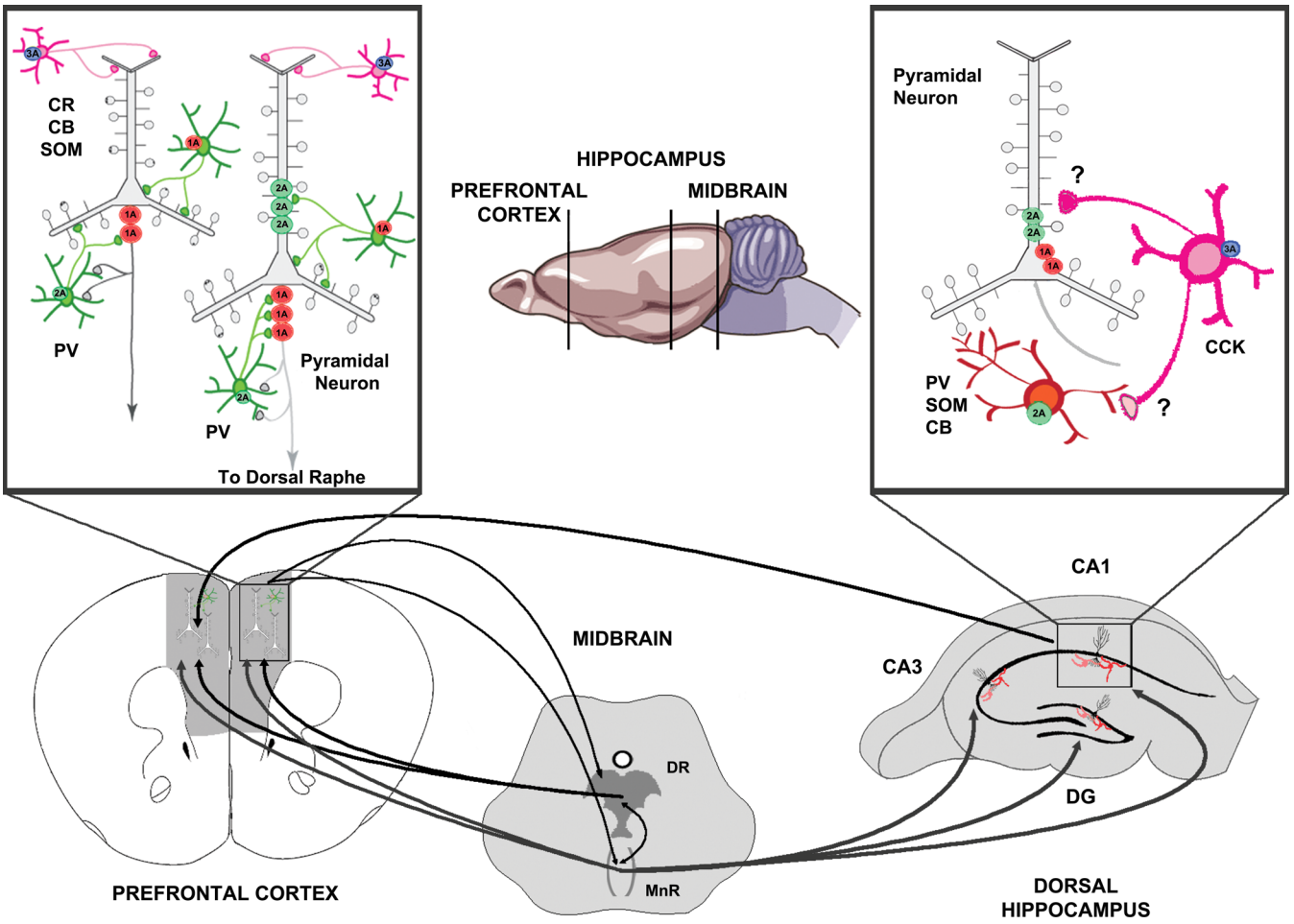


Figure 1. Anatomical connectivity of the serotonin system with the prefrontal cortex and the hippocampal complex. Serotonergic neurons in the dorsal and median raphe nuclei (DR and MnR, respectively) project to the PFC bilaterally. In turn, PFC sends afferents to both raphe nuclei. All hippocampal regions (CA1, CA3, and dentate gyrus (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, and 5-HT_{3A}R in blue).

Neuronal ensembles in PFC and HPC coordinate their activity to form functional neural networks following diverse dynamics during behavior. 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 behaviors (see ref 15 for review) 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 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] During exploration, theta (∼8 Hz) oscillations prevail[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 HPC in the form of synchronization of oscillatory activity during behavior.[25,28,29] The tight relationship between this synchrony and behavioral 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 revealed that 5-HT is a potent modulator of synaptic plasticity, and it is crucial for the maintenance of an excitatory−inhibitory balance (see ref 30 for review), 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.

