

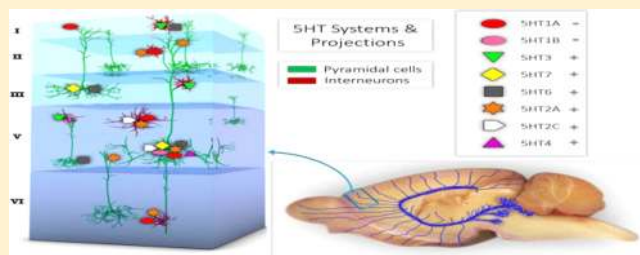
Serotonergic Regulation of Prefrontal Cortical Circuitries Involved in Cognitive Processing: A Review of Individual 5-HT Receptor Mechanisms and Concerted Effects of 5-HT Receptors Exemplified by the Multimodal Antidepressant Vortioxetine

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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 serotonergic 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-HT₁ 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 Ca²⁺ channels of the N- and P/Q-type in 5-HT neurons.⁹ The 5-HT₂ receptor family is stimulatory and signals via G-protein subunit G_q activation of phospholipase C (increasing the levels of inositol triphosphate and diacylglycerol). 5-HT₃ 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

receptor	function	expression		cell type	reference
		mRNA (layer)	protein (layer)		
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

^aI, inhibitory; S, stimulatory; –, absent; +, low; ++, moderate; +++, strong; ?, unknown; Pyr, pyramidal; IN, interneuron; P, parvalbumin; calbin, calbindin; calre, calretinin; Ast, astrocyte. ^bAlso in more shallow layers.

