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Review

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Serotonergic Regulation of Prefrontal Cortical Circuitries Involved in Cognitive Processing: A Review of Individual 5-HT Receptor Mechanisms and Concerted Effects of 5-HT Receptors Exemplified by the Multimodal Antidepressant Vortioxetine

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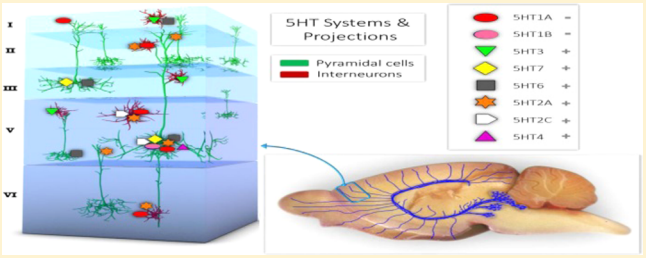
ABSTRACT: It has been known for several decades that serotonergic neurotransmission is a key regulator of cognitive function, mood, and sleep. Yet with the relatively recent discoveries of novel serotonin (5-HT) receptor subtypes, as well as an expanding knowledge of their expression level in certain brain regions and localization on certain cell types, their involvement in cognitive processes is still emerging. Of particular interest are cognitive processes impacted in neuropsychiatric and neurodegenerative disorders. The prefrontal cortex (PFC) is critical to normal cognitive processes, including attention, impulsivity, planning, decision-making, working memory, and learning or recall of learned memories. Furthermore, serotonergic dysregulation within the PFC is implicated in many neuropsychiatric disorders associated with prominent symptoms of cognitive dysfunction. Thus, it is important to better understand the overall makeup of serotonergic receptors in the PFC and on which cell types these receptors mediate their actions. In this Review, we focus on 5-HT receptor expression patterns within the PFC and how they influence cognitive behavior and neurotransmission. We further discuss the net effects of vortioxetine, an antidepressant acting through multiple serotonergic targets given the recent findings that vortioxetine improves cognition by modulating multiple neurotransmitter systems.



KEYWORDS: *Serotonin, receptor expression, frontal cortex, cognition, neurochemistry, cortical microcircuits*

THE SEROTONERGIC SYSTEM AND COGNITIVE FUNCTION

A number of psychiatric diseases prominently feature impairment in cognitive functions, thus understanding the neurophysiological processes that modulate the activity of neural assemblies within brain structures known to regulate cognition is an important step in the development of novel therapeutic strategies aimed at remediating these dysfunctions. Serotonergic neurotransmission is one such neurophysiological process, and importantly, dysregulation of serotonergic neurotransmission is implicated in major depressive disorder, schizophrenia, obsessive compulsive disorder,[1] as well as Alzheimer's, Huntington's, and Parkinson's diseases.[2,3]

Similar to the cholinergic system (see ref 4), the serotoninergic system plays a critical role in the functioning of many neuronal circuits involved in cognitive processing and mediates its net effect via both inhibitory and stimulatory activities. For example, γ-aminobutyric acid (GABAergic) and glutamatergic synaptic inputs in the cortex are modulated by different 5-HT receptor subtypes with distinct properties and can have opposing effects within a single brain system or local synapse. Moreover, the heterogeneity of cortical pyramidal neurons, interneurons, and 5-HT receptor subtype expression must be considered when assessing the overall action of serotonin. 5-HT receptors are expressed on both excitatory neurons and inhibitory interneurons and function in either a stimulatory or inhibitory manner depending on cell type or brain localization of a given cell (see Table 1), thereby rendering the net outcome of the neuromodulatory action of 5-HT on cortical microcircuitry dependent on the local 5-HT concentration, which receptors are expressed, the ratio of their expression to other subtypes, and the location of each receptor subtype on a cell (e.g., presynaptic autoreceptor or postsynaptic) and on which cell type.[5−8] Specifically, as outlined in Table 1 and discussed in greater detail below, the 5-HT_1 receptor family is inhibitory and signals via $G_{i/o}$ inhibition of adenylyl cyclase (decreasing cyclic adenosine monophosphate (cAMP)) but is also coupled to G-protein-coupled inwardly rectifying potassium channels (GIRKs). In addition, 5-HT_{1A} receptors inhibit voltage-gated Ca^{2+} channels of the N-and P/Q-type in 5-HT neurons.[9] The 5-HT_2 receptor family is stimulatory and signals via G-protein subunit Gq activation of phospholipase C (increasing the levels of inositol triphosphate and diacylglycerol). 5-HT_3 receptors open a nonselective Na^+/

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Table 1. Overview of Expression Pattern of 5-HT Receptor Subtypes in the Prefrontal Cortex[a]

		expression			
receptor	function	mRNA (layer)	protein (layer)	cell type	reference
5-HT_{1A}	I	++ (V, VI[b])	++ (V, VI[b])	Pyr, IN (PV+), IN (calbin+)	33, 53, 55
5-HT_{1B}	I	?	+ (?)	?	62
5-HT_{1D}	I	–	–	–	65, 66
5-HT_{2A}	S	+++ (III, V)	+++ (II, III, V) ++ (I, VI)	Pyr, IN	34, 53, 73
5-HT_{2C}	S	+ (V)	+	Pyr, IN (PV+)	34, 75–77
5-HT_3	S	++ (I–III)	++	IN (calbin+, calre+, CCK+)	88, 86, 87
5-HT_4	S	?	+ (?)	?	95
5-HT_5	I	?	++	?	102
5-HT_6	S	?	+ (I,III)	Pyr (III), Ast (I)	104
5-HT_7	S	++ (I–III, V)	+++ (I–III) ++ (V)	? Pyr (V)	127

[a]I, inhibitory; S, stimulatory; –, absent; +, low; ++, moderate; +++, strong; ?, unknown; Pyr, pyramidal; IN, interneuron; P, parvalbumin; calbin, calbindin; calre, calretinin; Ast, astrocyte. [b]Also in more shallow layers.

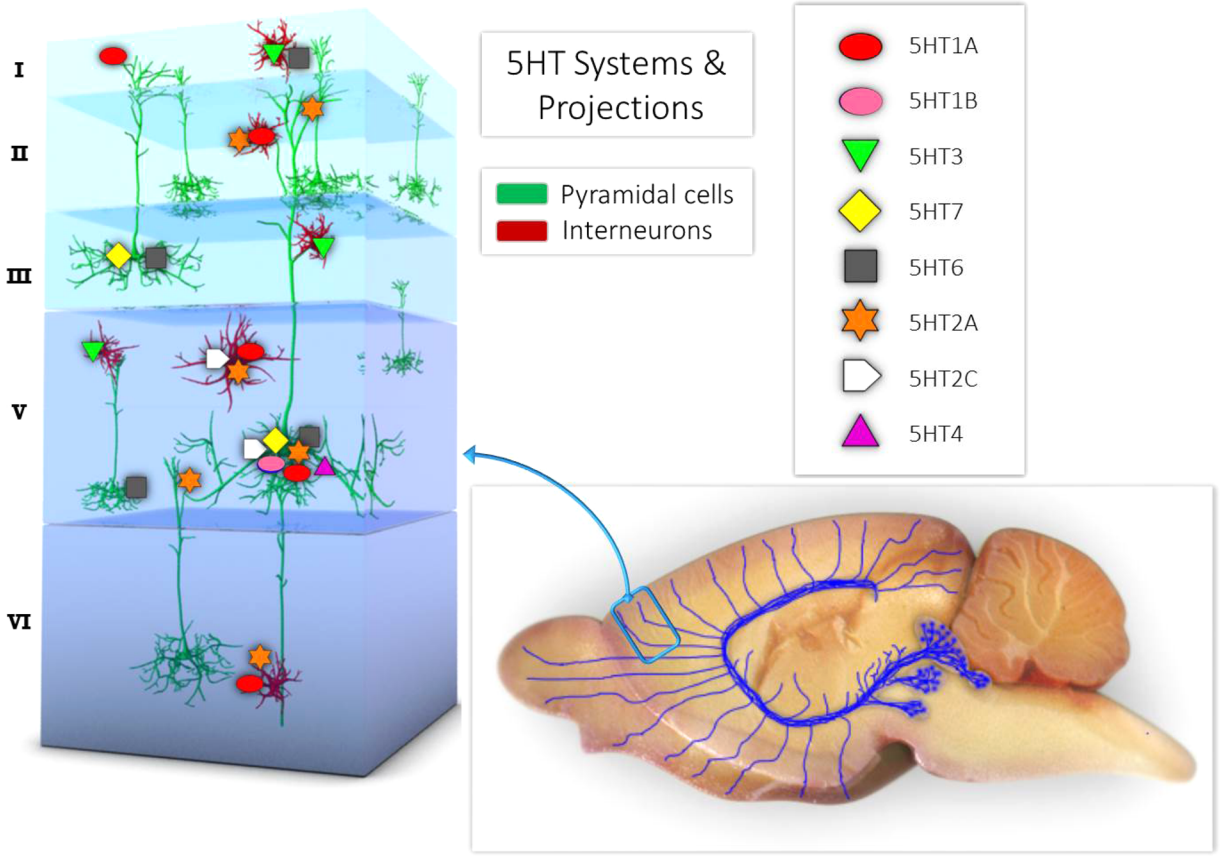

Figure 1. MRNAs for 5-HT_1 (5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}), 5-HT_2 (5-HT_{2A}, 5-HT_{2C}), 5-HT_3, and 5-HT_7 receptors have been detected in PFC tissue (Table 1) and 5-HT_{1A}, 5-HT_{1B}, 5-HT_{2A}, 5-HT_{2C}, and 5-HT_4 receptors are coexpressed on the same pyramidal neuron.[76] As illustrated in Figure 1 and in Table 1, layer I contains 5-HT_{1A} and 5-HT_6 receptors on apical dendrites of cortical pyramidal neurons, 5-HT_{3A} and 5-HT_6 receptors on somata of slow-spiking GABAergic interneurons;[2,103,104] layers II–III contain 5-HT_{2A}, 5-HT_6, and 5-HT_7 receptors on somata of small pyramidal neurons, 5-HT_{1A} and 5-HT_{2A} receptors on somata of fast-spiking parvalbumin-expressing GABAergic interneurons,[2] 5-HT_{3A} receptors on somata of slow-spiking interneurons,[2,88] and 5-HT_{1D} and 5-HT_{1D} receptors;[65,231] layers V–VI contain 5-HT_{2A} and 5-HT_6 receptors on apical dendrites of cortical pyramidal neurons,[2,103] 5-HT_{1A}, 5-HT_{1B}, 5-HT_{2A}, 5-HT_{2C}, 5-HT_4, 5-HT_6, and 5-HT_7 receptors on somata of large pyramidal neurons,[53,76,103,104,127,232] 5-HT_{1A} receptors on initial axon segment of pyramidal neurons,[2] 5-HT_{3A} receptors on non-PV interneurons (e.g., cholecystokinin),[88] 5-HT_{1A}, 5-HT_{2A}, and 5-HT_{2c} receptors on somata of fast-spiking parvalbumin-expressing GABAergic interneurons,[2,77] and 5-HT_{1D} receptors.[65,231]

K^+ ion channel, while 5-HT_4, 5-HT_6, and 5-HT_7 receptors signal via activation of adenylyl cyclase (increasing cAMP levels) and all are stimulatory. The 5-HT_5 receptors, which are coupled to $G_{i/o}$ and GIRKs, suppress adenylyl cyclase and are inhibitory.[10,11]

Serotonergic projection neurons from the dorsal raphe nucleus (DRN) innervate extensive regions of the forebrain

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Table 2. Effects of Various Serotonergic Manipulations on the Outcome of Cortical Dependent Cognitive Tests in Rodent Models[a]

mechanism	species	attention	impulsivity	flexibility	learning	memory
5-HT ↑						
PCA (acute)	rat	÷ RI[145]	÷ RI[145]			
SSRIs	rat	÷ 5-CSRTT[146] RI[145]	↓ 5-CSRTT[146] RI[145]	÷ RL[131] ↓/÷ AS[147−149] Ø stress-induced AS deficits[147−149]		↑ AUTO[150]
5-HT ↓						
tryptophan depletion	rat			÷ RL[151]	÷ RL[151]	
5,7-DHT	rat	÷ 5-CSRTT[152−154]	↑ 5-CSRTT[152−154]			
pCPA	rat					÷ PA[155] ↓ OR[140]
PCA (1 week)	rat					÷ AUTO[156]
5-HT$_{1A}$ receptor agonists						
8-OH-DPAT	rat	↓↑÷ 5-CSRTT[154,157,158] ↑RI[145] Ø CPP deficits in 5-CSRTT[158]	↑÷ 5-CSRTT[154,157,158] ÷ RT;[159] ↓ DD[160] ÷ RI[145] ↑ FCN[161] ↑DRL[162]	↑ AUTO[163]	↑ AUTO[164,165]	↓↑ PA[155,166] ↓ OR[167] ↑ AUTO[156] Ø Scop AUTO deficits[156]
NDO008	rat					↓ PA[155]
S15535	rat	↑ DNMS-S[168]				↑ SR[168]
S15535	mouse	↑ DNMS-S[168]				
Flesinoxan	rat					Ø pCPA OR deficits[140]
5-HT$_{1A}$ receptor antagonists						
WAY100635	rat	÷ 5-CSRTT[154,157,158] ÷ RI[145]	÷5-CSRTT[154,157,158] ÷ RI[145] ÷ DD[160] ↓ FCN[161]		÷ AUTO[125,165]	÷ AUTO[156]
NAN190	rat					÷ PA;[166] ÷ AUTO[150]
UH301	rat					÷ AUTO[156]
5-HT$_{1A}$ KO	mouse		÷ DRL[169]	÷ RL[169]	÷ AUTO[169]	
5-HT$_{1B}$ receptor antagonists						
GR127935 (5-HT$_{1B/1D}$)	rat				↑ AUTO[170]	
5-HT$_{1B}$ KO	mouse		↑ DRL[169]	÷ RL[169]	↑ AUTO[169]	
5-HT$_2$ receptor agonists						
DOI	rat	÷ 5-CSRTT[171−173] ÷ RI[145]	↑÷ 5-CSRTT[171−173] ↑RT[159] ÷ RI[145] ÷ DD[160]			
DOB	rat					↓ PA[155]
5-HT$_2$ receptor antagonists						
Ritanserin	rat	÷5-CSRTT[171] ÷ RI[145]	÷ 5-CSRTT[171] ÷ RI[145]		÷ AUTO[165]	÷ AUTO[150]
Ketanserin	rat	÷ 5-CSRTT[173−175]	↓÷ 5-CSRTT[171,174,175]			÷ DNMS-S[174] ÷ AUTO[150]
Methylsergide	rat	↓ 5-CSRTT[174]	↓ 5-CSRTT[173,174] ÷ DD[160]		÷ AUTO[165]	÷ DNMS-S[174]
SER082	rat		÷5-CSRTT[171]			
5-HT$_{2A}$ receptor antagonists						
M100907	rat	÷↑↓ 5-CSRTT[153,158,173,176−178,157] Ø CPP deficit in 5-CSRTT[158,176,178]	↓÷5-CSRTT[153,157,158,173,176] Ø CPP- or MK-801 deficit in 5-CSRTT[158,176−178]	↓÷ RL[149,179,180]	÷RL[179]	÷ AUTO[156]
M100907	mouse	÷ 5-CSRTT[173,181] Ø CPP deficit in 5-CSRTT[181]	↓÷ 5-CSRTT[173,181] Ø CPP-deficit in 5-CSRTT[181]			
MDL11939	rat					↓÷ OR[167]
5-HT$_{2C}$ receptor antagonists						
SB242084	rat	↓÷ 5-CSRTT[153,173,177]	↑ 5-CSRTT[153,173,177] ↓ SSRT[182]	↑ RL[179,180]	÷ RL[179]	÷ OR[167]
SB242084	mouse	↓ 5-CSRTT[173]	↑ 5-CSRTT[173]			