Furthermore, due to this anatomic 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

DOI: 10.1021/cn500350e
ACS Chem. Neurosci. 2015, 6, 1017−1025

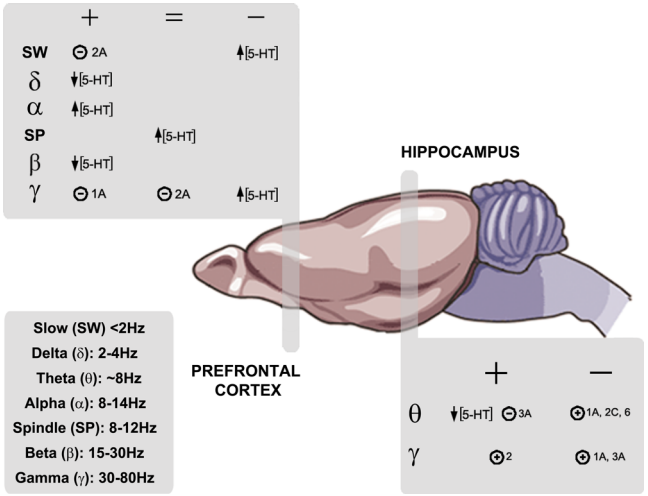


Figure 2. Serotonin modulation of neural oscillations in the prefrontal cortex and hippocampus. Recapitulative table showing the effects of 5-HT on specific oscillations present in the PFC and HPC and the receptors involved, including an increase (+), no effect (=), or reduction (−) in the amplitude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

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 this 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 analyzed 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 coexpress 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] whereas 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 ref 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 the 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, and 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] Because 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, direct evidence for the influence of 5-HT on the generation and modulation of these brain oscillations during behavior is absent. Some indirect evidence arises from 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 of the limbic system.[51,52] Interestingly, the dorsal HPC is innervated predominantly by the MnR and receives only

DOI: 10.1021/cn500350e
ACS Chem. Neurosci. 2015, 6, 1017−1025

afferents from a handful of 5-HT neurons in the DR (see ref 51 for review). All of 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 is expressed on the somata of pyramidal neurons, 5-HT_{2A}R on the body and apical dendrites of pyramidal neurons as well as on the majority of GABAergic interneurons, and 5-HT_{3A}R in nonparvalbumin cholecystokinin-expressing interneurons[30,54−56] (Figure 1).

Also in line with 5-HT modulation of neural activity in the PFC, activation of 5-HT_{1A}R reduces the firing rate of CA1 pyramidal neurons in vitro and in vivo in both anesthetized and awake rats,[57−59] and similar results have been obtained in pyramidal neurons of CA3 and the dentate gyrus (DG).[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 cotransmission.[64] Unlike 5-HT_{1A}R and 5-HT_{3A}R, the in vivo actions of 5-HT_2R on hippocampal neural activity remain unexplored. In vitro, 5-HT_2R modulates 5-HT-induced outward currents in hippocampal pyramidal neurons and facilitates 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, which is the oscillatory pattern associated with the 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-HT_6R (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 also has significant influence on hippocampal gamma oscillations in vitro. In rat hippocampal slices, carbachol-induced gamma oscillations are reduced by 5-HT in both CA1 and CA3. This suppression is mimicked by stimulation of 5-HT_{1A}R and 5-HT_{3A}R (the latter via desynchronization of parvalbumin-containing interneurons), whereas 5-HT_2R 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 HPC are anatomically and functionally connected. Some regions of the PFC receive direct projections from hippocampal CA1, whereas 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 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 accordance 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 the performance of laboratory animals in working memory tasks.[85] Theta oscillations may be particularly privileged to facilitate PFC−HPC interactions because 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 PFC and the HPC 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). On the basis of the direct interconnections between the PFC, HPC, and 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 selective inactivation/stimulation of 5-HT terminals locally in the 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 instead of 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 on the cellular imbalances of network activity observed in the disorder and the compensation produced by antipsychotic medication. First,

DOI: 10.1021/cn500350e
ACS Chem. Neurosci. 2015, 6, 1017−1025

acute administration of hallucinogens acting on 5-HT_{1A}R and 5-HT_{2A} receptors reduces slow oscillations in the PFC of anesthetized rats. These include 2,5-dimethoxy-4-iodoamphetamine (DOI), preferentially activating 5-HT_{2A}R, and 5-methoxy-*N*,*N*-dimethyltryptamine (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 the effects of 5-MeO-DMT in a similar way.[97,98] To date, 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 with 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, and this is an important issue that warrants 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 behavioral 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-$HT1_A$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 behavioral stereotypies, and this effect depends on excitatory projections to PFC from the ventral HPC.[107] So, 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, 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 on prefronto-hippocampal synchrony, including those acting on the 5-HT system, is urgently needed.