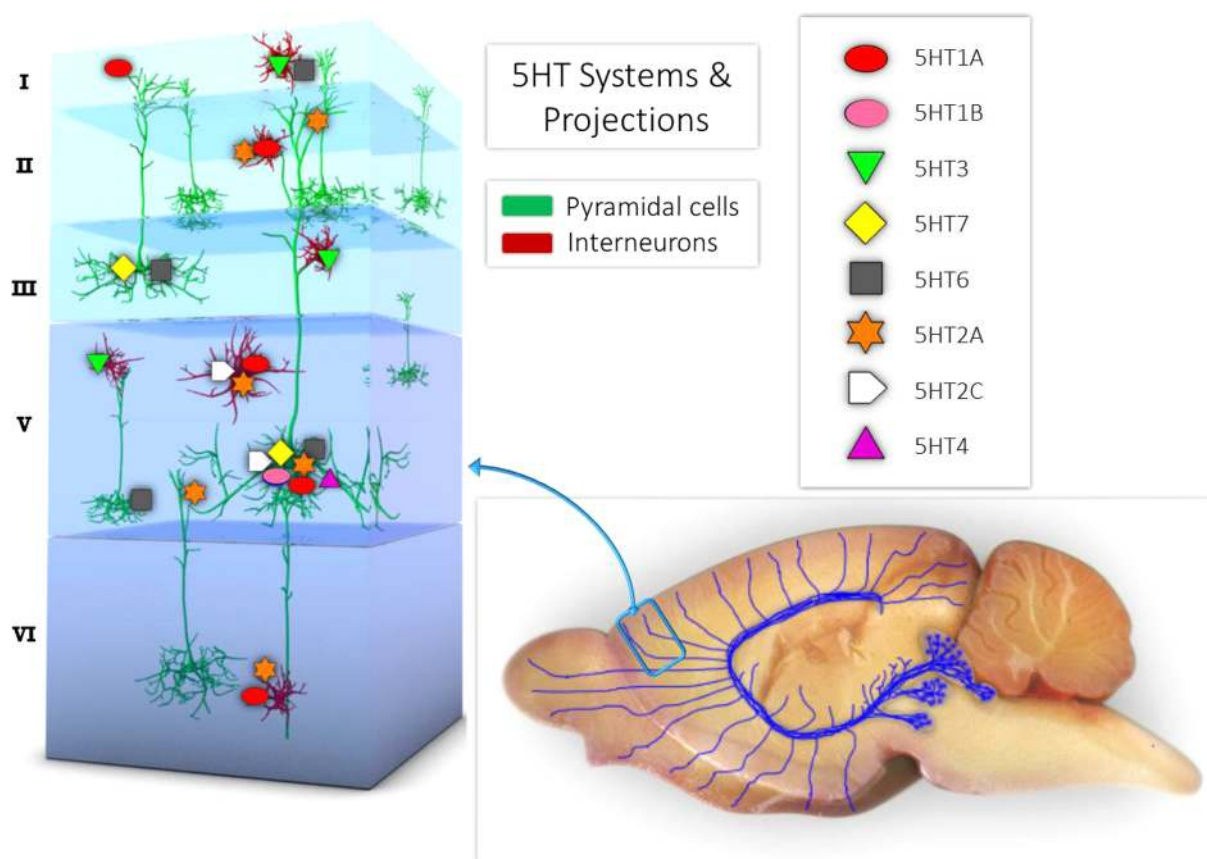


Figure 1. MRNAs for 5-HT₁ (5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}), 5-HT₂ (5-HT_{2A}, 5-HT_{2C}), 5-HT₃, and 5-HT₇ receptors have been detected in PFC tissue (Table 1) and 5-HT_{1A}, 5-HT_{1B}, 5-HT_{2A}, 5-HT_{2C}, and 5-HT₄ receptors are coexpressed on the same pyramidal neuron.⁷⁶ As illustrated in Figure 1 and in Table 1, layer I contains 5-HT_{1A} and 5-HT₆ receptors on apical dendrites of cortical pyramidal neurons, 5-HT_{3A} and 5-HT₆ receptors on somata of slow-spiking GABAergic interneurons;^{2,103,104} layers II–III contain 5-HT_{2A}, 5-HT₆, and 5-HT₇ 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-HT₆ receptors on apical dendrites of cortical pyramidal neurons,^{2,103} 5-HT_{1A}, 5-HT_{1B}, 5-HT_{2A}, 5-HT_{2C}, 5-HT₄, 5-HT₆, and 5-HT₇ 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-HT₄, 5-HT₆, and 5-HT₇ receptors signal via activation of adenylyl cyclase (increasing cAMP levels) and all are stimulatory. The 5-HT₅ 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

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} ∅ 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 ÷ AUTO ¹⁵⁶
PCA (1 week)	rat					
5-HT_{1A} receptor agonists						
8-OH-DPAT	rat	↓↑ 5-CSRTT ^{154,157,158} ↑ RI ¹⁴⁵ ∅ CPP deficits in 5-CSRTT ¹⁵⁸	↑ 5-CSRTT ^{154,157,158} ÷ RT ₁ ¹⁵⁹ ↓ DD ¹⁶⁰ ÷ RI ¹⁴⁵ ↑ FCN ¹⁶¹ ↑ DRL ¹⁶²	↑ AUTO ¹⁶³	↑ AUTO ^{164,165}	↓ PA ^{155,166} ↓ OR ¹⁶⁷ ↑ AUTO ¹⁵⁶ ∅ Scop AUTO deficits ¹⁵⁶
NDO008	rat					↓ PA ¹⁵⁵
S15535	rat	↑ DNMS-S ¹⁶⁸				↑ SR ¹⁶⁸
S15535	mouse	↑ DNMS-S ¹⁶⁸				
Flesinoxan	rat					∅ 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						
GRI27935 (5-HT _{1B/1D})	rat				↑ AUTO ¹⁷⁰	
5-HT _{1B} KO	mouse		↑ DRL ¹⁶⁹	÷ RL ¹⁶⁹	↑ AUTO ¹⁶⁹	
5-HT₂ receptor agonists						
DOI	rat	÷ 5-CSRTT ^{171–173} ÷ RI ¹⁴⁵	↑ 5-CSRTT ^{171–173} ↑ RT ₁ ¹⁵⁹ ÷ RI ¹⁴⁵ ÷ DD ¹⁶⁰			
DOB	rat					↓ PA ¹⁵⁵
5-HT₂ 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 ÷ 5-CSRTT ¹⁷¹		÷ AUTO ¹⁶⁵	÷ DNMS-S ¹⁷⁴
SER082	rat					
5-HT_{2A} receptor antagonists						
M100907	rat	÷↑ 5-CSRTT ^{153,158,173,176–178,157} ∅ CPP deficit in 5-CSRTT ^{158,176,178}	↓ 5-CSRTT ^{153,157,158,173,176} ∅ CPP- or MK-801 deficit in 5-CSRTT ^{158,176–178}	↓ 5-CSRTT ^{153,157,158,173,176} ↓ ÷ RL ^{149,179,180}	÷ RL ¹⁷⁹	÷ AUTO ¹⁵⁶
M100907	mouse	÷ 5-CSRTT ^{173,181} ∅ CPP deficit in 5-CSRTT ¹⁸¹	↓ 5-CSRTT ^{173,181} ∅ 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			

Table 2. continued

mechanism	species	attention	impulsivity	flexibility	learning	memory
5-HT₃ 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-HT₆ 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-HT₆ 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 Ø PCP deficits in OR ¹²⁰
Idalopirdine	rat					
5-HT₇ receptor agonists						
AS19	rat			÷ AS ¹⁹¹	↑ AUTO ¹²⁵	
5-HT₇ 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