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Table 2. continued

mechanism	species	attention	impulsivity	flexibility	learning	memory
5-HT$_3$ receptor antagonists						
Ondansetron	rat	÷ 5-CSRTT[183]	÷ 5-CSRTT[183] Ø AMPA-induced deficit in 5-CSRTT[183]		÷ AUTO[165]	Ø pCPA OR deficits[140]
Granisetron	rat			↑ FC[184]		
MDL72222	rat	÷ RI[145]	↓ RI[145]			÷ AUTO[150]
5-HT$_6$ receptor agonists						
EMD386088	rat			↑ AS[185] Ø ketamine deficit in AS[185]		÷ FC[186] Ø Scop and MK801 deficit in FC[186] and ketamine deficit in OR[185]
E6801	rat					÷ FC[186] Ø Scop and MK801 induced deficit in FC[186]
WAY181187	rat			↑ AS[187]		
5-HT$_6$ receptor antagonists						
SB399885	rat			↑ ÷AS[187,188]		↑ AUTO[164] and OR[117] Ø Scop or MK801 deficit in AUTO[164] Scop induced deficit in OR[117]
SB357134	rat					↑ AUTO[46] Ø SCOP or MK801 deficit[46]
SB271046	rat			↑ AS[188] Ø PCP deficit in AS[189]		↑ OR;[190] FC[186] Ø SCOP or MK801 deficit in FC[186]
Ro046790	rat				↑ AUTO[165]	÷↑ OR[105,190] Ø Scop deficit in OR[105]
Idalopirdine	rat					Ø PCP deficits in OR[120]
5-HT$_7$ receptor agonists						
AS19	rat			÷ AS[191]	↑ AUTO[125]	
5-HT$_7$ receptor antagonists						
SB269970	rat			↑ AS[131,192] Ø stress or ketamine deficit in AS[131,192]	÷ AUTO[125]	÷ OR[192] Ø ketamine deficit in OR[192]

[a]ago, agonist; ant, antagonist; ÷, no effect; ↑, increase/improve; ↓, decrease/impair; Ø, prevented/blocked deficits; RI, reflection-impulsivity test; RL, reversal learning; AS, attentional set-shifting; 5-CSRTT, 5-choice serial reaction time task; AUTO, autoshaping; FC, fear conditioning; NOR, novel object recognition; 4-CSRTT, 4-choice serial reaction time task; SDR, serial discrimination reversal learning; PA, passive avoidance; RT, reaction time task; DD, delayed discounting; OR, object recognition; RA, repeated acquisition task; OT, object tracking task; WCS, Wisconsin card sorting; WMS-V, Wechsler memory scale-revised verbal memory composite; DNMS-S, delayed nonmatching to sample-spatial; SR, social recognition; DSST, digit symbol substitution test; DRL, differential reinforcement of low rate; ADAS-cog, Alzheimer's Disease Assessment Scale-cognitive subscale; ST, subject tracking; SSRT, stop signal reaction time task; SA, spontaneous alternation; DRL, differential-reinforcement-of-low-rate; FCN, fixed-consecutive number.

neocortex, as well as the nucleus accumbens and striatum,[5,12] supplying these areas necessary for higher cognitive functions with serotonin (5-HT) (Figure 1). Of particular interest for serotonergic regulation of cognitive function are the serotonergic pathways to the prefrontal cortex (PFC), given that this area is critical for complex cognitive behavior, including working memory, attention, and decision-making.[13,14]

Here we review the literature and discuss the current understanding of serotonergic regulation of cognitive processes in the PFC from an anatomical, 5-HT receptor expression pattern, physiological, pharmacological, neurochemical, and behavioral perspective. Our Review relies to a large extent on empirical data obtained from studies in rodents. To a lesser extent but where it is possible, these data will be discussed in the context of what is known from studies in humans. Also, we focus this Review on those cognitive processes less dependent upon emotions. For serotonergic regulation of cognitive processes that are more emotion-laden (e.g., affective or "hot" cognition) and impaired in many neuropsychiatric disorders, please refer to other publications.[15−18]

THE PREFRONTAL CORTEX (PFC) AND COGNITIVE FUNCTIONS

As mentioned, the PFC is important for regulation of complex cognitive functions. Executive functioning requires participation and coordination of activity between diffuse anatomical and functional brain areas, with appropriate afferent input to the frontal lobes, particularly the PFC, so this region may participate to a greater extent than other areas of the brain in functions considered to be "executive".[13,19−22] In example, highly selective focus on task-relevant information dictated by the prefrontal cortex supports the episodic processing or binding of task/object-related information in other systems, including those concerned with the description of sensory inputs, the generation of motor commands, the representation of long-term or semantic knowledge, and the assessment of motivational significance.[23,24] Moreover, the PFC coordinates functions associated with several higher order cognitive tasks such as rule-based and goal-directed behavior, decision-making, working memory, reward seeking, reversal learning, sensory discrimination, behavioral flexibility, sustained attention, and

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Table 3. Neurochemical changes induced by modulation of 5-HT receptor subtype action[a]

mechanism	5-HT	ACh	DA	NA	HA
5-HT ↑					
5-HT			↑[50]		
PCA (acute)	↑[193]	↑[194]	↑[193]		
SSRIs:					
fluoxetine	↑[195]		↑[195,196]		
citalopram	↑[197]				
5-HT ↓					
5,7-DHT	↓[198]	÷[198]			
pCPA	↓[195]	Ø[194]	÷[195]		
5-HT$_{1A}$ receptor agonists					
8-OH-DPAT	÷[199−201]	↑[202]	↑[196,201]	↑[201]	
F13640	↓[59]		↑[59]		
MM5	↓[200]		÷[200]		
MC1	↓[200]		↓[200]		
Flesinoxan	↓[203,204]		↑[204]	↓,[205] ↑[204]	
5-HT$_{1A}$ receptor antagonists					
WAY100635	÷,[199] ↑[206]		Ø,[59] ↑[206]		
NAN190			↓[207]		
UH301	↑[197]				
5-HT$_{1A}$ KO			↓[208]		
5-HT$_{1B}$ receptor agonists					
CP93129	↓[209−211]	↑[212]	↑[50]		
CP94253	↓[213]		↑[50]		
5-HT$_{1B}$ receptor antagonists					
GR127935 (5-HT$_{1B/1D}$)	÷,[214] ↑[210]		Ø[50]		
5-HT$_{1B}$ KO	↑[209]				
5-HT$_2$ receptor agonists					
DOI (5-HT$_{2A/2C}$)	↑[215]	↑[216]	↑[215]	↑[215]	
5-HT$_2$ antagonists					
Ritanserin			↑[217]		
5-HT$_{2A}$ receptor antagonists					
M100907	↓[215]		↓,[215] ↑[218]	↓[215]	÷[219]
5-HT$_{2C}$ receptor antagonists					
SB242084	÷[204]		↑[218,204]	↑[204]	÷[219]
5-HT$_3$ receptor agonists					
NMQ			↑[220]		
m-CPBG		Ø[221]			
5-HT$_3$ receptor antagonists					
Ondansetron		↑[222]	↓[220]		
MDL72222			÷[50]		
BRL46470A			↓[220]		
5-HT$_4$ receptor agonists					
prucalopride		↑[96]			↑[96]
PRX-03140		÷[96]			↑[96]
5-HT$_4$ receptor antagonists					
SDZ 205−557		Ø[223]			
RS23597		Ø[194,224]			
GR113803		Ø[194,224]			
5-HT$_6$ receptor agonists					
WAY181187	↓[111]	↓[111]		÷[111]	
5-HT$_6$ receptor antagonists					
SB271046	↑,[218] ÷[225]		÷[225]	÷[225]	
Ro046790					÷[219]
5-HT$_7$ receptor antagonists					
SB269970	↓,[130] ↑[226]		↑[226]	↑[226]	
multiple 5-HT receptor actions					
Vilazodone (SSRI + 5-HT$_{1A}$ ant)	↑[227,201]		÷[201]	÷[201]	
Flibanserin (5-HT$_{1A}$ ago +5-HT$_{2A}$ ant)	↓[228]		↑[228]	↑[228]	
Vortioxetine (5-HT$_{3,7,1D}$ ant + 5-HT$_{1B}$ partial ago + 5-HT$_{1A}$ ago + SERT inhibitor)	↑[229]	↑[230]	↑[229]	↑[229]	↑[230]

[a]÷, no effect; ↑, increase/improve; ↓, decrease/impair; Ø, prevented/blocked pharmacological-increases.

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behavioral impulse control and regulation (see[21]). Furthermore, the PFC is uniquely able to handle information that represents, selects, maintains, and coordinates cognitive thoughts and behavioral goals and can perform computations related to executive control within its own microcircuits.[3,25−28]

As Puig and colleagues[2,29] have defined, layer I contains apical dendrites of cortical pyramidal neurons, axons from local and long-distance cortical and subcortical inputs, and somata of several types of slow-spiking GABAergic interneurons that provide feed-forward inhibition onto pyramidal neuron dendrites. Layers II and III contain the somata of small pyramidal neurons and several types of interneurons, including both slow- and fast-spiking interneurons. Layer IV is not defined in the rat PFC. Layers V and VI contain the somata of large pyramidal neurons and several interneuron subtypes, but mostly parvalbumin fast-spiking interneurons (see Figure 1). The PFC has a modular minicolumnar architecture with interlaminar microcircuits (Figure 1) wherein aggregates of neurons with afferent and efferent connections from many brain regions converge.[3] Sensory-to-motor integration is performed in supragranular layers (II−III), whereas the output of the infragranular layers (V−VI) provides selection-related signals, which are sent back to the infragranular layers and the other areas comprising the network, forming interlaminar loops.[27] Within these loops, the activity of projection (pyramidal) neurons in the PFC depends on glutamatergic inputs from cortical and subcortical areas and is locally modulated by GABA interneurons.[30] Furthermore, catecholaminergic and serotonergic axons innervate the PFC and modulate neuronal activity through various inhibitory and excitatory receptors throughout the laminar organization of the cortex.[8,21,31−39]

SEROTONERGIC REGULATION OF CORTICAL CIRCUITS IN THE PFC AND ITS IMPACT ON COGNITIVE FUNCTION

5-HT is predicted to exert complex effects on cortical circuits, which depends on local endogenous 5-HT tone, 5-HT receptor subtype expression, and the cognitive task in question. In studies with healthy subjects or depressed patients, lowering the endogenous 5-HT tone through depletion of the 5-HT precursor tryptophan (i.e., acute trytophan depletion or ATD) had a generally neutral (no effect) effect and in a few instances a negative effect on cognitive function in humans, that is, memory consolidation (reviewed in refs 40 and 41). Lowering of endogenous 5-HT tone generally had no effect in rodents except (depending on test conditions) a negative effect on episodic memory (Table 2). Furthermore, both in humans[42] and rodents, lowering of 5-HT tone consistently increased impulsive behavior. Likewise, the overall effects of increasing 5-HT tone by treatment with a selective serotnin reuptake inhibitor (SSRI) were limited in humans.[40] Studies in rodents have consistently shown that SSRIs reverse the stress-induced deficits in cognitive flexibility and decreased impulsive behavior, but otherwise have limited effects (Table 2). The overall observation that 5-HT is "cognition neutral" likely reflects a net effect of oppositely directed effects on cognitive function mediated by the 5-HT receptor subtypes below. This is discussed in context of each receptor subtype below.

The serotonergic system interacts heavily with the other neuromodulatory systems such as acetylcholine (ACh), dopamine (DA), and noradrenaline (NA).[14,43,44] For example, serotonergic and cholinergic interactions play an important role in mediating cognitive behaviors,[45] 5-HT- and DA-mediated modulatory activity influences a wide variety of cerebral functions instrumental to cognition,[46] including learning and memory[47,48] and decision-making.[49] Table 3 reviews the impact of 5-HT receptor action on neurochemical release in the PFC. In general, elevated 5-HT in the PFC, whether effected through SSRIs or other means, will also result in elevated DA.[50] Typically, 5-HT_{1A} and 5-HT_{1B} receptor agonism will decrease 5-HT and increase DA and ACh release, while 5-HT_{1A} and 5-HT_{1B} receptor antagonism will increase 5-HT and may decrease DA levels (see Table 3). Reviewing 5-$HT_{2A/2C}$ receptor action has yielded inconsistent findings as to whether it increased or decreased 5-HT and/or DA. 5-HT_3 receptor agonism appears to increase DA, while antagonism decreases DA but also increases ACh levels. 5-HT_4 receptor agonism increases ACh and antagonism blocks the induction of ACh by 5-HT_4 receptor agonists or 3,4-methylenedioxy-methamphetamine (MDMA). 5-HT_4 agonism also increases histamine (HA) levels. 5-HT_6 receptor agonism decreases while antagonism increases 5-HT. 5-HT_7 receptor action has variable effect on 5-HT and seems to elevate DA and NA levels. Overall the data are incomplete; however, it is clear that the diverse expression pattern of 5-HT receptors in the PFC is primed to maintain a proper balance of excitation and inhibition in response to incoming stimuli (afferent information) by modulating multiple neurotransmitter systems implicated in cognition. The balance of hyperpolarizing and depolarizing currents is thought to effectively adjust the level of pyramidal neuron excitability, which can be modified not only by afferent input but also by receptor expression levels. This ability to modulate in both a stimulatory and an inhibitory manner is likely the key to rapidly adjusting neuronal responses to extreme changes in behavior.[51] A survey of the effects of 5-HT receptor selective compounds is presented in the following sections. Please note that it is important to point out that the receptor localization studies referenced below are mostly based on studies in rodents. Where possible, studies in human or primate are also cited. Also, it is important to mention that for most of the 5-HT receptors the lack of reliable antibody is a major impediment to understanding its cellular localization, although in situ hybridization is helpful in this regard.