Some patients with major depression also show abnormal oscillatory activities. More specifically, depressed patients that respond to selective serotonin reuptake inhibitors (SSRIs) have greater alpha oscillations in some cortical areas compared with nonresponders and healthy control subjects.[109] This is consistent with correlations between increased alpha oscillations and blood 5-HT levels mentioned above, suggesting that 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] In contrast, genetically engineered mice with deficient 5-HT transporter function, a mouse model of emotional dysregulation in which 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 dynamic communication between brain areas often located far from one another 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 MnR innervate the PFC massively, 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, 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 in both the PFC and HPC. Despite these complementary actions on neuronal activity, locally elevated 5-HT systematically desynchronizes neural oscillations (with the exception of cortical spindles), which 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 behavior. 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 be able to do so. From a clinical perspective, resolving this issue may be of high importance since recent investigations have suggested that impaired prefronto-hippocampal synchrony may underlie psychotic symptoms in schizophrenia. Furthermore, a series of studies carried out in animal models of schizophrenia (PCP models) have demonstrated that antipsychotic medication that targets the serotonergic system can restore the observed network imbalances, at least in the PFC. In closing, and more generally,

DOI: 10.1021/cn500350e
ACS Chem. Neurosci. 2015, 6, 1017−1025

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.

AUTHOR INFORMATION

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We thank M. Alemany for helpful comments about the manuscript. M.V.P. is the 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.

REFERENCES

(1) Puig, M. V., and Gulledge, A. T. (2011) Serotonin and prefrontal cortex function: neurons, networks, and circuits. *Mol. Neurobiol. 44* (3), 449−464.
(2) Celada, P., Puig, M. V., and Artigas, F. (2013) Serotonin modulation of cortical neurons and networks. *Front. Integr. Neurosci. 7*, 25.
(3) Meneses, A., and Perez-Garcia, G. (2007) 5-HT1A receptors and memory. *Neurosci. Biobehav. Rev. 31* (5), 705−727.
(4) Ögren, S. O., Eriksson, T. M., Elvander-Tottie, E., D'Addario, C., Ekström, J. C., Svenningsson, P., Meister, B., Kehr, J., and Stiedl, O. (2008) The role of 5-HT1A receptors in learning and memory. *Behav. Brain Res. 195* (1), 54−77.
(5) Shimizu, S., Mizuguchi, Y., and Ohno, Y. (2013) Improving the treatment of schizophrenia: role of 5-HT receptors in modulating cognitive and extrapyramidal motor functions. *CNS Neurol. Disord.: Drug Targets 12* (6), 861−869.
(6) Amodeo, D. A., Jones, J. H., Sweeney, J. A., and Ragozzino, M. E. (2014) Risperidone and the 5-HT2A receptor antagonist M100907 improve probabilistic reversal learning in BTBR T + tf/J mice. *Autism Research 7* (5), 555−567.
(7) Koskinen, T., Ruotsalainen, S., Puumala, T., Lappalainen, R., Koivisto, E., Männistö, P. T., and Sirviö, J. (2000) Activation of 5-HT2A receptors impairs response control of rats in a five-choice serial reaction time task. *Neuropharmacology 39* (3), 471−481.
(8) Robbins, T. W. (2005) Chemistry of the mind: neurochemical modulation of prefrontal cortical function. *J. Comp. Neurol. 493* (1), 140−146.
(9) Miller, E. K., and Cohen, J. D. (2001) An integrative theory of prefrontal cortex function. *Annu. Rev. Neurosci. 24*, 167−202.
(10) Robbins, T. W., and Arnsten, A. F. (2009) The neuropsychopharmacology of fronto-executive function: monoaminergic modulation. *Annu. Rev. Neurosci. 32* (1), 267−287.
(11) Kehagia, A. A., Murray, G. K., and Robbins, T. W. (2010) Learning and cognitive flexibility: frontostriatal function and monoaminergic modulation. *Curr. Opin. Neurobiol. 20*, 199−204.
(12) Robbins, T. W. (2007) Shifting and stopping: fronto-striatal substrates, neurochemical modulation and clinical implications. *Philos. Trans. R. Soc., B 362* (1481), 917−932.