5-HT_{1A} Receptors. 5-HT_{1A} receptors are inhibitory G-protein coupled receptors that hyperpolarize neuronal membranes by the downstream activation of inwardly rectifying K^+ channels.[52] Cells expressing mRNA for the 5-HT_{1A} receptor are scattered throughout the layers of the cortex, but its strongest expression has been noted in layers V and VI.[33] However, it should be noted that this pattern can differ between cortical subregions. For example, in the anterior cingulate cortex (ACC), expression was strongest in layers II and V.[33] Similar to the pattern of mRNA expression, binding to 5-HT_{1A} receptors using tritiated (±)-8-hydroxy-2-(*n*-dipropylamino)tetralin ([^{3}H]8-OH-DPAT) in the frontal cortex was strongest in layers V and VI, but was present at weaker levels in more shallow cortical layers.[33] On the basis of mRNA and protein colabeling studies, it has been demonstrated that 5-HT_{1A} receptors are present in a subpopulation of both GABAergic interneurons and glutamatergic principle cells in the frontal cortex.[53] Moreover, the proportion of these cells that express 5-HT_{1A} heteroreceptors varies extensively by cortical subregion. Speaking broadly, cortical GABAergic interneurons and pyramidal cells commonly express 5-HT_{1A} receptors;[54,55] however, in medial prefrontal cortex (mPFC) subregions

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such as the prelimbic (PL) and infralimbic (IL) cortex, only between 40 and 60% of pyramidal neurons and approximately 20% of interneurons express 5-HT_{1A} heteroreceptors.[53] For a more detailed description of 5-HT_{1A} receptor localization and function, the reader is pointed to Mengod and colleagues (e.g., refs 6, 31, 54, 56, and 57).

Given their hyperpolarizing influence on cellular membranes, it can be expected that 5-HT_{1A} receptor agonists such as 8-OH-DPAT or flesinoxan will inhibit the firing of cells expressing this receptor. Given that both principle cells and interneurons express 5-HT_{1A} receptors in mPFC regions such as the PL and IL cortex, it should be expected that activation of 5-HT_{1A} receptors will have a mix of excitatory and inhibitory influences on the output of these cortical regions. And indeed, electrophysiological evidence suggests that acute administration of 5-HT_{1A} receptor agonists leads to increases in pyramidal neuron firing that are thought to be the result of a disinhibition secondary to reducing interneuron firing.[58−61] However, the majority of frontal cortex pyramidal cells showed a mix of effects on their firing rate, for example an early increase in firing followed by inhibition,[61] which is likely to be related to 5-HT_{1A} receptor stimulation on pyramidal neurons.

In line with the oppositely directed functional responses to 5-HT_{1A} receptor stimulation, the effects of 5-HT_{1A} receptor selective ligands was highly variable within and across cognitive domains in preclinical studies (Table 2) as well as in clinical studies of selective 5-HT_{1A} receptor agonists.[40] In addition, differences in the administration route (systemic injections vs direct prefrontal cortex infusions), testing conditions (such as signal strength and length of intertrial intervals used in 5-choice serial reaction time task), and strain of animals used in different studies may have further complicated these reported outcomes in behavioral tasks, most notably in studies on 8-OH-DPAT. In contrast, 5-HT_{1A} receptor antagonists were cognitively neutral; that is, they did not affect cognitive function in any preclinical tests and similar findings were observed in 5-HT_{1A} receptor knockout mice (Table 2).

5-HT_{1B} and 5-HT_{1D} Receptors. 5-HT_{1B} receptors are G-protein coupled receptors that are related to $G_{i/o}$. 5-HT_{1B} receptor stimulation is negatively coupled to adenylyl cyclase activity and has an inhibitory influence on cellular activity. However, 5-HT_{1B} receptor functions have not been extensively studied in the frontal cortex. Autoradiographic and immunohistochemical evidence demonstrates that 5-HT_{1B} receptors are present in the frontal cortex at weak to moderate levels (for review, see ref 62), and on the basis of autoradiographic data seem to have a similar expression levels throughout the cortical layers (Pehrson, unpublished data). The cell types that express these receptors in the frontal cortex are not well understood at this time. On an ultrastructural level, 5-HT_{1B} receptors are generally thought to be expressed either presynaptically on serotonin terminals or as heteroreceptors on dendrites colocalized with AMPA or NMDA receptors.[62−64] However, these data on 5-HT_{1B} receptor localization were generated in other brain regions, and we have not been able to identify any studies that have investigated this topic specifically in the frontal cortex. 5-HT_{1B} receptors mediate 5-HT suppression of evoked fast excitatory postsynaptic current (EPSC) in layer V pyramidal neurons in response to nearby electrical stimulation of cortical afferents, and its activation typically results in hyperpolarization of pyramidal neurons but can also modulate release of DA, glutamate, GABA, and ACh. 5-HT_{1B} receptor activation reduces the amplitude of NMDA and non-NMDA components of synaptic potentials recorded intracellularly in layer V pyramidal neurons. Effects of 5-HT_{1B} receptor selective ligands on cognitive function have not been studied much, in part due to lack of selective compounds. However, it appears that 5-HT_{1B} receptor antagonism may have a positive effect on learning and memory consolidation (Table 2). To the best knowledge of the authors, no selective 5-HT_{1B} receptor ligands have been studied for effects on cognitive function in humans.

Anatomical studies of 5-HT_{1D} receptor mRNA and protein expression suggest there is little to no 5-HT_{1D} receptor expression in the frontal cortex.[65,66] Stimulation of 5-HT_{1D} receptors in the raphe nuclei decreases the amount of 5-HT released in cell body regions,[67,68] but does not appear to directly modulate the firing activity of neurons.[69] Furthermore, no 5-HT_{1D} selective ligands have been studied in tests of cognitive function.

5-HT_{2A} and 5-HT_{2C} Receptors. 5-HT_{2A} and 5-HT_{2C} receptors are G-protein coupled receptors that have a depolarizing effect on neuronal membranes by increasing intracellular Ca^{2+} (thereby increasing spontaneous EPSCs) and inositol phosphate concentrations secondary to its coupling to $G_{q/11}$.[70,71] In the frontal cortex, 5-HT_{2A} receptor mRNA is strongly expressed in layers III and V, with a weaker expression found in layer VI (for reviews, see refs 53 and 72). Consistent with a postsynaptic expression pattern, immunohistochemical localization of 5-HT_{2A} receptors follows a pattern very similar to that of its mRNA expression, with high levels in cortical layers III and V,[73,74] although it seems that 5-HT_{2A} receptors are expressed at some level in all cortical layers.[73] mRNA colocalization studies examining 5-HT_{2A} receptor mRNA along with mRNA for vesicular glutamate transporter 1 (vGluT1) or glutamic acid decarboxylase (GAD) (probes labeling pyramidal and interneurons, respectively) suggest that 5-HT_{2A} receptors are expressed in both pyramidal cells and interneurons in frontal cortical regions, although the level of expression varies based on subcortical regions.[53] Celada and colleagues suggested that, in regions such as the PL and ACC, approximately 50−60% of pyramidal neurons express 5-HT_{2A} receptors, while a much smaller proportion express 5-HT_{2A} receptors in the ventral portions of the IL cortex. Additionally, these authors demonstrated that only about 20% of interneurons express 5-HT_{2A} receptors in the frontal cortex.[53] Thus, as observed for 5-HT_{1A} receptors, 5-HT_{2A} receptor stimulation can be expected to have mixed effects on neuronal firing in the frontal cortex, with some excitation due to local effects on pyramidal neurons as well as inhibition due to stimulation of GABAergic subpopulations.

5-HT_{2C} receptor mRNA and proteins are thought to be expressed in the frontal cortex, although the intensity of their expression is relatively weak.[34,75] 5-HT_{2C} receptor mRNA expression is strongest in layer V,[34] and in this region 5-HT_{2C} receptors are thought to be expressed in a subset of pyramidal neurons and fast-spiking interneurons.[76,77] Moreover, 5-HT_{2C} receptor mRNA and protein expression are generally thought to be similar, which is consistent with the idea that 5-HT_{2C} receptors are expressed postsynaptically as heteroreceptors.[78]

Although our specific understanding of the effect of 5-$HT_{2A/2C}$ receptors on frontal cortex activity is limited by the availability of selective and brain-penetrating agonists, the available data suggest that 5-$HT_{2A/2C}$ receptor stimulation using DOI leads to an overall activation of population spikes in the frontal cortex,[79] although the effects of this agonist on firing in

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other frontal cortex regions such as the orbitofrontal cortex and ACC have a primarily inhibitory effect.[80−83]

Interestingly, chronic administration of 5-HT_{2A} receptor antagonists was reported to downregulate 5-HT_{2A} receptors,[84] which would change the overall effect of 5-HT in PFC. Whereas 5-HT_2 receptor agonists or antagonists overall have limited effects in attention test, selective 5-HT_{2A} receptor antagonists have variable effects on attention and impulsivity, with some studies showing no effects, inhibitory or stimulatory effects on attention and impulsivity. Similarly, 5-HT_{2C} receptor antagonists either show no effect on or impair attention, while at the same time increasing impulsive behavior in 5-choice serial reaction time task (Table 2). The fact that this antagonist reduced impulsivity in stop-signal reaction task may reflect the difference in the underlying neurocircuitry for these different tasks. Interestingly, in spite of the variable effects of the selective 5-HT_{2A} receptor antagonist M100907 on its own, it was found consistently to counteract attention and impulsivity deficits induced by the NMDA receptor antagonist CPP (Table 2). 5-HT_{2A} receptor antagonism had variable effect in tests of cognitive flexibility, whereas 5-HT_{2C} receptor antagonism seemed to improve this measure. Overall, 5-HT_2 receptor modulation appeared to produce limited effects in learning and memory tests in rodents. Similarly, 5-HT_2 receptor antagonism appears to have little effect on cognitive function in humans.[40]

5-HT_3 Receptors. 5-HT_3 receptors are the only known serotonergic receptors that are not G-protein coupled and exist as excitatory ligand-gated ion channels. In the frontal cortex, 5-HT_3 receptor mRNA has its strongest expression in layers I−III,[85,86] although it appears to be present at low levels in deeper cortical layers. Assessments of protein expression using immunohistochemistry or autoradiography show a similar although more diffuse anatomical expression pattern that is distributed throughout the cortical lamina[87] (Pehrson, unpublished data), suggesting that 5-HT_3 receptors are postsynaptically expressed. Studies attempting to assess which type of cells express 5-HT_3 receptors in the frontal cortex suggest that they are exclusively expressed on GABAergic interneurons,[86] and more specifically on interneurons expressing cholecystokinin, or the calcium binding proteins calbindin or calretinin.[86,88]

Based on this pattern of expression, 5-HT_3 receptors in the frontal cortex can be conceived of as a selective mechanism for 5-HT-mediated fast excitatory drive in cortical GABAergic interneurons. Consistent with this theoretical framework, pharmacological activation of 5-HT_3 receptors suppresses the overall activation state of cortical pyramidal neurons.[89,90] Conversely, 5-HT_3 receptor antagonists inhibit the activity of cortical interneurons[86] and increase the activity level of cortical pyramidal neurons.[91] Studies in rodents of 5-HT_3 receptor selective antagonist activity on cognitive function showed limited and variable effects depending on the behavioral task, but it may have some positive effects on memory in rodents and man,[40] (Table 2). Moreover, these limited effects may in part be explained by the poor CNS penetration of 5-HT_3 receptor antagonists such as ondansetron.[92]

5-HT_4 Receptors. 5-HT_4 receptors are G-protein coupled receptors that have stimulatory effects on cellular activation states through increases in the activity of adenylyl cyclase and cAMP, mediated via an association with Gs.[93] In the developing cortex, activation of 5-HT_4 receptors in layer V elicits a robust inward current (increase in sEPSCs) by exciting pyramidal neurons.[94] Unfortunately, little is known about the relationship of 5-HT_4 receptors to circuit activity in the frontal cortex, beyond an autoradiographic demonstration that 5-HT_4 receptor binding sites are weakly present in the frontal cortex.[95] The activation of 5-HT_4 receptors has dual effects (enhancement or reduction) on GABA-evoked currents in PFC pyramidal neurons.[53] Johnson et al. demonstrated that 5-HT_4 receptor agonism (prucalopride or PRX-03140) increases cortical ACh and HA levels.[96] Effects of 5-HT_4 receptor selective ligands on cognitive function have been studied very little. However, in line with the functional effects the partial agonist RS67333 was found to improve performance in an object recognition test.[97] Previous reports indicate that 5-HT_4 receptor activation enhances cognition in preclinical models such as spontaneous alternation and delayed matching and 5-HT_4 receptor agonists were also shown to reverse muscarinic receptor antagonist-induced cognitive deficits when administered alone or in combination with acetylcholinesterase inhibitors (see ref 96). Lastly, it should be noted that 5-HT_4 receptors have been identified not only on cortical glutamatergic neurons but also on hippocampal glutamatergic neurons and that both of these mediate the enhancement of ACh release elicited by 5-HT_4 agonists. Thus, the procognitive effects elicited by activation of 5-HT_4 receptors could be driven in part via hippocampal mechanisms.[98,99]

5-HT_5 Receptors. Mechanistic studies of the 5-HT_5 receptor suggest that this G-protein coupled receptor is associated either with Gi/o or with inwardly rectifying K^+ channels.[100,101] Immunohistochemical evidence has confirmed that the 5-HT_5 receptor is expressed at a weak or moderately weak level in the rodent cortex.[102] Speaking broadly about cortical expression patterns, Oliver et al. found the strongest pattern of expression in layers II and IV, although it is not clear from this study if such a pattern would be maintained in frontal cortical areas that lack a well-defined layer IV. The pattern of mRNA expression and the cell types that express 5-HT_5 receptors in the frontal cortex are not well understood at this time. Evidence suggests that the blockade of 5-HT_{5A} receptors impairs short- and long-term memory (24 h), while its stimulation might facilitate it[46] although more work is needed to be certain of these effects.

5-HT_6 Receptors. Although 5-HT_6 receptor localization has been reported at the cellular level in pyramidal cells and GABAergic interneurons,[103−106] these findings remain to be validated, due to the lack of specific 5-HT_6 receptor antibodies. However, numerous studies have mapped 5-HT_6 receptors to the prefrontal cortex by ligand binding autoradiography[107−109] and shown them to be postsynaptically located.[110]

Several lines of evidence suggest that modulation of 5-HT_6 receptor activity results in the regulation of multiple neurotransmitter systems in the prefrontal cortex. In vivo microdialysis has demonstrated that the 5-HT_6 receptor agonist WAY-181187 increases extracellular levels of GABA and decreases DA and 5-HT levels, while not impacting NE or glutamate levels.[111] Whole-cell patch clamp recordings on pyramidal neurons in the prefrontal cortex did however demonstrate that another agonist, ST-1936, inhibits cortical glutamatergic transmission.[112,113] Conversely, antagonism of the 5-HT_6 receptor with SB271046 has been demonstrated by in vivo microdialysis to increase extracellular levels of glutamate in the prefrontal cortex.[114,115] Reports on the effects of 5-HT_6 receptor antagonism on monoamines are less consistent, showing either an increase in DA and NE levels with SB271046[116] or a lack of effect on monoamines with the

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same compound.[115] The literature consistently reports that facilitation of cholinergic transmission contributes to the procognitive effects of 5-HT$_6$ receptor antagonism. Two studies have demonstrated that 5-HT$_6$ receptor antagonists increase ACh in the prefrontal cortex; however, these studies employed a cholinesterase inhibitor in the dialysis fluid, which does not allow for a firm conclusion on the effects of the antagonists alone.[117,118] Collectively, these studies suggest that 5-HT$_6$ receptors regulate multiple neurotransmitter systems in the prefrontal cortex, possibly through effects on glutamatergic and GABAergic neurons, where the receptor has been reported to be localized.

In preclinical models, blockade of 5-HT$_6$ receptors improves cortical performance in different learning and memory paradigms[119−121] and a few 5-HT$_6$ receptor antagonists are in clinical development for cognitive disorders, most notably for Alzheimer's disease.[122,123] 5-HT$_6$ receptor agonism has also been reported to have procognitive effects in preclinical studies, a paradox that is currently not understood. Table 2 summarizes studies showing that 5-HT$_6$ receptor agonists and/or antagonists have been found to improve cortical performance in different paradigms assessing cognitive flexibility and learning and memory or to reverse deficits induced by scopolamine and NMDA receptor antagonists such as ketamine and phencyclidine (PCP).

5-HT$_7$ Receptors. 5-HT$_7$ receptors are stimulatory G-protein coupled receptors that act via stimulation of cAMP production through Gs. These receptors have been found in the PFC[124,125] expressed on GABAergic interneurons[126] or in layer V pyramidal cells and more superficially on small neurons in layers I−III.[127] This pattern of expression is consistent with electrophysiological evidence showing that activation of cortical 5-HT$_7$ receptors in layer V elicits a robust inward current (increase in spontaneous EPSCs) by exciting pyramidal neurons,[128] and increases the firing rate of glutamatergic neurons.[129] We are not aware of any immunohistochemical evidence confirming the presence of 5-HT$_7$ receptors on GABAergic interneurons in the frontal cortex; however, 5-HT$_7$ receptors have been identified on GABAergic cells in other brain regions, such as in cerebellar purkinje cells. 5-HT$_7$ receptor activation induces either an increase or a decrease in GABA release and may do so partially due to increased glutamate release from excitatory terminals located on interneurons,[128] while 5-HT$_7$ receptor antagonism induces inhibition of 5-HT efflux indirectly via activation of GABA$_A$ receptors.[130] In other words, activation of 5-HT$_7$ receptors located on GABA interneurons decrease GABA release thereby decreasing the inhibitory tone on 5-HT neurons resulting in increased 5-HT efflux. In the presence of GABAergic tone, 5-HT$_7$ receptor antagonists would decrease 5-HT efflux.[130] Yet further work is needed to ascertain the mechanisms by which 5-HT$_7$ receptors produce these effects.

Nevertheless, 5-HT$_7$ receptors seem to play an important role in cognition. Selective 5-HT$_7$ receptor antagonists facilitate extradimensional set-shifting in chronically stressed and unstressed control rats and promote cognitive flexibility when given in combination with a subeffective dose of escitalopram in naïve rats.[131] Subchronic treatment during adolescence (43−45 to 47−49 days old) in rats, with a 5-HT$_7$ receptor agonist (LP-211 0.250 mg/kg/day) resulted in long-term rearrangement and increased strength of connectivity within and between "limbic" and "cortical" loops and reduced anxiety-related behavior.[132,133] 5-HT$_7$ receptor blockade may also contribute to the effectiveness of vortioxetine in restoring reversal learning compromised by chronic stress.[134] Lastly, vortioxetine, probably via its 5-HT$_7$ receptor antagonism, induced a significant effect on circadian rhythm and presented promnesic properties in rodents (increased time spent exploring a novel object during a retention test).[135] These results suggest that antagonism of 5-HT$_7$ receptors may contribute to mechanisms underlying procognitive effects and may therefore have therapeutic implications in frontal-like deficits associated with stress-related disorders.[131]

Combined Actions at 5-HT Receptors as a Strategy for Improving Cognitive Dysfunction, Exemplified by the Antidepressant Vortioxetine. The main conclusion drawn from the above is that through its diversely distributed receptor subtypes, 5-HT modulates cortical networks via complex interactions with multiple neurotransmitter systems that are critical for the regulation of cognitive function. Except for maybe selective 5-HT$_6$ receptor ligands, where a number of compounds are being explored clinically as cognitive enhancers,[120,122] compounds targeting a single serotonergic receptor subtype have shown limited or variable effects on cognitive function. This is possibly due to redundancies in the transmitter systems, which imply that modulating a single receptor target will be counteracted by other receptor mechanisms to maintain a homeostasis. An approach to amplify the cognitive enhancing response could be to develop drugs that modulate cortical networks through a combined effect of multiple serotonergic targets.

The multimodal antidepressant vortioxetine is an example of a drug acting through multiple serotonergic targets. In recombinant cell lines expressing human and rat targets, vortioxetine is a 5-HT$_3$, 5-HT$_7$, and 5-HT$_{1D}$ receptor antagonist, a 5-HT$_{1B}$ receptor partial agonist, and a 5-HT$_{1A}$ receptor agonist as well as an inhibitor of the 5-HT transporter (SERT).[136] Clinical studies have shown that vortioxetine significantly improves predefined cognitive outcome measures across a range of cognitive domains in patients suffering from major depressive disorder.[137−139] In preclinical animal models, vortioxetine reverses cognitive deficits induced by various disruptors such as 5-HT depletion, NMDA and muscarinic cholinergic receptor antagonists, fear, stress, and age and across a broad range of cognitive paradigms involving memory and learning and cognitive flexibility.[134,140−142] In line with vortioxetine's beneficial effects against multiple cognitively disrupting mechanisms, electrophysiology studies in rats have shown that vortioxetine produces an activation of cortical pyramidal neurons, likely due to 5-HT$_3$ receptor antagonism-mediated inhibition of GABA interneurons,[143] and electrophysiology and microdialysis studies have shown that vortioxetine enhances noradrenergic, dopaminergic, cholinergic, and histaminergic neurotransmission in the mPFC (Table 3). Thus, vortioxetine's concerted modulation of various serotonergic receptors appears overall to produce a more robust effect on cognitive function than modulation of the individual 5-HT receptors, and the mechanisms underlying these effects involve activation of multiple neurotransmitter systems that are critical for cognitive processing.

CONCLUSION

This Review has focused on several key findings that emphasize the important role of each 5-HT receptor in cognitive functioning with a specific focus on the prefrontal cortex. It is evident that more studies are needed to understand how 5-HT

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contributes to the modulation of cortical circuitries and that better tool compounds are needed for some 5-HT receptor subtypes. In spite of these shortcomings, the totality of behavioral and neurobiological studies has increased our understanding of the contribution of 5-HT and its receptors to cognitive function, which does not appear to be linked exclusively to the activation (or inactivation) of one particular 5-HT receptor subtype. On the contrary, converging evidence indicates that different subtypes of receptors potentially interact to contribute to a particular function. This is the case for 5-HT_{1A}, 5-HT_{1B}, 5-HT_3, and 5-HT_4 receptor subtypes in hippocampal functions, but probably also for those functions dependent on cortical control.[144] Studies are clearly needed to shed light on such interactive mechanisms in the PFC. A deeper understanding of serotonergic control of cortical circuitries will increase the understanding of the interplay of the various 5-HT receptor subtypes and their role in cognition. This may potentially open up the field for new drug target profiles that can prove to be beneficial for treatment of cognitive dysfunctions in patients.

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Notes

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ABBREVIATIONS

5,7-DHT, 5,7-dihydroxytryptamine; 5-HT, serotonin (5-hydroxytryptamine); 8-OH-DPAT, (±)-8-hydroxy-2-(*n*-dipropylamino)tetralin; ACh, acetylcholine; ACC, anterior cingulate cortex; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; AMPAR, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; ATD, acute trytophan depletion; cAMP, cyclic adenosine monophosphate; BRL46470, endo-*N*-(8-methyl-8-azabicyclo[3.2.1]oct-3yl)-2,3-dihydro-3,3-dimethyl-indole-1-carboxamide (ricasetron); CP93129, 3-(1,2,5,6-tetrahydropyrid-4-yl)pyrrolo[3,2-*b*]pyrid-5-one; CP94253, 3-(1,2,5,6-tetrahydro-4-pyridyl)-5-propoxypyrolo[3,2-*b*]pyridine; CPP, 3-(2-carboxypiperazin-4-yl)propyl-1-phosphonic acid; DA, dopamine; DOI, (±)-1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane; DRN, dorsal raphe nucleus; EPSC, excitatory postsynaptic current; F13640, (3-chloro-4-fluoro-phenyl)-[4-fluoro-4-([(5-methyl-pyridin-2-yl-methyl)-amino]-methyl)piperidin-1-yl]methanone, fumaric acid salt; GABA, γ-aminobutyric acid; GIRKs, G-protein-coupled inwardly rectifying potassium channels; GLU, glutamate; GR127935, (*N*-[4-methoxy-3-(4-methyl-1-piperazinyl)phenyl]-2′-methyl-4′-(5-methyl-1, 2,4-oxadiazol-3-yl)-[1,1-biphenyl]-4-carboxamide)); HA, histamine; LP-211, *N*-(4-cyanophenylmethyl)-4-(2-diphenyl)-1-piperazinehexanamide; M100907, (*R*)-(+)-(2,3-dimethoxyphenyl)-1-[2(4-fluorophenylethyl)]-4-piperidine-methanol (formerly MDL100907); m-CPBG, 1-(*m*-chlorophenyl)-biguanide; MC1, 1-[4-(2-methyl-4-chinolin-2-yl-piperazin-1-yl)-butyl]-8-azaspiro [4.5]decano-7,9-dion; MDL72222, 3-tropanyl-3,5-dichlorobenzoate; MM5, 1-[4-(4-chinolin-2-yl-piperazin-1yl)-butyl]piperidin-2-one; NA, noradrenaline; NAChR, nicotinic acetylcholine receptor; NAN-190, 1-(2-methoxyphenyl)-4-[4-(2-phthalimido)butyl]piperazine; NE, norepinephrine; NMDA, *N*-methyl-D-aspartate; NMDAR, *N*-methyl-D-aspartate receptor; NMQ, *n*-methylquipazine; PCA, *p*-chloroamphetamine; Pcpa, *p*-chlorophenylalanine; PCP, phencyclidine; PFC, prefrontal cortex; RS67333, 1-(4-amino-5-chloro-2-methoxy-phenyl)-3-[1(*n*-butyl)-4-piperidinyl]-1-propanone HCl; S15535, 1-(2,3-dihydro-1,4-benzodioxin-8-yl)-4-(2,3-dihydro-1*H*-inden-2-yl)piperazine; Scop, scopolamine; SERT, 5-HT transporter; SB242084, 6-chloro-5-methyl-1-[[2-[(2-methyl-3-pyridyl)oxy]-5-pyridyl]carbamoyl]-indoline; SB269970, (2*R*)-1-[(3-hydroxyphenyl)sulfonyl]-2-[2-(4-methyl-1-piperidinyl)ethyl]-pyrrolidine; SB271046, 5-chloro-*N*-(4-methoxy-3-piperazin-1-ylphenyl)-3-methyl-1-benzothiophene-2-sulfonamide; SB357134, *N*-(2,5-dibromo-3-fluorophenyl)-4-methoxy-3-(1-piperazinyl)benzenesulfonamide; SB399885, *N*-(3,5-dichloro-2-methoxyphenyl)-4-methoxy-3-(1-piperazinyl)-benzenesulfonamide; SDZ 205-557, 4-amino-5-chloro-2-methoxybenzoic acid 2-(diethylamino)ethyl ester hydrochloride; SSRI, selective serotonin reuptake inhibitor; ST-1936, 2-methyl-5-chloro-*N*,*N*-dimethyltryptamine; WAY100635, *N*-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-*N*-2-pyridinylcyclohexanecarboxamide maleate; WAY181187, 2-(1-[6-chloroimidazo[2,1-*b*][1,3]thiazole-5-sulfonyl]-1*H*-indol-3-yl)-ethan-1-amine

REFERENCES

(1) Clarke, H. F., Dalley, J. W., Crofts, H. S., Robbins, T. W., and Roberts, A. C. (2004) Cognitive inflexibility after prefrontal serotonin depletion. *Science 304*, 878−880.

(2) Puig, M. V., and Gulledge, A. T. (2011) Serotonin and prefrontal cortex function: Neurons, networks, and circuits. *Mol. Neurobiol. 44*, 449−464.

(3) Opris, I., and Casanova, M. F. (2014) Prefrontal cortical minicolumn: From executive control to disrupted cognitive processing. *Brain 137*, 1863−1875.

(4) Leiser, S. C., Bowlby, M. R., Comery, T. A., and Dunlop, J. (2009) A cog in cognition: How the alpha 7 nicotinic acetylcholine receptor is geared towards improving cognitive deficits. *Pharmacol. Ther. 122*, 302−311.

(5) Lesch, K. P., and Waider, J. (2012) Serotonin in the modulation of neural plasticity and networks: Implications for neurodevelopmental disorders. *Neuron 76*, 175−191.

(6) de Almeida, J., Palacios, J. M., and Mengod, G. (2008) Distribution of 5-HT and DA receptors in primate prefrontal cortex: Implications for pathophysiology and treatment. *Prog. Brain Res. 172*, 101−115.

(7) Cruz, D. A., Eggan, S. M., Azmitia, E. C., and Lewis, D. A. (2004) Serotonin1A receptors at the axon initial segment of prefrontal pyramidal neurons in schizophrenia. *Am. J. Psychiatry 161*, 739−742.

(8) 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*, 1−14.

(9) Maejima, T., Masseck, O. A., Mark, M. D., and Herlitze, S. (2013) Modulation of firing and synaptic transmission of serotonergic neurons by intrinsic G protein-coupled receptors and ion channels. *Front. Integr. Neurosci. 7*, 40.

(10) Glennon, R. A., Dukat, M., and Westkaemper, R. B. (2000) Serotonin Receptor Subtypes and Ligands. In *Psychopharmacology: The Fourth Generation of Progress* (Bloom, F. E., and Kupfer, D. J., Eds.), Raven Press, New York.

(11) Aghajanian, G. K., and Sanders-Bush, E. (2002) Serotonin. In *Neuropsychopharmacology: The Fifth Generation of Progress* (Davis, K. L., Charney, D., Coyle, J. T., and Nemeroff, C., Eds.), Lippincott, Williams, & Wilkins, Philadelphia.

(12) Peyron, C., Petit, J. M., Rampon, C., Jouvet, M., and Luppi, P. H. (1998) Forebrain afferents to the rat dorsal raphe nucleus demonstrated by retrograde and anterograde tracing methods. *Neuroscience 82*, 443−468.