(13) Buzsáki, G., and Moser, E. I. (2013) Memory, navigation and theta rhythm in the hippocampal-entorhinal system. *Nat. Neurosci. 16* (2), 130−138.
(14) Dickerson, B. C., and Eichenbaum, H. (2009) The episodic memory system: neurocircuitry and disorders. *Neuropsychopharmacology 35* (1), 86−104.
(15) Engel, A. K., Fries, P., and Singer, W. (2001) Dynamic predictions: oscillations and synchrony in top-down processing. *Nat. Rev. Neurosci. 2*, 704−716.
(16) Buzsaki, G. (2004) Large-scale recording of neuronal ensembles. *Nat. Neurosci. 7*, 446−451.
(17) Buzsaki, G., Logothetis, N., and Singer, W. (2013) Scaling brain size, keeping timing: evolutionary preservation of brain rhythms. *Neuron 80*, 751−764.
(18) Benchenane, K., Tiesinga, P. H., and Battaglia, F. P. (2011) Oscillations in the prefrontal cortex: a gateway to memory and attention. *Curr. Opin. Neurobiol. 21*, 475−485.
(19) Fries, P. (2009) Neuronal gamma-band synchronization as a fundamental process in cortical computation. *Annu. Rev. Neurosci. 32*, 209−224.
(20) Jensen, O., Gips, B., Bergmann, T. O., and Bonnefond, M. (2014) Temporal coding organized by coupled alpha and gamma oscillations prioritize visual processing. *Trends Neurosci. 37* (7), 357−369.
(21) Schroeder, C. E., and Lakatos, P. (2009) Low-frequency neuronal oscillations as instruments of sensory selection. *Trends Neurosci. 32* (1), 9−18.
(22) Womelsdorf, T., and Fries, P. (2007) The role of neuronal synchronization in selective attention. *Curr. Opin. Neurobiol. 17* (2), 154−160.
(23) Steriade, M. (2006) Grouping of brain rhythms in corticothalamic systems. *Neuroscience 137* (4), 1087−1106.
(24) Buzsáki, G., and Draguhn, A. (2004) Neuronal oscillations in cortical networks. *Science 304* (5679), 1926−1929.
(25) Jones, M. W., and Wilson, M. A. (2005) Theta rhythms coordinate hippocampal-prefrontal interactions in a spatial memory task. *PLoS Biol. 3*, e402.
(26) Buzsáki, G. (2002) Theta oscillations in the hippocampus. *Neuron 33* (3), 325−340.
(27) Draguhn, A., Keller, M., and Reichinnek, S. (2014) Coordinated network activity in the hippocampus. *Front. Neurol. Neurosci. 34*, 26−35.
(28) Gordon, J. A. (2011) Oscillations and hippocampal−prefrontal synchrony. *Curr. Opin. Neurobiol. 21* (3), 486−491.
(29) Siapas, A. G., Lubenov, E. V., and Wilson, M. A. (2005) Prefrontal phase locking to hippocampal theta oscillations. *Neuron 46* (1), 141−151.
(30) Lesch, K.-P., and Waider, J. (2012) Serotonin in the modulation of neural plasticity and networks: implications for neurodevelopmental disorders. *Neuron 76* (1), 175−191.
(31) Amargós-Bosch, M., Bortolozzi, A., Puig, M. V., Serrats, J., Adell, A., Celada, P., Toth, M., Mengod, G., and Artigas, F. (2004) Co-expression and in vivo interaction of serotonin1A and serotonin2A receptors in pyramidal neurons of prefrontal cortex. *Cereb. Cortex 14* (3), 281−299.
(32) Puig, M. V., Watakabe, A., Ushimaru, M., Yamamori, T., and Kawaguchi, Y. (2010) Serotonin modulates fast-spiking interneuron and synchronous activity in the rat prefrontal cortex through 5-HT1A and 5-HT2A receptors. *J. Neurosci. 30* (6), 2211−2222.
(33) Puig, M. V., Santana, N., Celada, P., Mengod, G., and Artigas, F. (2004) In vivo excitation of GABA interneurons in the medial prefrontal cortex through 5-HT3 receptors. *Cereb. Cortex 14* (12), 1365−1375.
(34) Hajós, M., Gartside, S. E., Varga, V., and Sharp, T. (2003) In vivo inhibition of neuronal activity in the rat ventromedial prefrontal cortex by midbrain-raphe nuclei: role of 5-HT1A receptors. *Neuropharmacology 45* (1), 72−81.
(35) Puig, M. V., Artigas, F., and Celada, P. (2005) Modulation of the activity of pyramidal neurons in rat prefrontal cortex by raphe stimulation in vivo: involvement of serotonin and GABA. *Cereb. Cortex 15* (1), 1−14.
(36) Avesar, D., and Gulledge, A. T. (2012) Selective serotonergic excitation of callosal projection neurons. *Front. Neural Circuits 6*, 12.
(37) Pollak Dorocic, I., Fürth, D., Xuan, Y., Johansson, Y., Pozzi, L., Silberberg, G., Carlén, M., and Meletis, K. (2014) A whole-brain atlas of inputs to serotonergic neurons of the dorsal and median raphe nuclei. *Neuron 83* (3), 663−678.