DOI: 10.1021/cn500340j
ACS Chem. Neurosci. 2015, 6, 970−986

(13) Robbins, T. W. (2000) From arousal to cognition: The integrative position of the prefrontal cortex. *Prog. Brain Res. 126*, 469−483.
(14) Robbins, T. W., and Roberts, A. C. (2007) Differential regulation of fronto-executive function by the monoamines and acetylcholine. *Cerebr. Cortex 17* (Suppl 1), i151−160.
(15) Miskowiak, K. W., and Carvalho, A. F. (2014) Hot" cognition in major depressive disorder: A systematic review. *CNS Neurol. Disord.: Drug Targets 13*, 1787−1803.
(16) Harmer, C. J., Goodwin, G. M., and Cowen, P. J. (2009) Why do antidepressants take so long to work? A cognitive neuropsychological model of antidepressant drug action. *Br. J. Psychiatry 195*, 102−108.
(17) Roiser, J. P., Elliott, R., and Sahakian, B. J. (2012) Cognitive mechanisms of treatment in depression. *Neuropsychopharmacology 37*, 117−136.
(18) Robinson, O. J., and Sahakian, B. J. (2009) A double dissociation in the roles of serotonin and mood in healthy subjects. *Biol. Psychiatry 65*, 89−92.
(19) Alvarez, J. A., and Emory, E. (2006) Executive function and the frontal lobes: a meta-analytic review. *Neuropsychol. Rev. 16*, 17−42.
(20) Uylings, H. B., Groenewegen, H. J., and Kolb, B. (2003) Do rats have a prefrontal cortex? *Behav. Brain Res. 146*, 3−17.
(21) Chandler, D. J., Lamperski, C. S., and Waterhouse, B. D. (2013) Identification and distribution of projections from monoaminergic and cholinergic nuclei to functionally differentiated subregions of prefrontal cortex. *Brain Res. 1522*, 38−58.
(22) Miller, E. K., and Cohen, J. D. (2001) An integrative theory of prefrontal cortex function. *Annu. Rev. Neurosci. 24*, 167−202.
(23) Duncan, J. (2001) An adaptive coding model of neural function in prefrontal cortex. *Nat. Rev. Neurosci. 2*, 820−829.
(24) Hommel, B. (2004) Event files: Feature binding in and across perception and action. *Trends Cognit. Sci. 8*, 494−500.
(25) Opris, I., Fuqua, J. L., Huettl, P. F., Gerhardt, G. A., Berger, T. W., Hampson, R. E., and Deadwyler, S. A. (2012) Closing the loop in primate prefrontal cortex: inter-laminar processing. *Front. Neural Circuits 6*, 88.
(26) Opris, I., Hampson, R. E., Gerhardt, G. A., Berger, T. W., and Deadwyler, S. A. (2012) Columnar processing in primate pFC: Evidence for executive control microcircuits. *J. Cognit. Neurosci. 24*, 2334−2347.
(27) Opris, I. (2013) Inter-laminar microcircuits across neocortex: Repair and augmentation. *Front. Syst. Neurosci. 7*, 80.
(28) Opris, I., Santos, L., Gerhardt, G. A., Song, D., Berger, T. W., Hampson, R. E., and Deadwyler, S. A. (2013) Prefrontal cortical microcircuits bind perception to executive control. *Sci. Rep. 3*, 2285.
(29) Puig, M. V. (2011) Serotonergic modulation of the prefrontal cortex: From neurons to brain waves. In *Psychiatric Disorders—Worldwide Advances* (Uehara, T., Ed.), InTech, Rijeka, Croatia.
(30) Amargos-Bosch, M., Adell, A., and Artigas, F. (2007) Antipsychotic drugs reverse the AMPA receptor-stimulated release of 5-HT in the medial prefrontal cortex. *J. Neurochem. 102*, 550−561.
(31) Amargos-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*, 281−299.
(32) Araneda, R., and Andrade, R. (1991) 5-Hydroxytryptamine2 and 5-hydroxytryptamine 1A receptors mediate opposing responses on membrane excitability in rat association cortex. *Neuroscience 40*, 399−412.
(33) Pompeiano, M., Palacios, J. M., and Mengod, G. (1992) Distribution and cellular localization of mRNA coding for 5-HT1A receptor in the rat brain: correlation with receptor binding. *J. Neurosci. 12*, 440−453.
(34) Pompeiano, M., Palacios, J. M., and Mengod, G. (1994) Distribution of the serotonin 5-HT2 receptor family mRNAs: comparison between 5-HT2A and 5-HT2C receptors. *Brain Res. Mol. Brain Res. 23*, 163−178.
(35) Chandler, D. J., Waterhouse, B. D., and Gao, W. J. (2014) New perspectives on catecholaminergic regulation of executive circuits: evidence for independent modulation of prefrontal functions by midbrain dopaminergic and noradrenergic neurons. *Front. Neural Circuits 8*, 53.
(36) Aghajanian, G. K., and Marek, G. J. (1997) Serotonin induces excitatory postsynaptic potentials in apical dendrites of neocortical pyramidal cells. *Neuropharmacology 36*, 589−599.
(37) Aghajanian, G. K., and Marek, G. J. (1999) Serotonin, via 5-HT2A receptors, increases EPSCs in layer V pyramidal cells of prefrontal cortex by an asynchronous mode of glutamate release. *Brain Res. 825*, 161−171.
(38) Marek, G. J., and Aghajanian, G. K. (1998) The electrophysiology of prefrontal serotonin systems: therapeutic implications for mood and psychosis. *Biol. Psychiatry 44*, 1118−1127.
(39) Marek, G. J., and Aghajanian, G. K. (1999) 5-HT2A receptor or alpha1-adrenoceptor activation induces excitatory postsynaptic currents in layer V pyramidal cells of the medial prefrontal cortex. *Eur. J. Pharmacol. 367*, 197−206.
(40) Cowen, P., and Sherwood, A. C. (2013) The role of serotonin in cognitive function: Evidence from recent studies and implications for understanding depression. *J. Psychopharmacol. 27*, 575−583.
(41) Mendelsohn, D., Riedel, W. J., and Sambeth, A. (2009) Effects of acute tryptophan depletion on memory, attention and executive functions: A systematic review. *Neurosci. Biobehav. Rev. 33*, 926−952.
(42) Worbe, Y., Savulich, G., Voon, V., Fernandez-Egea, E., and Robbins, T. W. (2014) Serotonin depletion induces "waiting impulsivity" on the human four-choice serial reaction time task: cross-species translational significance. *Neuropsychopharmacology 39*, 1519−1526.
(43) Briand, L. A., Gritton, H., Howe, W. M., Young, D. A., and Sarter, M. (2007) Modulators in concert for cognition: Modulator interactions in the prefrontal cortex. *Progr. Neurobiol. 83*, 69−91.
(44) Fink, K. B., and Gothert, M. (2007) 5-HT receptor regulation of neurotransmitter release. *Pharmacol. Rev. 59*, 360−417.
(45) Steckler, T., and Sahgal, A. (1995) The role of serotonergic-cholinergic interactions in the mediation of cognitive behaviour. *Behav. Brain Res. 67*, 165−199.
(46) Gonzalez, R., Chavez-Pascacio, K., and Meneses, A. (2013) Role of 5-HT5A receptors in the consolidation of memory. *Behav. Brain Res. 252*, 246−251.
(47) Boulougouris, V., and Tsaltas, E. (2008) Serotonergic and dopaminergic modulation of attentional processes. *Prog. Brain Res. 172*, 517−542.
(48) Olvera-Cortes, M. E., Anguiano-Rodriguez, P., Lopez-Vazquez, M. A., and Alfaro, J. M. (2008) Serotonin/dopamine interaction in learning. *Prog. Brain Res. 172*, 567−602.
(49) Rogers, R. D. (2011) The roles of dopamine and serotonin in decision making: Evidence from pharmacological experiments in humans. *Neuropsychopharmacology 36*, 114−132.
(50) Iyer, R. N., and Bradberry, C. W. (1996) Serotonin-mediated increase in prefrontal cortex dopamine release: Pharmacological characterization. *J. Pharmaol. Exp. Ther. 277*, 40−47.
(51) Jacobs, B. L., and Azmitia, E. C. (1992) Structure and function of the brain serotonin system. *Physiol. Rev. 72*, 165−229.
(52) Luscher, C., Jan, L. Y., Stoffel, M., Malenka, R. C., and Nicoll, R. A. (1997) G protein-coupled inwardly rectifying K+ channels (GIRKs) mediate postsynaptic but not presynaptic transmitter actions in hippocampal neurons. *Neuron 19*, 687−695.
(53) Celada, P., Puig, M. V., and Artigas, F. (2013) Serotonin modulation of cortical neurons and networks. *Front. Integr. Neurosci. 7*, 25.
(54) de Almeida, J., and Mengod, G. (2008) Serotonin 1A receptors in human and monkey prefrontal cortex are mainly expressed in pyramidal neurons and in a GABAergic interneuron subpopulation: Implications for schizophrenia and its treatment. *J. Neurochem. 107*, 488−496.
(55) Aznar, S., Qian, Z., Shah, R., Rahbek, B., and Knudsen, G. M. (2003) The 5-HT1A serotonin receptor is located on calbindin- and

DOI: 10.1021/cn500340j
ACS Chem. Neurosci. 2015, 6, 970−986

parvalbumin-containing neurons in the rat brain. *Brain Res. 959*, 58−67.
(56) Mengod, G., Palacios, J. M., and Cortés, R. (2015) Cartography of 5-HT1A and 5-HT2A receptor subtypes in prefrontal cortex and its projections. *ACS Chem. Neurosci.*, DOI: 10.1021/acschemneuro.5b00023.
(57) Santana, N., Bortolozzi, A., Serrats, J., Mengod, G., and Artigas, F. (2004) Expression of serotonin1A and serotonin2A receptors in pyramidal and GABAergic neurons of the rat prefrontal cortex. *Cereb. Cortex 14*, 1100−1109.
(58) Levkovitz, Y., and Segal, M. (1997) Serotonin 5-HT1A receptors modulate hippocampal reactivity to afferent stimulation. *J. Neurosci. 17*, 5591−5598.
(59) Llado-Pelfort, L., Assie, M. B., Newman-Tancredi, A., Artigas, F., and Celada, P. (2012) In vivo electrophysiological and neurochemical effects of the selective 5-HT1A receptor agonist, F13640, at pre- and postsynaptic 5-HT1A receptors in the rat. *Psychopharmacology 221*, 261−272.
(60) Llado-Pelfort, L., Assie, M. B., Newman-Tancredi, A., Artigas, F., and Celada, P. (2010) Preferential in vivo action of F15599, a novel 5-HT(1A) receptor agonist, at postsynaptic 5-HT(1A) receptors. *Br. J. Pharmacol. 160*, 1929−1940.
(61) Llado-Pelfort, L., Santana, N., Ghisi, V., Artigas, F., and Celada, P. (2012) 5-HT1A receptor agonists enhance pyramidal cell firing in prefrontal cortex through a preferential action on GABA interneurons. *Cerebr. Cortex 22*, 1487−1497.
(62) Sari, Y. (2004) Serotonin1B receptors: From protein to physiological function and behavior. *Neurosci. Biobehav. Rev. 28*, 565−582.
(63) Peddie, C. J., Davies, H. A., Colyer, F. M., Stewart, M. G., and Rodriguez, J. J. (2010) A subpopulation of serotonin 1B receptors colocalize with the AMPA receptor subunit GluR2 in the hippocampal dentate gyrus. *Neurosci. Lett. 485*, 251−255.
(64) Peddie, C. J., Davies, H. A., Colyer, F. M., Stewart, M. G., and Rodriguez, J. J. (2008) Dendritic colocalisation of serotonin1B receptors and the glutamate NMDA receptor subunit NR1 within the hippocampal dentate gyrus: An ultrastructural study. *J. Chem. Neuroanat. 36*, 17−26.
(65) Bruinvels, A. T., Landwehrmeyer, B., Gustafson, E. L., Durkin, M. M., Mengod, G., Branchek, T. A., Hoyer, D., and Palacios, J. M. (1994) Localization of 5-HT1B, 5-HT1D alpha, 5-HT1E and 5-HT1F receptor messenger RNA in rodent and primate brain. *Neuropharmacology 33*, 367−386.
(66) Bruinvels, A. T., Palacios, J. M., and Hoyer, D. (1993) Autoradiographic characterisation and localisation of 5-HT1D compared to 5-HT1B binding sites in rat brain. *Naunyn-Schmiedeberg's Arch. Pharmacol. 347*, 569−582.
(67) Davidson, C., and Stamford, J. A. (1995) Evidence that 5-hydroxytryptamine release in rat dorsal raphe nucleus is controlled by 5-HT1A, 5-HT1B and 5-HT1D autoreceptors. *Br. J. Pharmacol. 114*, 1107−1109.
(68) Starkey, S. J., and Skingle, M. (1994) 5-HT1D as well as 5-HT1A autoreceptors modulate 5-HT release in the guinea-pig dorsal raphe nucleus. *Neuropharmacology 33*, 393−402.
(69) Roberts, C., Price, G. W., and Jones, B. J. (1997) The role of 5-HT(1B/1D) receptors in the modulation of 5-hydroxytryptamine levels in the frontal cortex of the conscious guinea pig. *Eur. J. Pharmacol. 326*, 23−30.
(70) 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*, 427−439.
(71) Conn, P. J., and Sanders-Bush, E. (1986) Regulation of serotonin-stimulated phosphoinositide hydrolysis: Relation to the serotonin 5-HT-2 binding site. *J. Neurosci. 6*, 3669−3675.
(72) de Almeida, J., and Mengod, G. (2007) Quantitative analysis of glutamatergic and GABAergic neurons expressing 5-HT(2A) receptors in human and monkey prefrontal cortex. *J. Neurochem. 103*, 475−486.
(73) Cornea-Hebert, V., Riad, M., Wu, C., Singh, S. K., and Descarries, L. (1999) Cellular and subcellular distribution of the serotonin 5-HT2A receptor in the central nervous system of adult rat. *J. Comp. Neurol. 409*, 187−209.
(74) Miner, L. A., Backstrom, J. R., Sanders-Bush, E., and Sesack, S. R. (2003) Ultrastructural localization of serotonin2A receptors in the middle layers of the rat prelimbic prefrontal cortex. *Neuroscience 116*, 107−117.
(75) Mengod, G., Nguyen, H., Le, H., Waeber, C., Lubbert, H., and Palacios, J. M. (1990) The distribution and cellular localization of the serotonin 1C receptor mRNA in the rodent brain examined by in situ hybridization histochemistry. Comparison with receptor binding distribution. *Neuroscience 35*, 577−591.
(76) Feng, J., Cai, X., Zhao, J., and Yan, Z. (2001) Serotonin receptors modulate GABA(A) receptor channels through activation of anchored protein kinase C in prefrontal cortical neurons. *J. Neurosci. 21*, 6502−6511.
(77) Liu, S., Bubar, M. J., Lanfranco, M. F., Hillman, G. R., and Cunningham, K. A. (2007) Serotonin2C receptor localization in GABA neurons of the rat medial prefrontal cortex: Implications for understanding the neurobiology of addiction. *Neuroscience 146*, 1677−1688.
(78) Clemett, D. A., Punhani, T., Duxon, M. S., Blackburn, T. P., and Fone, K. C. (2000) Immunohistochemical localisation of the 5-HT2C receptor protein in the rat CNS. *Neuropharmacology 39*, 123−132.
(79) Puig, M. V., Celada, P., Diaz-Mataix, L., and Artigas, F. (2003) In vivo modulation of the activity of pyramidal neurons in the rat medial prefrontal cortex by 5-HT2A receptors: relationship to thalamocortical afferents. *Cereb. Cortex 13*, 870−882.
(80) Ashby, C. R., Jr., Edwards, E., Harkins, K., and Wang, R. Y. (1989) Effects of (±)-DOI on medial prefrontal cortical cells: A microiontophoretic study. *Brain Res. 498*, 393−396.
(81) Ashby, C. R., Jr., Jiang, L. H., Kasser, R. J., and Wang, R. Y. (1990) Electrophysiological characterization of 5-hydroxytryptamine2 receptors in the rat medial prefrontal cortex. *J. Pharmacol. Exp. Ther. 252*, 171−178.
(82) Ashby, C. R., Jr., and Wang, R. Y. (1990) Effects of antipsychotic drugs on 5-HT2 receptors in the medial prefrontal cortex: Microiontophoretic studies. *Brain Res. 506*, 346−348.
(83) Wood, J., Kim, Y., and Moghaddam, B. (2012) Disruption of prefrontal cortex large scale neuronal activity by different classes of psychotomimetic drugs. *J. Neurosci. 32*, 3022−3031.
(84) Gray, J. A., and Roth, B. L. (2001) Paradoxical trafficking and regulation of 5-HT(2A) receptors by agonists and antagonists. *Brain Res. Bull. 56*, 441−451.
(85) 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*, 1365−1375.
(86) Puig, M. V., Celada, P., and Artigas, F. (2004) [Serotonergic control of prefrontal cortex]. *Rev. Neurol. 39*, 539−547.
(87) Morales, M., Battenberg, E., de Lecea, L., Sanna, P. P., and Bloom, F. E. (1996) Cellular and subcellular immunolocalization of the type 3 serotonin receptor in the rat central nervous system. *Brain Res.. Mol. Brain Res. 36*, 251−260.
(88) 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*, 3157−3167.
(89) Ashby, C. R., Jr., Minabe, Y., Edwards, E., and Wang, R. Y. (1991) 5-HT3-like receptors in the rat medial prefrontal cortex: An electrophysiological study. *Brain Res. 550*, 181−191.
(90) Ferezou, I., Cauli, B., Hill, E. L., Rossier, J., Hamel, E., and Lambolez, B. (2002) 5-HT3 receptors mediate serotonergic fast synaptic excitation of neocortical vasoactive intestinal peptide/cholecystokinin interneurons. *J. Neurosci. 22*, 7389−7397.
(91) Reznic, J., and Staubli, U. (1997) Effects of 5-HT3 receptor antagonism on hippocampal cellular activity in the freely moving rat. *J. Neurophysiol. 77*, 517−521.
(92) Hakkarainen, J. J., Jalkanen, A. J., Kaariainen, T. M., Keski-Rahkonen, P., Venalainen, T., Hokkanen, J., Monkkonen, J., Suhonen,

M., and Forsberg, M. M. (2010) Comparison of in vitro cell models in predicting in vivo brain entry of drugs. *Int. J. Pharm. 402*, 27−36.
(93) Chapin, E. M., Haj-Dahmane, S., Torres, G., and Andrade, R. (2002) The 5-HT(4) receptor-induced depolarization in rat hippocampal neurons is mediated by cAMP but is independent of I(h). *Neurosci. Lett. 324*, 1−4.
(94) Beique, J. C., Chapin-Penick, E. M., Mladenovic, L., and Andrade, R. (2004) Serotonergic facilitation of synaptic activity in the developing rat prefrontal cortex. *J. Physiol. 556*, 739−754.
(95) Waeber, C., Sebben, M., Nieoullon, A., Bockaert, J., and Dumuis, A. (1994) Regional distribution and ontogeny of 5-HT4 binding sites in rodent brain. *Neuropharmacology 33*, 527−541.
(96) Johnson, D. E., Drummond, E., Grimwood, S., Sawant-Basak, A., Miller, E., Tseng, E., McDowell, L. L., Vanase-Frawley, M. A., Fisher, K. E., Rubitski, D. M., Stutzman-Engwall, K. J., Nelson, R. T., Horner, W. E., Gorczyca, R. R., Hajos, M., and Siok, C. J. (2012) The 5-hydroxytryptamine4 receptor agonists prucalopride and PRX-03140 increase acetylcholine and histamine levels in the rat prefrontal cortex and the power of stimulated hippocampal theta oscillations. *J. Pharm. Exp. Ther. 341*, 681−691.
(97) Levallet, G., Hotte, M., Boulouard, M., and Dauphin, F. (2009) Increased particulate phosphodiesterase 4 in the prefrontal cortex supports 5-HT4 receptor-induced improvement of object recognition memory in the rat. *Psychopharmacology 202*, 125−139.
(98) Mohler, E. G., Shacham, S., Noiman, S., Lezoualc'h, F., Robert, S., Gastineau, M., Rutkowski, J., Marantz, Y., Dumuis, A., Bockaert, J., Gold, P. E., and Ragozzino, M. E. (2007) VRX-03011, a novel 5-HT4 agonist, enhances memory and hippocampal acetylcholine efflux. *Neuropharmacology 53*, 563−573.
(99) Penas-Cazorla, R., and Vilaro, M. T. (2014) Serotonin 5-HT receptors and forebrain cholinergic system: Receptor expression in identified cell populations. *Brain Struct. Funct.*, DOI: 10.1007/s00429-014-0864-z.
(100) Francken, B. J., Jurzak, M., Vanhauwe, J. F., Luyten, W. H., and Leysen, J. E. (1998) The human 5-ht5A receptor couples to Gi/Go proteins and inhibits adenylate cyclase in HEK 293 cells. *Eur. J. Pharmacol. 361*, 299−309.
(101) Goodfellow, N. M., Bailey, C. D., and Lambe, E. K. (2012) The native serotonin 5-HT(5A) receptor: Electrophysiological characterization in rodent cortex and 5-HT(1A)-mediated compensatory plasticity in the knock-out mouse. *J. Neurosci. 32*, 5804−5809.
(102) Oliver, K. R., Kinsey, A. M., Wainwright, A., and Sirinathsinghji, D. J. (2000) Localization of 5-ht(5A) receptor-like immunoreactivity in the rat brain. *Brain Res. 867*, 131−142.
(103) Lorke, D. E., Lu, G., Cho, E., and Yew, D. T. (2006) Serotonin 5-HT2A and 5-HT6 receptors in the prefrontal cortex of Alzheimer and normal aging patients. *BMC Neurosci. 7*, 36.
(104) Marazziti, D., Baroni, S., Pirone, A., Giannaccini, G., Betti, L., Testa, G., Schmid, L., Palego, L., Borsini, F., Bordi, F., Piano, I., Gargini, C., Castagna, M., Catena-Dell'osso, M., and Lucacchini, A. (2013) Serotonin receptor of type 6 (5-HT6) in human prefrontal cortex and hippocampus post-mortem: An immunohistochemical and immunofluorescence study. *Neurochem. Int. 62*, 182−188.
(105) Woolley, M. L., Marsden, C. A., Sleight, A. J., and Fone, K. C. (2003) Reversal of a cholinergic-induced deficit in a rodent model of recognition memory by the selective 5-HT6 receptor antagonist, Ro 04-6790. *Psychopharmacology 170*, 358−367.
(106) Woolley, M. L., Marsden, C. A., and Fone, K. C. (2004) 5-ht6 receptors. *Curr. Drug Targets: CNS Neurol. Disord. 3*, 59−79.
(107) East, S. Z., Burnet, P. W., Leslie, R. A., Roberts, J. C., and Harrison, P. J. (2002) 5-HT6 receptor binding sites in schizophrenia and following antipsychotic drug administration: Autoradiographic studies with [125I]SB-258585. *Synapse 45*, 191−199.
(108) Zhang, X., Andren, P. E., Glennon, R. A., and Svenningsson, P. (2011) Distribution, level, pharmacology, regulation, and signaling of 5-HT6 receptors in rats and marmosets with special reference to an experimental model of parkinsonism. *J. Comp. Neurol. 519*, 1816−1827.
(109) Roberts, P. D., Spiros, A., and Geerts, H. (2012) Simulations of symptomatic treatments for Alzheimer's disease: computational analysis of pathology and mechanisms of drug action. *Alzheimer's Res. Ther. 4*, 50.
(110) Gerard, C., el Mestikawy, S., Lebrand, C., Adrien, J., Ruat, M., Traiffort, E., Hamon, M., and Martres, M. P. (1996) Quantitative RT-PCR distribution of serotonin 5-HT6 receptor mRNA in the central nervous system of control or 5,7-dihydroxytryptamine-treated rats. *Synapse 23*, 164−173.
(111) Schechter, L. E., Lin, Q., Smith, D. L., Zhang, G., Shan, Q., Platt, B., Brandt, M. R., Dawson, L. A., Cole, D., Bernotas, R., Robichaud, A., Rosenzweig-Lipson, S., and Beyer, C. E. (2008) Neuropharmacological profile of novel and selective 5-HT6 receptor agonists: WAY-181187 and WAY-208466. *Neuropsychopharmacology 33*, 1323−1335.
(112) Tassone, A., Madeo, G., Schirinzi, T., Vita, D., Puglisi, F., Ponterio, G., Borsini, F., Pisani, A., and Bonsi, P. (2011) Activation of 5-HT6 receptors inhibits corticostriatal glutamatergic transmission. *Neuropharmacology 61*, 632−637.
(113) Tassone, A., Madeo, G., Sciamanna, G., Pisani, A., and Bonsi, P. (2010) Electrophysiology of 5-HT6 receptors. *Int. Rev. Neurobiol. 94*, 111−128.
(114) Dawson, L. A. (2011) The central role of 5-HT6 receptors in modulating brain neurochemistry. *Int. Rev. Neurobiol. 96*, 1−26.
(115) Dawson, L. A., Nguyen, H. Q., and Li, P. (2001) The 5-HT(6) receptor antagonist SB-271046 selectively enhances excitatory neurotransmission in the rat frontal cortex and hippocampus. *Neuropsychopharmacology 25*, 662−668.
(116) Lacroix, L. P., Dawson, L. A., Hagan, J. J., and Heidbreder, C. A. (2004) 5-HT6 receptor antagonist SB-271046 enhances extracellular levels of monoamines in the rat medial prefrontal cortex. *Synapse 51*, 158−164.
(117) Hirst, W. D., Stean, T. O., Rogers, D. C., Sunter, D., Pugh, P., Moss, S. F., Bromidge, S. M., Riley, G., Smith, D. R., Bartlett, S., Heidbreder, C. A., Atkins, A. R., Lacroix, L. P., Dawson, L. A., Foley, A. G., Regan, C. M., and Upton, N. (2006) SB-399885 is a potent, selective 5-HT6 receptor antagonist with cognitive enhancing properties in aged rat water maze and novel object recognition models. *Eur. J. Pharmacol. 553*, 109−119.
(118) Riemer, C., Borroni, E., Levet-Trafit, B., Martin, J. R., Poli, S., Porter, R. H., and Bos, M. (2003) Influence of the 5-HT6 receptor on acetylcholine release in the cortex: Pharmacological characterization of 4-(2-bromo-6-pyrrolidin-1-ylpyridine-4-sulfonyl)phenylamine, a potent and selective 5-HT6 receptor antagonist. *J. Med. Chem. 46*, 1273−1276.
(119) Upton, N., Chuang, T. T., Hunter, A. J., and Virley, D. J. (2008) 5-HT6 receptor antagonists as novel cognitive enhancing agents for Alzheimer's disease. *Neurotherapeutics 5*, 458−469.
(120) Arnt, J., Bang-Andersen, B., Grayson, B., Bymaster, F. P., Cohen, M. P., DeLapp, N. W., Giethlen, B., Kreilgaard, M., McKinzie, D. L., Neill, J. C., Nelson, D. L., Nielsen, S. M., Poulsen, M. N., Schaus, J. M., and Witten, L. M. (2010) Lu AE58054, a 5-HT6 antagonist, reverses cognitive impairment induced by subchronic phencyclidine in a novel object recognition test in rats. *Int. J. Neuropsychopharmacol. 13*, 1021−1033.
(121) Arnt, J., and Olsen, C. K. (2011) 5-HT6 receptor ligands and their antipsychotic potential. *Int. Re. Neurobiol. 96*, 141−161.
(122) Wilkinson, D., Windfeld, K., and Colding-Jorgensen, E. (2014) Safety and efficacy of idalopirdine, a 5-HT6 receptor antagonist, in patients with moderate Alzheimer's disease (LADDER): A randomised, double-blind, placebo-controlled phase 2 trial, *The Lancet. Neurology 13*, 1092−1099.
(123) Ramirez, M. J. (2013) 5-HT6 receptors and Alzheimer's disease. *Alzheimer's Res. Ther. 5*, 15.
(124) Perez-Garcia, G., Gonzalez-Espinosa, C., and Meneses, A. (2006) An mRNA expression analysis of stimulation and blockade of 5-HT7 receptors during memory consolidation. *Behav. Brain Res. 169*, 83−92.