DOI: 10.1021/cn500350e
ACS Chem. Neurosci. 2015, 6, 1017−1025

(38) Celada, P., Puig, M. V., Casanovas, J. M., Guillazo, G., and Artigas, F. (2001) Control of dorsal raphe serotonergic neurons by the medial prefrontal cortex: Involvement of serotonin-1A, GABA(A), and glutamate receptors. *J. Neurosci. 21* (24), 9917−9929.
(39) McGinty, D. J., and Harper, R. M. (1976) Dorsal raphe neurons: depression of firing during sleep in cats. *Brain Res. 101* (3), 569−575.
(40) Puig, M. V., Ushimaru, M., and Kawaguchi, Y. (2008) Two distinct activity patterns of fast-spiking interneurons during neocortical UP states. *Proc. Natl. Acad. Sci. U.S.A. 105* (24), 8428−8433.
(41) Bollimunta, A., Mo, J., Schroeder, C. E., and Ding, M. (2011) Neuronal mechanisms and attentional modulation of corticothalamic α oscillations. *J. Neurosci. 31* (13), 4935−4943.
(42) Bonnefond, M., and Jensen, O. (2012) Alpha oscillations serve to protect working memory maintenance against anticipated distracters. *Curr. Biol. 22* (20), 1969−1974.
(43) Buschman, T. J., Denovellis, E. L., Diogo, C., Bullock, D., and Miller, E. K. (2012) Synchronous oscillatory neural ensembles for rules in the prefrontal cortex. *Neuron 76* (4), 838−846.
(44) Jensen, O., Gelfand, J., Kounios, J., and Lisman, J. E. (2002) Oscillations in the alpha band (9−12 Hz) increase with memory load during retention in a short-term memory task. *Cereb. Cortex 12* (8), 877−882.
(45) Puig, M. V., and Miller, E. K. (2012) The role of prefrontal dopamine D1 receptors in the neural mechanisms of associative learning. *Neuron 74*, 874−886.
(46) Puig, M. V., and Miller, E. K. (2015) Neural substrates of dopamine D2 receptor modulated executive functions in the monkey prefrontal cortex. *Cereb. Cortex 35* (9), 4104−4111.
(47) Puig, M. V., Antzoulatos, E. G., and Miller, E. K. (2014) Prefrontal dopamine in associative learning and memory. *Neuroscience 282 C*, 217−229.
(48) Buzsáki, G., and Wang, X.-J. (2012) Mechanisms of gamma oscillations. *Annu. Rev. Neurosci. 35* (1), 203−225.
(49) Fumoto, M., Oshima, T., Kamiya, K., Kikuchi, H., Seki, Y., Nakatani, Y., Yu, X., Sekiyama, T., Sato-Suzuki, I., and Arita, H. (2010) Ventral prefrontal cortex and serotonergic system activation during pedaling exercise induces negative mood improvement and increased alpha band in EEG. *Behav. Brain Res. 213* (1), 1−9.
(50) Yu, X., Fumoto, M., Nakatani, Y., Sekiyama, T., Kikuchi, H., Seki, Y., Sato-Suzuki, I., and Arita, H. (2011) Activation of the anterior prefrontal cortex and serotonergic system is associated with improvements in mood and EEG changes induced by Zen meditation practice in novices. *International Journal of Psychophysiology 80* (2), 103−111.
(51) Hensler, J. G. (2006) Serotonergic modulation of the limbic system. *Neurosci. Biobehav. Rev. 30* (2), 203−214.
(52) Wyss, J. M., Swanson, L. W., and Cowan, W. M. (1979) A study of subcortical afferents to the hippocampal formation in the rat. *Neuroscience 4* (4), 463−476.
(53) Banerjee, P., Mehta, M., and Kanjilal, B. (2007) The 5-HT1A receptor: a signaling hub linked to emotional balance. In *Serotonin Receptors in Neurobiology* (Chattopadhyay, A., Ed), ch. 7, CRC Press, London.
(54) Morales, M., and Bloom, F. E. (1997) The 5-HT3 receptor is present in different subpopulations of GABAergic neurons in the rat telencephalon. *J. Neurosci. 17* (9), 3157−3167.
(55) Xu, T., and Pandey, S. C. (2000) Cellular localization of serotonin2A (5HT2A) receptors in the rat brain. *Brain Res. Bull. 51* (6), 499−505.
(56) Bombardi, C., and Di Giovanni, G. (2013) Functional anatomy of 5-HT2A receptors in the amygdala and hippocampal complex: relevance to memory functions. *Exp. Brain Res. 230* (4), 427−439.
(57) Tada, K., Kasamo, K., Ueda, N., Suzuki, T., Kojima, T., and Ishikawa, K. (1991) Anxiolytic 5-hydroxytryptamine1A agonists suppress firing activity of dorsal hippocampus CA1 pyramidal neurons through a postsynaptic mechanism: single-unit study in unanesthetized, unrestrained rats. *J. Pharmacol. Exp. Ther. 288* (2), 843−848.