DOI: 10.1021/cn500340j
ACS Chem. Neurosci. 2015, 6, 970−986

(125) Perez-Garcia, G., and Meneses, A. (2009) Memory time-course: mRNA 5-HT1A and 5-HT7 receptors. *Behav. Brain Res. 202*, 102−113.
(126) Vysokanov, A., Flores-Hernandez, J., and Surmeier, D. J. (1998) mRNAs for clozapine-sensitive receptors co-localize in rat prefrontal cortex neurons. *Neurosci. Lett. 258*, 179−182.
(127) Neumaier, J. F., Sexton, T. J., Yracheta, J., Diaz, A. M., and Brownfield, M. (2001) Localization of 5-HT(7) receptors in rat brain by immunocytochemistry, in situ hybridization, and agonist stimulated cFos expression. *J. Chem. Neuroanat. 21*, 63−73.
(128) Tokarski, K., Kusek, M., and Hess, G. (2011) 5-HT7 receptors modulate GABAergic transmission in rat hippocampal CA1 area. *J. Physiol. Pharmacol. 62*, 535−540.
(129) Fan, L. L., Zhang, Q. J., Liu, J., Feng, J., Gui, Z. H., Ali, U., Zhang, L., Hou, C., Wang, T., Hui, Y. P., Sun, Y. N., and Wu, Z. H. (2011) In vivo effect of 5-HT(7) receptor agonist on pyramidal neurons in medial frontal cortex of normal and 6-hydroxydopamine-lesioned rats: an electrophysiological study. *Neuroscience 190*, 328−338.
(130) Roberts, C., Thomas, D. R., Bate, S. T., and Kew, J. N. (2004) GABAergic modulation of 5-HT7 receptor-mediated effects on 5-HT efflux in the guinea-pig dorsal raphe nucleus. *Neuropharmacology 46*, 935−941.
(131) Nikiforuk, A. (2012) Selective blockade of 5-HT7 receptors facilitates attentional set-shifting in stressed and control rats. *Behav. Brain Res. 226*, 118−123.
(132) Canese, R., Zoratto, F., Altabella, L., Porcari, P., Mercurio, L., de Pasquale, F., Butti, E., Martino, G., Lacivita, E., Leopoldo, M., Laviola, G., and Adriani, W. (2015) Persistent modification of forebrain networks and metabolism in rats following adolescent exposure to a 5-HT7 receptor agonist. *Psychopharmacology 232*, 75−89.
(133) Ruocco, L. A., Treno, C., Gironi Carnevale, U. A., Arra, C., Boatto, G., Nieddu, M., Pagano, C., Illiano, P., Barbato, F., Tino, A., Carboni, E., Laviola, G., Lacivita, E., Leopoldo, M., Adriani, W., and Sadile, A. G. (2014) Prepuberal stimulation of 5-HT7-R by LP-211 in a rat model of hyper-activity and attention-deficit: permanent effects on attention, brain amino acids and synaptic markers in the fronto-striatal interface. *PloS One 9*, e83003.
(134) Wallace, A., Pehrson, A. L., Sanchez, C., and Morilak, D. A. (2014) Vortioxetine restores reversal learning impaired by 5-HT depletion or chronic intermittent cold stress in rats. *Int. J. Neuropsychopharmacol. 17*, 1695−1706.
(135) Westrich, L., Haddjeri, N., Dkhissi-Benyahya, O., and Sánchez, C. (2015) Involvement of 5-HT7 receptors in vortioxetine's modulation of circadian rhythms and episodic memory in rodents. *Neuropharmacology 89*, 382−390.
(136) Sanchez, C., Asin, K. E., and Artigas, F. (2015) Vortioxetine, a novel antidepressant with multimodal activity: Review of preclinical and clinical data. *Pharmacol. Ther. 145*, 43−57.
(137) Katona, C., Hansen, T., and Olsen, C. K. (2012) A randomized, double-blind, placebo-controlled, duloxetine-referenced, fixed-dose study comparing the efficacy and safety of Lu AA21004 in elderly patients with major depressive disorder. *Int. Clin. Psychopharmacol. 27*, 215−223.
(138) McIntyre, R. S., Lophaven, S., and Olsen, C. K. (2014) A randomized, double-blind, placebo-controlled study of vortioxetine on cognitive function in depressed adults. *Int. J. Neuropsychopharmacol. 17*, 1557−1567.
(139) Fava, M., Lophaven, S., and Olsen, C. K. (2014) Effects of vortioxetine on cognitive symptoms of major depressive disorder (MDD). *Int. J. Neuropsychopharmacol. 17*, 61−62.
(140) du Jardin, K. G., Jensen, J. B., Sanchez, C., and Pehrson, A. L. (2014) Vortioxetine dose-dependently reverses 5-HT depletion-induced deficits in spatial working and object recognition memory: a potential role for 5-HT1A receptor agonism and 5-HT3 receptor antagonism. *Eur. Neuropsychopharmacol. 24*, 160−171.
(141) Jensen, J. B., du Jardin, K. G., Song, D., Budac, D., Smagin, G., Sanchez, C., and Pehrson, A. L. (2014) Vortioxetine, but not escitalopram or duloxetine, reverses memory impairment induced by central 5-HT depletion in rats: evidence for direct 5-HT receptor modulation. *Eur. Neuropsychopharmacol. 24*, 148−159.
(142) Pehrson, A. L., Leiser, S. C., Gulinello, M., Dale, E., Li, Y., Waller, J. A., and Sanchez, C. (2014) Treatment of cognitive dysfunction in major depressive disorder—A review of the preclinical evidence for efficacy of selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors and the multimodal-acting antidepressant vortioxetine. *Eur. J. Pharmacol.*, DOI: 10.1016/j.ejphar.2014.07.044.
(143) Riga, M. S., Celada, P., Sanchez, C., and Artigas, F. . (2013) Role of 5-HT3 receptors in the mechanism of action of the investigational antidepressant vortioxetine. *Eur. Neuropsychopharmacol. 23*, S393−394.
(144) Buhot, M. C. (1997) Serotonin receptors in cognitive behaviors. *Curr. Opin. Neurobio. 7*, 243−254.
(145) Evenden, J. L. (1999) The pharmacology of impulsive behaviour in rats VII: The effects of serotonergic agonists and antagonists on responding under a discrimination task using unreliable visual stimuli. *Psychopharmacology 146*, 422−431.
(146) Baarendse, P. J., and Vanderschuren, L. J. (2012) Dissociable effects of monoamine reuptake inhibitors on distinct forms of impulsive behavior in rats. *Psychopharmacology 219*, 313−326.
(147) Bondi, C. O., Rodriguez, G., Gould, G. G., Frazer, A., and Morilak, D. A. (2008) Chronic unpredictable stress induces a cognitive deficit and anxiety-like behavior in rats that is prevented by chronic antidepressant drug treatment. *Neuropsychopharmacology 33*, 320−331.
(148) Danet, M., Lapiz-Bluhm, S., and Morilak, D. A. (2010) A cognitive deficit induced in rats by chronic intermittent cold stress is reversed by chronic antidepressant treatment. *Int. J. Neuropsychopharmacol. 13*, 997−1009.
(149) Furr, A., Lapiz-Bluhm, M. D., and Morilak, D. A. (2012) 5-HT2A receptors in the orbitofrontal cortex facilitate reversal learning and contribute to the beneficial cognitive effects of chronic citalopram treatment in rats. *Int. J. Neuropsychopharmacol. 15*, 1295−1305.
(150) Meneses, A., and Hong, E. (1995) Effect of fluoxetine on learning and memory involves multiple 5-HT systems. *Pharmacol., Biochem. Behav. 52*, 341−346.
(151) van der Plasse, G., and Feenstra, M. G. (2008) Serial reversal learning and acute tryptophan depletion. *Behav. Brain Res. 186*, 23−31.
(152) Harrison, A. A., Everitt, B. J., and Robbins, T. W. (1997) Central 5-HT depletion enhances impulsive responding without affecting the accuracy of attentional performance: Interactions with dopaminergic mechanisms. *Psychopharmacology 133*, 329−342.
(153) Winstanley, C. A., Theobald, D. E., Dalley, J. W., Glennon, J. C., and Robbins, T. W. (2004) 5-HT2A and 5-HT2C receptor antagonists have opposing effects on a measure of impulsivity: Interactions with global 5-HT depletion. *Psychopharmacology 176*, 376−385.
(154) Carli, M., and Samanin, R. (2000) The 5-HT(1A) receptor agonist 8-OH-DPAT reduces rats' accuracy of attentional performance and enhances impulsive responding in a five-choice serial reaction time task: Role of presynaptic 5-HT(1A) receptors. *Psychopharmacology 149*, 259−268.
(155) Misane, I., Johansson, C., and Ogren, S. O. (1998) Analysis of the 5-HT1A receptor involvement in passive avoidance in the rat. *Br. J. Pharmacol. 125*, 499−509.
(156) Meneses, A., and Hong, E. (1999) 5-HT1A receptors modulate the consolidation of learning in normal and cognitively impaired rats. *Neurobiol. Learn. Mem. 71*, 207−218.
(157) Winstanley, C. A., Chudasama, Y., Dalley, J. W., Theobald, D. E., Glennon, J. C., and Robbins, T. W. (2003) Intra-prefrontal 8-OH-DPAT and M100907 improve visuospatial attention and decrease impulsivity on the five-choice serial reaction time task in rats. *Psychopharmacology 167*, 304−314.
(158) Carli, M., Baviera, M., Invernizzi, R. W., and Balducci, C. (2006) Dissociable contribution of 5-HT1A and 5-HT2A receptors in the medial prefrontal cortex to different aspects of executive control

DOI: 10.1021/cn500340j
ACS Chem. Neurosci. 2015, 6, 970−986

such as impulsivity and compulsive perseveration in rats. *Neuropsychopharmacology 31*, 757−767.
(159) Blokland, A., Sik, A., and Lieben, C. (2005) Evaluation of DOI, 8-OH-DPAT, eticlopride and amphetamine on impulsive responding in a reaction time task in rats. *Behav. Pharmacol. 16*, 93−100.
(160) Yates, J. R., Perry, J. L., Meyer, A. C., Gipson, C. D., Charnigo, R., and Bardo, M. T. (2014) Role of medial prefrontal and orbitofrontal monoamine transporters and receptors in performance in an adjusting delay discounting procedure. *Brain Res. 1574*, 26−36.
(161) Pattij, T., and Schoffelmeer, A. N. (2014) Serotonin and inhibitory response control: Focusing on the role of 5-HT receptors. *Eur. J. Pharmacol.*, DOI: 10.1016/j.ejphar.2014.05.064.
(162) Marek, G. J., Li, A. A., and Seiden, L. S. (1989) Evidence for involvement of 5-hydroxytryptamine1 receptors in antidepressant-like drug effects on differential-reinforcement-of-low-rate 72-second behavior. *J. Pharmacol. Exp. Ther. 250*, 60−71.
(163) Balleine, B. W., Fletcher, N., and Dickinson, A. (1996) Effect of the 5-HT1A agonist, 8-OH-DPAT on instrumental performance in rats. *Psychopharmacology 125*, 79−88.
(164) Perez-Garcia, G., and Meneses, A. (2005) Oral administration of the 5-HT6 receptor antagonists SB-357134 and SB-399885 improves memory formation in an autoshaping learning task. *Pharmacol., Biochem. Behav. 81*, 673−682.
(165) Meneses, A. (2001) Effects of the 5-HT(6) receptor antagonist Ro 04-6790 on learning consolidation. *Behav. Brain Res. 118*, 107−110.
(166) Mello e Souza, T., Rodrigues, C., Souza, M. M., Vinade, E., Coitinho, A., Choi, H., and Izquierdo, I. (2001) Involvement of the serotonergic type 1A (5-HT1A) receptor in the agranular insular cortex in the consolidation of memory for inhibitory avoidance in rats. *Behav. Pharmacol. 12*, 349−353.
(167) Bekinschtein, P., Renner, M. C., Gonzalez, M. C., and Weisstaub, N. (2013) Role of medial prefrontal cortex serotonin 2A receptors in the control of retrieval of recognition memory in rats. *J. Neurosci. 33*, 15716−15725.
(168) Millan, M. J., Gobert, A., Roux, S., Porsolt, R., Meneses, A., Carli, M., Di Cara, B., Jaffard, R., Rivet, J. M., Lestage, P., Mocaer, E., Peglion, J. L., and Dekeyne, A. (2004) The serotonin1A receptor partial agonist S15535 [4-(benzodioxan-5-yl)1-(indan-2-yl)piperazine] enhances cholinergic transmission and cognitive function in rodents: a combined neurochemical and behavioral analysis. *J. Pharmacol. Exp. Ther. 311*, 190−203.
(169) Pattij, T., Broersen, L. M., van der Linde, J., Groenink, L., van der Gugten, J., Maes, R. A., and Olivier, B. (2003) Operant learning and differential-reinforcement-of-low-rate 36-s responding in 5-HT1A and 5-HT1B receptor knockout mice. *Behav. Brain Res. 141*, 137−145.
(170) Meneses, A., Terron, J. A., and Hong, E. (1997) Effects of the 5-HT receptor antagonists GR127935 (5-HT1B/1D) and MDL100907 (5-HT2A) in the consolidation of learning. *Behav. Brain Res. 89*, 217−223.
(171) Koskinen, T., Ruotsalainen, S., Puumala, T., Lappalainen, R., Koivisto, E., Mannisto, P. T., and Sirvio, J. (2000) Activation of 5-HT2A receptors impairs response control of rats in a five-choice serial reaction time task. *Neuropharmacology 39*, 471−481.
(172) Wischhof, L., Hollensteiner, K. J., and Koch, M. (2011) Impulsive behaviour in rats induced by intracortical DOI infusions is antagonized by co-administration of an mGlu2/3 receptor agonist. *Behav. Pharmacol. 22*, 805−813.
(173) Fletcher, P. J., Tampakeras, M., Sinyard, J., and Higgins, G. A. (2007) Opposing effects of 5-HT(2A) and 5-HT(2C) receptor antagonists in the rat and mouse on premature responding in the five-choice serial reaction time test. *Psychopharmacology 195*, 223−234.
(174) Ruotsalainen, S., Sirvio, J., Jakala, P., Puumala, T., MacDonald, E., and Riekkinen, P., Sr. (1997) Differential effects of three 5-HT receptor antagonists on the performance of rats in attentional and working memory tasks. *Eur. Neuropsychopharmacol. 7*, 99−108.
(175) Passetti, F., Dalley, J. W., and Robbins, T. W. (2003) Double dissociation of serotonergic and dopaminergic mechanisms on attentional performance using a rodent five-choice reaction time task. *Psychopharmacology 165*, 136−145.
(176) Carli, M., Baviera, M., Invernizzi, R. W., and Balducci, C. (2004) The serotonin 5-HT2A receptors antagonist M100907 prevents impairment in attentional performance by NMDA receptor blockade in the rat prefrontal cortex. *Neuropsychopharmacology 29*, 1637−1647.
(177) Higgins, G. A., Enderlin, M., Haman, M., and Fletcher, P. J. (2003) The 5-HT2A receptor antagonist M100,907 attenuates motor and "impulsive-type" behaviours produced by NMDA receptor antagonism. *Psychopharmacology 170*, 309−319.
(178) Agnoli, L., and Carli, M. (2012) Dorsal-striatal 5-HT(2)A and 5-HT(2)C receptors control impulsivity and perseverative responding in the 5-choice serial reaction time task. *Psychopharmacology 219*, 633−645.
(179) Boulougouris, V., Glennon, J. C., and Robbins, T. W. (2008) Dissociable effects of selective 5-HT2A and 5-HT2C receptor antagonists on serial spatial reversal learning in rats. *Neuropsychopharmacology 33*, 2007−2019.
(180) Boulougouris, V., and Robbins, T. W. (2010) Enhancement of spatial reversal learning by 5-HT2C receptor antagonism is neuroanatomically specific. *J. Neurosci. 30*, 930−938.
(181) Pozzi, L., Greco, B., Sacchetti, G., Leoni, G., Invernizzi, R. W., and Carli, M. (2010) Blockade of serotonin 2A receptors prevents PCP-induced attentional performance deficit and CREB phosphorylation in the dorsal striatum of DBA/2 mice. *Psychopharmacology 208*, 387−399.
(182) Humby, T., Eddy, J. B., Good, M. A., Reichelt, A. C., and Wilkinson, L. S. (2013) A novel translational assay of response inhibition and impulsivity: effects of prefrontal cortex lesions, drugs used in ADHD, and serotonin 2C receptor antagonism. *Neuropsychopharmacology 38*, 2150−2159.
(183) Muir, J. L., Everitt, B. J., and Robbins, T. W. (1995) Reversal of visual attentional dysfunction following lesions of the cholinergic basal forebrain by physostigmine and nicotine but not by the 5-HT3 receptor antagonist, ondansetron. *Psychopharmacology 118*, 82−92.
(184) Park, S. M., and Williams, C. L. (2012) Contribution of serotonin type 3 receptors in the successful extinction of cued or contextual fear conditioned responses: interactions with GABAergic signaling. *Rev. Neurosci. 23*, 555−569.
(185) Nikiforuk, A., Fijal, K., Potasiewicz, A., Popik, P., and Kos, T. (2013) The 5-hydroxytryptamine (serotonin) receptor 6 agonist EMD 386088 ameliorates ketamine-induced deficits in attentional set shifting and novel object recognition, but not in the prepulse inhibition in rats. *J. Psychopharmacol. 27*, 469−476.
(186) Woods, S., Clarke, N. N., Layfield, R., and Fone, K. C. (2012) 5-HT(6) receptor agonists and antagonists enhance learning and memory in a conditioned emotion response paradigm by modulation of cholinergic and glutamatergic mechanisms. *Br. J. Pharmacol. 167*, 436−449.
(187) Burnham, K. E., Baxter, M. G., Bainton, J. R., Southam, E., Dawson, L. A., Bannerman, D. M., and Sharp, T. (2010) Activation of 5-HT(6) receptors facilitates attentional set shifting. *Psychopharmacology 208*, 13−21.
(188) Hatcher, P. D., Brown, V. J., Tait, D. S., Bate, S., Overend, P., Hagan, J. J., and Jones, D. N. (2005) 5-HT6 receptor antagonists improve performance in an attentional set shifting task in rats. *Psychopharmacology 181*, 253−259.
(189) Rodefer, J. S., Nguyen, T. N., Karlsson, J. J., and Arnt, J. (2008) Reversal of subchronic PCP-induced deficits in attentional set shifting in rats by sertindole and a 5-HT6 receptor antagonist: comparison among antipsychotics. *Neuropsychopharmacology 33*, 2657−2666.
(190) King, M. V., Sleight, A. J., Woolley, M. L., Topham, I. A., Marsden, C. A., and Fone, K. C. (2004) 5-HT6 receptor antagonists reverse delay-dependent deficits in novel object discrimination by enhancing consolidation—An effect sensitive to NMDA receptor antagonism. *Neuropharmacology 47*, 195−204.
(191) Nikiforuk, A., and Popik, P. (2013) Amisulpride promotes cognitive flexibility in rats: The role of 5-HT7 receptors. *Behav. Brain Res. 248*, 136−140.