(58) Kasamo, K., Suzuki, T., Tada, K., Ueda, N., Matsuda, E., and Kojima, T. (2000) Effects of a benzodioxan derivative MKC-242 on the firing activity of the dorsal hippocampus CA1 pyramidal neurons in awake and urethane- anaesthetized rats: in vivo electrophysiological evidence for a 5-HT 1A agonistic property. *Int. J. Neuropsychopharmacol. 3* (2), 99−108.
(59) Hirose, A., Sasa, M., Akaike, A., and Takaori, S. (1990) Inhibition of hippocampal CA1 neurons by 5-hydroxytryptamine, derived from the dorsal raphe nucleus and the 5-hydroxytryptamine1A agonist SM-3997. *Neuropharmacology 29* (2), 93−101.
(60) Johnston, A., McBain, C. J., and Fisahn, A. (2014) 5-Hydroxytryptamine1A receptor-activation hyperpolarizes pyramidal cells and suppresses hippocampal gamma oscillations via Kir3 channel activation. *J. Physiol. 592* (19), 4187−4199.
(61) El Mansari, M., and Blier, P. (2008) In vivo electrophysiological assessment of the putative antidepressant Wf-516 in the rat raphe dorsalis, locus coeruleus and hippocampus. *Naunyn-Schmiedeberg's Arch. Pharmacol. 376* (5), 351−361.
(62) Shen, R. Y., and Andrade, R. (1998) 5-Hydroxytryptamine2 receptor facilitates GABAergic neurotransmission in rat hippocampus. *J. Pharmacol. Exp. Ther 285* (2), 805−812.
(63) Piguet, P., and Galvan, M. (1994) Transient and long-lasting actions of 5-HT on rat dentate gyrus neurones in vitro. *J. Physiol. 481* (3), 629−639.
(64) Varga, V., Losonczy, A., Zemelman, B. V., Borhegyi, Z., Nyiri, G., Domonkos, A., Hangya, B., Holderith, N., Magee, J. C., and Freund, T. F. (2009) Fast synaptic subcortical control of hippocampal circuits. *Science 326* (5951), 449−453.
(65) Uneyama, H., Munakata, M., and Akaike, N. (1992) 5-HT response of rat hippocampal pyramidal cell bodies. *NeuroReport 3* (7), 633−636.
(66) Marrosu, F., Fornal, C. A., Metzler, C. W., and Jacobs, B. L. (1996) 5-HT1A agonists induce hippocampal theta activity in freely moving cats: role of presynaptic 5-HT1A receptors. *Brain Res. 739* (1−2), 192−200.
(67) Kinney, G. G., Kocsis, B., and Vertes, R. P. (1995) Injections of muscimol into the median raphe nucleus produce hippocampal theta rhythm in the urethane anesthetized rat. *Psychopharmacology 120* (3), 244−248.
(68) Vertes, R. P., Kinney, G. G., Kocsis, B., and Fortin, W. J. (1994) Pharmacological suppression of the median raphe nucleus with serotonin1a agonists, 8-OH-DPAT and buspirone, produces hippocampal theta rhythm in the rat. *Neuroscience 60* (2), 441−451.
(69) Olvera-Cortés, M. E., Gutiérrez-Guzmán, B. E., López-Loeza, E., Hernández-Pérez, J. J., and López-Vázquez, M. A. (2013) Serotonergic modulation of hippocampal theta activity in relation to hippocampal information processing. *Exp. Brain Res. 230* (4), 407−426.
(70) Gutiérrez-Guzmán, B. E., Hernández-Pérez, J. J., González-Burgos, I., Feria-Velásco, A., Medina, R., Guevara, M.Á., and Olvera-Cortés, M. E. (2011) Hippocampal serotonin depletion facilitates place learning concurrent with an increase in CA1 high frequency theta activity expression in the rat. *Eur. J. Pharmacol. 652* (1−3), 73−81.
(71) Kocsis, B., Varga, V., Dahan, L., and Sik, A. (2006) Serotonergic neuron diversity: identification of raphe neurons with discharges time-locked to the hippocampal theta rhythm. *Proc. Natl. Acad. Sci. U.S.A. 103* (4), 1059−1064.
(72) Hirose, A., Tsuji, R., Shimizu, H., Tatsuno, T., Tanaka, H., Kumasaka, Y., and Nakamura, M. (1990) Inhibition by 8-hydroxy-2-(di-*n*-propylamino) tetralin and SM-3997, a novel anxiolytic drug, of the hippocampal rhythmical slow activity mediated by 5-hydroxytryptamine1A receptors. *Naunyn-Schmiedeberg's Arch. Pharmacol. 341* (1−2), 8−13.
(73) Ly, S., Pishdari, B., Lok, L. L., Hajos, M., and Kocsis, B. (2013) Activation of 5-HT6 receptors modulates sleep-wake activity and hippocampal theta oscillation. *ACS Chem. Neurosci. 4* (1), 191−199.
(74) Hajós, M., Hoffmann, W. E., and Weaver, R. J. (2003) Regulation of septo-hippocampal activity by 5-hydroxytryptamine2C receptors. *J. Pharmacol. Exp. Ther 306* (2), 605−615.
(75) Sörman, E., Wang, D., Hajos, M., and Kocsis, B. (2011) Control of hippocampal theta rhythm by serotonin: Role of 5-HT2c receptors. *Neuropharmacology 61* (3), 489−494.