DOI: 10.1021/cn500340j
ACS Chem. Neurosci. 2015, 6, 970−986

(192) Nikiforuk, A., Kos, T., Fijal, K., Holuj, M., Rafa, D., and Popik, P. (2013) Effects of the selective 5-HT7 receptor antagonist SB-269970 and amisulpride on ketamine-induced schizophrenia-like deficits in rats. *PloS One 8*, e66695.
(193) Iyer, R. N., Sprouse, J. S., Aghajanian, G. K., Roth, R. H., and Bradberry, C. W. (1994) Tryptophan pretreatment augmentation of p-chloroamphetamine-induced serotonin and dopamine release and reduction of long-term neurotoxicity. *Biochem. Pharmacol. 48*, 1501−1508.
(194) Yamaguchi, T., Suzuki, M., and Yamamoto, M. (1997) Evidence for 5-HT4 receptor involvement in the enhancement of acetylcholine release by p-chloroamphetamine in rat frontal cortex. *Brain Res. 772*, 95−101.
(195) Pozzi, L., Invernizzi, R., Garavaglia, C., and Samanin, R. (1999) Fluoxetine increases extracellular dopamine in the prefrontal cortex by a mechanism not dependent on serotonin: A comparison with citalopram. *J. Neurochem. 73*, 1051−1057.
(196) Assie, M. B., Ravailhe, V., Faucillon, V., and Newman-Tancredi, A. (2005) Contrasting contribution of 5-hydroxytryptamine 1A receptor activation to neurochemical profile of novel antipsychotics: frontocortical dopamine and hippocampal serotonin release in rat brain. *J. Pharmacol. Exp. Ther. 315*, 265−272.
(197) Arborelius, L., Nomikos, G. G., Hertel, P., Salmi, P., Grillner, P., Hook, B. B., Hacksell, U., and Svensson, T. H. (1996) The 5-HT1A receptor antagonist (S)-UH-301 augments the increase in extracellular concentrations of 5-HT in the frontal cortex produced by both acute and chronic treatment with citalopram. *Naunyn-Schmiedeberg's Arch. Pharmacol. 353*, 630−640.
(198) Dekker, A. J., and Thal, L. J. (1993) Independent effects of cholinergic and serotonergic lesions on acetylcholine and serotonin release in the neocortex of the rat. *Neurochem. Res. 18*, 277−283.
(199) Calcagno, E., Carli, M., and Invernizzi, R. W. (2006) The 5-HT(1A) receptor agonist 8-OH-DPAT prevents prefrontocortical glutamate and serotonin release in response to blockade of cortical NMDA receptors. *J. Neurochem. 96*, 853−860.
(200) Iskra-Jopa, J., Golembiowska, K., Dziubina, A., Cybulski, M., Duszynska, B., and Chilmonczyk, Z. (2005) In-vivo effects of the 1,2,4-piperazine derivatives MMS and MC1, putative 5-HT agonists, on dopamine and serotonin release in rat prefrontal cortex. *J. Pharm. Pharmacol. 57*, 205−211.
(201) Hughes, Z. A., Starr, K. R., Langmead, C. J., Hill, M., Bartoszyk, G. D., Hagan, J. J., Middlemiss, D. N., and Dawson, L. A. (2005) Neurochemical evaluation of the novel 5-HT1A receptor partial agonist/serotonin reuptake inhibitor, vilazodone. *Eur. J. Pharmacol. 510*, 49−57.
(202) Katsu, H. (2001) Selective 5-HT1A receptor agonist, 8-OH-DPAT, locally administered into the dorsal raphe nucleus increased extracellular acetylcholine concentrations in the medial prefrontal cortex of conscious rats. *Nippon Shinkei, Seishin Yakurigaku Zasshi 21*, 121−123.
(203) Tsuji, K. (2002) [Effect of (±)-pindolol on the central 5-HT1A receptor by the use of in vivo microdialysis and hippocampal slice preparations]. *Nippon Shinkei, Seishin Yakurigaku Zasshi 22*, 85−95.
(204) Millan, M. J., Brocco, M., Gobert, A., Dorey, G., Casara, P., and Dekeyne, A. (2001) Anxiolytic properties of the selective, non-peptidergic CRF(1) antagonists, CP154,526 and DMP695: a comparison to other classes of anxiolytic agent. *Neuropsychopharmacology 25*, 585−600.
(205) Pudovkina, O. L., Kawahara, Y., de Vries, J., and Westerink, B. H. (2001) The release of noradrenaline in the locus coeruleus and prefrontal cortex studied with dual-probe microdialysis. *Brain Res. 906*, 38−45.
(206) Hiramatsu, N., Ago, Y., Hasebe, S., Nishimura, A., Mori, K., Takuma, K., and Matsuda, T. (2013) Synergistic effect of 5-HT1A and sigma1 receptor activation on prefrontal dopaminergic transmission under circulating steroid deficiency. *Neuropharmacology 75*, 53−61.
(207) Wedzony, K., Mackowiak, M., Fijal, K., and Golembiowska, K. (1996) Ipsapirone enhances the dopamine outflow via 5-HT1A receptors in the rat prefrontal cortex. *Eur. J. Pharmacol. 305*, 73−78.
(208) Bortolozzi, A., Masana, M., Diaz-Mataix, L., Cortes, R., Scorza, M. C., Gingrich, J. A., Toth, M., and Artigas, F. (2010) Dopamine release induced by atypical antipsychotics in prefrontal cortex requires 5-HT(1A) receptors but not 5-HT(2A) receptors. *Int. J. Neuropsychopharmacol. 13*, 1299−1314.
(209) de Groote, L., Olivier, B., and Westenberg, H. G. (2002) Extracellular serotonin in the prefrontal cortex is limited through terminal 5-HT(1B) autoreceptors: a microdialysis study in knockout mice. *Psychopharmacology 162*, 419−424.
(210) Hertel, P., Nomikos, G. G., and Svensson, T. H. (1999) The antipsychotic drug risperidone interacts with auto- and hetero-receptors regulating serotonin output in the rat frontal cortex. *Neuropharmacology 38*, 1175−1184.
(211) Trillat, A. C., Malagie, I., Scearce, K., Pons, D., Anmella, M. C., Jacquot, C., Hen, R., and Gardier, A. M. (1997) Regulation of serotonin release in the frontal cortex and ventral hippocampus of homozygous mice lacking 5-HT1B receptors: In vivo microdialysis studies. *J. Neurochem. 69*, 2019−2025.
(212) Consolo, S., Arnaboldi, S., Ramponi, S., Nannini, L., Ladinsky, H., and Baldi, G. (1996) Endogenous serotonin facilitates in vivo acetylcholine release in rat frontal cortex through 5-HT 1B receptors. *J. Pharmacology Exp. Ther. 277*, 823−830.
(213) Ferdyn-Drosik, M., Nowak, P., Bojanek, K., Balasz, M., Kasperski, J., Skaba, D., Muchacki, R., and Kostrzewa, R. M. (2010) Neonatal DSP-4 treatment impairs 5-HT(1B) receptor reactivity in adult rats. Behavioral and biochemical studies. *Pharmacol. Rep. 62*, 608−620.
(214) Sharp, T., Umbers, V., and Gartside, S. E. (1997) Effect of a selective 5-HT reuptake inhibitor in combination with 5-HT1A and 5-HT1B receptor antagonists on extracellular 5-HT in rat frontal cortex in vivo. *Br. J. Pharmacol. 121*, 941−946.
(215) Franberg, O., Marcus, M. M., and Svensson, T. H. (2012) Involvement of 5-HT2A receptor and alpha2-adrenoceptor blockade in the asenapine-induced elevation of prefrontal cortical monoamine outflow. *Synapse 66*, 650−660.
(216) Nair, S. G., and Gudelsky, G. A. (2004) Activation of 5-HT2 receptors enhances the release of acetylcholine in the prefrontal cortex and hippocampus of the rat. *Synapse 53*, 202−207.
(217) Pehek, E. A. (1996) Local infusion of the serotonin antagonists ritanserin or ICS 205,930 increases in vivo dopamine release in the rat medial prefrontal cortex. *Synapse 24*, 12−18.
(218) Mork, A., Witten, L. M., and Arnt, J. (2009) Effect of sertindole on extracellular dopamine, acetylcholine, and glutamate in the medial prefrontal cortex of conscious rats: A comparison with risperidone and exploration of mechanisms involved. *Psychopharmacology 206*, 39−49.
(219) Fell, M. J., Katner, J. S., Rasmussen, K., Nikolayev, A., Kuo, M. S., Nelson, D. L., Perry, K. W., and Svensson, K. A. (2012) Typical and atypical antipsychotic drugs increase extracellular histamine levels in the rat medial prefrontal cortex: contribution of histamine h(1) receptor blockade. *Front. Psychiatry 3*, 49.
(220) Kurata, K., Ashby, C. R., Jr., Oberlender, R., Tanii, Y., Kurachi, M., Rini, N. J., and Strecker, R. E. (1996) The characterization of the effect of locally applied N-methylquipazine, a 5-HT3 receptor agonist, on extracellular dopamine levels in the anterior medial prefrontal cortex in the rat: An in vivo microdialysis study. *Synapse 24*, 313−321.
(221) Huang, M., Felix, A. R., Kwon, S., Lowe, D., Wallace, T., Santarelli, L., and Meltzer, H. Y. (2014) The alpha-7 nicotinic receptor partial agonist/5-HT3 antagonist RG3487 enhances cortical and hippocampal dopamine and acetylcholine release. *Psychopharmacology 231*, 2199−2210.
(222) Diez-Ariza, M., Garcia-Alloza, M., Lasheras, B., Del Rio, J., and Ramirez, M. J. (2002) GABA(A) receptor antagonists enhance cortical acetylcholine release induced by 5-HT(3) receptor blockade in freely moving rats. *Brain Res. 956*, 81−85.
(223) Nair, S. G., and Gudelsky, G. A. (2005) 3,4-Methylenedioxymethamphetamine (MDMA) enhances the release of acetylcholine

DOI: 10.1021/cn500340j
ACS Chem. Neurosci. 2015, 6, 970−986

by 5-HT4 and D1 receptor mechanisms in the rat prefrontal cortex. *Synapse 58*, 229−235.
(224) Yamaguchi, T., Suzuki, M., and Yamamoto, M. (1997) Facilitation of acetylcholine release in rat frontal cortex by indeloxazine hydrochloride: involvement of endogenous serotonin and 5-HT4 receptors. *Naunyn-Schmiedeberg's Arch. Pharmacol. 356*, 712−720.
(225) Russell, M. G., and Dias, R. (2002) Memories are made of this (perhaps): a review of serotonin 5-HT(6) receptor ligands and their biological functions. *Curr. Top. Med. Chem. 2*, 643−654.
(226) Wesolowska, A., and Kowalska, M. (2008) Influence of serotonin 5-HT(7) receptor blockade on the behavioral and neurochemical effects of imipramine in rats. *Pharmacol. Rep. 60*, 464−474.
(227) van Amsterdam, C., and Seyfried, C. A. (2014) Mechanism of action of the bimodal antidepressant vilazodone: Evidence for serotonin1A-receptor-mediated auto-augmentation of extracellular serotonin output. *Psychopharmacology 231*, 2547−2558.
(228) Allers, K. A., Dremencov, E., Ceci, A., Flik, G., Ferger, B., Cremers, T. I., Ittrich, C., and Sommer, B. (2010) Acute and repeated flibanserin administration in female rats modulates monoamines differentially across brain areas: a microdialysis study. *J. Sex. Med. 7*, 1757−1767.
(229) Mork, A., Pehrson, A., Brennum, L. T., Nielsen, S. M., Zhong, H., Lassen, A. B., Miller, S., Westrich, L., Boyle, N. J., Sanchez, C., Fischer, C. W., Liebenberg, N., Wegener, G., Bundgaard, C., Hogg, S., Bang-Andersen, B., and Stensbol, T. B. (2012) Pharmacological effects of Lu AA21004: a novel multimodal compound for the treatment of major depressive disorder. *J. Pharmacol. Exp. Ther. 340*, 666−675.
(230) Mork, A., Montezinho, L. P., Miller, S., Trippodi-Murphy, C., Plath, N., Li, Y., Gulinello, M., and Sanchez, C. (2013) Vortioxetine (Lu AA21004), a novel multimodal antidepressant, enhances memory in rats. *Pharmacol., Biochemi. Behav. 105*, 41−50.
(231) Barone, P., Jordan, D., Atger, F., Kopp, N., and Fillion, G. (1994) Quantitative autoradiography of 5-HT1D and 5-HT1E binding sites labelled by [3H]5-HT, in frontal cortex and the hippocampal region of the human brain. *Brain Res. 638*, 85−94.
(232) Beique, J. C., Campbell, B., Perring, P., Hamblin, M. W., Walker, P., Mladenovic, L., and Andrade, R. (2004) Serotonergic regulation of membrane potential in developing rat prefrontal cortex: coordinated expression of 5-hydroxytryptamine (5-HT)1A, 5-HT2A, and 5-HT7 receptors. *J. Neurosci. 24*, 4807−4817.

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