DOI: 10.1021/cn500350e
ACS Chem. Neurosci. 2015, 6, 1017−1025

(76) Kantor, S., Jakus, R., Molnar, E., Gyongyosi, N., Toth, A., Detari, L., and Bagdy, G. (2005) Despite similar anxiolytic potential, the 5-hydroxytryptamine 2C receptor antagonist SB-242084 [6-Chloro-5-methyl-1-[2-(2-methylpyrid-3-yloxy)-pyrid-5-yl carbamoyl] Indoline] and chlordiazepoxide produced differential effects on electroencephalogram power spectra. *J. Pharmacol. Exp. Ther. 315* (2), 921−30.
(77) Staubli, U., and Xu, F. B. (1995) Effects of 5-HT3 receptor antagonism on hippocampal theta rhythm, memory, and LTP induction in the freely moving rat. *J. Neurosci. 15* (3), 2445−2452.
(78) Krause, M., and Jia, Y. (2005) Serotonergic modulation of carbachol-induced rhythmic activity in hippocampal slices. *Neuropharmacology 48* (3), 381−390.
(79) Wójtowicz, A. M., van den Boom, L., Chakrabarty, A., Maggio, N., Haq, R. U., Behrens, C. J., and Heinemann, U. (2009) Monoamines block kainate- and carbachol-induced gamma-oscillations but augment stimulus-induced gamma-oscillations in rat hippocampus in vitro. *Hippocampus 19* (3), 273−288.
(80) Huang, Y., Yoon, K., Ko, H., Jiao, S., Ito, W., Wu, J.-Y., Yung, W. H., Lu, B., and Morozov, A. (2014) 5-HT3a Receptors modulate hippocampal gamma oscillations by regulating synchrony of parvalbumin-positive interneurons. *Cereb. Cortex*, DOI: 10.1093/cercor/bhu209.
(81) Warburton, E. C., and Brown, M. W. (2015) Neural circuitry for rat recognition memory. *Behav. Brain Res. 285*, 131−139.
(82) Condé, F., Maire-Lepoivre, E., Audinat, E., and Crépel, F. (1995) Afferent connections of the medial frontal cortex of the rat. II. Cortical and subcortical afferents. *J. Comp. Neurol. 352* (4), 567−593.
(83) Floresco, S. B., Seamans, J. K., and Phillips, A. G. (1997) Selective roles for hippocampal, prefrontal cortical, and ventral striatal circuits in radial-arm maze tasks with or without a delay. *J. Neurosci. 17* (5), 1880−1890.
(84) Churchwell, J. C., Morris, A. M., Musso, N. D., and Kesner, R. P. (2010) Prefrontal and hippocampal contributions to encoding and retrieval of spatial memory. *Neurobiol. Learn. Mem. 93* (3), 415−421.
(85) Sigurdsson, T., Stark, K. L., Karayiorgou, M., Gogos, J. A., and Gordon, J. A. (2010) Impaired hippocampal−prefrontal synchrony in a genetic mouse model of schizophrenia. *Nature 464* (7289), 763−767.
(86) Benchenane, K., Peyrache, A., Khamassi, M., Tierney, P. L., Gioanni, Y., Battaglia, F. P., and Wiener, S. I. (2010) Coherent theta oscillations and reorganization of spike timing in the hippocampal-prefrontal network upon learning. *Neuron 66*, 921−936.
(87) Wang, R. Y., and Aghajanian, G. K. (1982) Correlative firing patterns of serotonergic neurons in rat dorsal raphe nucleus. *J. Neurosci. 2* (1), 11−16.
(88) Wang, D.-H., and Wong-Lin, K. (2013) Comodulation of dopamine and serotonin on prefrontal cortical rhythms: a theoretical study. *Front. Integr. Neurosci. 7*, 54.
(89) Başar, E., and Güntekin, B. (2013) Review of delta, theta, alpha, beta, and gamma response oscillations in neuropsychiatric disorders. *Electroencephalogr. Clin. Neurophysiol., Suppl. 62*, 303−341.
(90) Basar-Eroglu, C., Schmiedt-Fehr, C., Marbach, S., Brand, A., and Mathes, B. (2008) Altered oscillatory alpha and theta networks in schizophrenia. *Brain Res. 1235*, 143−152.
(91) Liu, T. Y., Hsieh, J. C., Chen, Y. S., Tu, P. C., Su, T. P., and Chen, L. F. (2012) Different patterns of abnormal gamma oscillatory activity in unipolar and bipolar disorder patients during an implicit emotion task. *Neuropsychologia 50* (7), 1514−1520.
(92) Uhlhaas, P. J., and Singer, W. (2010) Abnormal neural oscillations and synchrony in schizophrenia. *Nat. Rev. Neurosci. 11* (2), 100−113.
(93) Cho, R. Y., Konecky, R. O., and Carter, C. S. (2006) Impairments in frontal cortical gamma synchrony and cognitive control in schizophrenia. *Proc. Natl. Acad. Sci. U.S.A. 103* (52), 19878−19883.
(94) Hoffmann, R., Hendrickse, W., Rush, A. J., and Armitage, R. (2000) Slow-wave activity during non-REM sleep in men with schizophrenia and major depressive disorders. *Psychiatry Res. 95* (3), 215−225.
(95) Spencer, K. M., Nestor, P. G., Niznikiewicz, M. A., Salisbury, D. F., Shenton, M. E., and McCarley, R. W. (2003) Abnormal neural synchrony in schizophrenia. *J. Neurosci. 23* (19), 7407−7411.
(96) Meltzer, H., and Massey, B. (2011) The role of serotonin receptors in the action of atypical antipsychotic drugs. *Curr. Opin. Pharmacol. 11* (1), 59−67.
(97) Celada, P., Puig, M. V., Díaz-Mataix, L., and Artigas, F. (2008) The hallucinogen DOI reduces low-frequency oscillations in rat prefrontal cortex: reversal by antipsychotic drugs. *Biol. Psychiatry 64* (5), 392−400.
(98) Riga, M. S., Soria, G., Tudela, R., Artigas, F., and Celada, P. (2014) The natural hallucinogen 5-MeO-DMT, component of Ayahuasca, disrupts cortical function in rats: reversal by antipsychotic drugs. *Int. J. Neuropsychopharmacol. 17* (8), 1269−1282.
(99) Schulz, S. B., Heidmann, K. E., Mike, A., Klaft, Z.-J., Heinemann, U., and Gerevich, Z. (2012) First and second generation antipsychotics influence hippocampal gamma oscillations by interactions with 5-HT3 and D3 receptors. *Br. J. Pharmacol. 167* (7), 1480−1491.
(100) Anderson, P. M., Pinault, D., O'Brien, T. J., and Jones, N. C. (2014) Chronic administration of antipsychotics attenuates ongoing and ketamine-induced increases in cortical γ oscillations. *Int. J. Neuropsychopharmacol. 17* (11), 1895−1904.
(101) Hashimoto, K., Fujita, Y., Shimizu, E., and Iyo, M. (2005) Phencyclidine-induced cognitive deficits in mice are improved by subsequent subchronic administration of clozapine, but not haloperidol. *Eur. J. Pharmacol. 519* (1−2), 114−117.
(102) Grayson, B., Idris, N. F., and Neill, J. C. (2007) Atypical antipsychotics attenuate a sub-chronic PCP-induced cognitive deficit in the novel object recognition task in the rat. *Behav. Brain Res. 184* (1), 31−38.
(103) Meltzer, H. Y., Horiguchi, M., and Massey, B. W. (2011) The role of serotonin in the NMDA receptor antagonist models of psychosis and cognitive impairment. *Psychopharmacology 213* (2−3), 289−305.
(104) Horiguchi, M., and Meltzer, H. Y. (2012) The role of 5-HT1A receptors in phencyclidine (PCP)-induced novel object recognition (NOR) deficit in rats. *Psychopharmacology 221* (2), 205−215.
(105) Kargieman, L., Santana, N., Mengod, G., Celada, P., and Artigas, F. (2007) Antipsychotic drugs reverse the disruption in prefrontal cortex function produced by NMDA receptor blockade with phencyclidine. *Proc. Natl. Acad. Sci. U.S.A. 104* (37), 14843−14848.
(106) Kargieman, L., Riga, M. S., Artigas, F., and Celada, P. (2012) Clozapine reverses Phencyclidine-induced desynchronization of prefrontal cortex through a 5-HT(1A) receptor-dependent mechanism. *Neuropsychopharmacology 37* (3), 723−733.
(107) Jodo, E., Suzuki, Y., Katayama, T., Hoshino, K.-Y., Takeuchi, S., Niwa, S.-I., and Kayama, Y. (2005) Activation of medial prefrontal cortex by phencyclidine is mediated via a hippocampo-prefrontal pathway. *Cereb. Cortex 15* (5), 663−669.
(108) Jodo, E. (2013) The role of the hippocampo-prefrontal cortex system in phencyclidine-induced psychosis: a model for schizophrenia. *J. Physiol. (Paris) 107* (6), 434−440.
(109) Bruder, G. E., Sedoruk, J. P., Stewart, J. W., McGrath, P. J., Quitkin, F. M., and Tenke, C. E. (2008) Electroencephalographic alpha measures predict therapeutic response to a selective serotonin reuptake inhibitor antidepressant: pre- and post-treatment findings. *Biol. Psychiatry 63* (12), 1171−1177.
(110) Jacobsen, J. P. R., Siesser, W. B., Sachs, B. D., Peterson, S., Cools, M. J., Setola, V., Folgering, J. H., Flik, G., and Caron, M. G. (2012) Deficient serotonin neurotransmission and depression-like serotonin biomarker alterations in tryptophan hydroxylase 2 (Tph2) loss-of-function mice. *Mol. Psychiatry 17* (7), 694−704.
(111) Dzirasa, K., Kumar, S., Sachs, B. D., Caron, M. G., and Nicolelis, M. A. (2013) Cortical−amygdalar circuit dysfunction in a genetic mouse model of serotonin deficiency. *J. Neurosci. 33* (10), 4505−4513.
(112) Narayanan, V., Heiming, R. S., Jansen, F., Lesting, J., Sachser, N., Pape, H.-C., and Seidenbecher, T. (2011) Social defeat: impact on

DOI: 10.1021/cn500350e
ACS Chem. Neurosci. 2015, 6, 1017−1025

fear extinction and amygdala-prefrontal cortical theta synchrony in 5-HTT deficient mice. *PloS One 6* (7), e22600.

DOI: 10.1021/cn500350e
ACS Chem. Neurosci. 2015, 6, 1017−1025