^aago, 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

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	∅ ¹⁹⁴	± ¹⁹⁵		
5-HT_{1A} receptor agonists					
8-OH-DPAT	± ^{199–201}	↑ ²⁰²	↑ ^{196,201}	↑ ²⁰¹	
F13640	↓ ⁵⁹		↑ ⁵⁹		
MMS	↓ ²⁰⁰		± ²⁰⁰		
MC1	↓ ²⁰⁰		↓ ²⁰⁰		
Flesinoxan	↓ ^{203,204}		↑ ²⁰⁴	↓ ²⁰⁵ ↑ ²⁰⁴	
5-HT_{1A} receptor antagonists					
WAY100635	± ¹⁹⁹ ↑ ²⁰⁶		∅, 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		∅ ⁵⁰		
5-HT _{1B} KO	↑ ²⁰⁹				
5-HT₂ receptor agonists					
DOI (5-HT _{2A/2C})	↑ ²¹⁵	↑ ²¹⁶	↑ ²¹⁵	↑ ²¹⁵	
5-HT₂ 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-HT₃ receptor agonists					
NMQ			↑ ²²⁰		
m-CPBG		∅ ²²¹			
5-HT₃ receptor antagonists					
Ondansetron		↑ ²²²	↓ ²²⁰		
MDL72222			± ⁵⁰		
BRL46470A			↓ ²²⁰		
5-HT₄ receptor agonists					
prucalopride		↑ ⁹⁶			↑ ⁹⁶
PRX-03140		± ⁹⁶			↑ ⁹⁶
5-HT₄ receptor antagonists					
SDZ 205–557		∅ ²²³			
RS23597		∅ ^{194,224}			
GR113803		∅ ^{194,224}			
5-HT₆ receptor agonists					
WAY181187	↓ ¹¹¹	↓ ¹¹¹		± ¹¹¹	
5-HT₆ receptor antagonists					
SB271046	↑ ²¹⁸ ± ²²⁵		± ²²⁵	± ²²⁵	
Ro046790					± ²¹⁹
5-HT₇ 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; ∅, prevented/blocked pharmacological-increases.

behavioral impulse control and regulation (see²¹). 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 tryptophan 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 humans⁴² 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 serotonin 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 decrease 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-HT₃ receptor agonism appears to increase DA, while antagonism decreases DA but also increases ACh levels. 5-HT₄ receptor agonism increases ACh and antagonism blocks the induction of ACh by 5-HT₄ receptor agonists or 3,4-methylenedioxy-methamphetamine (MDMA). 5-HT₄ agonism also increases histamine (HA) levels. 5-HT₆ receptor agonism decreases while antagonism increases 5-HT. 5-HT₇ 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 (\pm)-8-hydroxy-2-(*n*-dipropylamino)tetralin ([³H]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

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 Ca²⁺ (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

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-HT₂ 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-HT₂ receptor modulation appeared to produce limited effects in learning and memory tests in rodents. Similarly, 5-HT₂ receptor antagonism appears to have little effect on cognitive function in humans.⁴⁰

5-HT₃ Receptors. 5-HT₃ 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-HT₃ 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 lamina⁸⁷ (Pehrson, unpublished data), suggesting that 5-HT₃ receptors are postsynaptically expressed. Studies attempting to assess which type of cells express 5-HT₃ 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-HT₃ 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-HT₃ receptors suppresses the overall activation state of cortical pyramidal neurons.^{89,90} Conversely, 5-HT₃ receptor antagonists inhibit the activity of cortical interneurons⁸⁶ and increase the activity level of cortical pyramidal neurons.⁹¹ Studies in rodents of 5-HT₃ 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-HT₃ receptor antagonists such as ondansetron.⁹²

5-HT₄ Receptors. 5-HT₄ 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-HT₄ 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-HT₄ receptors to circuit activity in the frontal cortex, beyond an autoradiographic demonstration that 5-HT₄ receptor binding sites are weakly present in the frontal cortex.⁹⁵ The activation of 5-HT₄ receptors has dual effects (enhancement or reduction) on GABA-evoked currents in PFC pyramidal neurons.⁵³ Johnson et al. demonstrated that 5-HT₄ receptor agonism (prucalopride or PRX-03140) increases cortical ACh and HA levels.⁹⁶ Effects of 5-HT₄ 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-HT₄ receptor activation enhances cognition in preclinical models such as spontaneous alternation and delayed matching and 5-HT₄ 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-HT₄ 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-HT₄ agonists. Thus, the procognitive effects elicited by activation of 5-HT₄ receptors could be driven in part via hippocampal mechanisms.^{98,99}

5-HT₅ Receptors. Mechanistic studies of the 5-HT₅ 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-HT₅ 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-HT₅ 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 it⁴⁶ although more work is needed to be certain of these effects.

5-HT₆ Receptors. Although 5-HT₆ 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-HT₆ receptor antibodies. However, numerous studies have mapped 5-HT₆ 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-HT₆ receptor activity results in the regulation of multiple neurotransmitter systems in the prefrontal cortex. In vivo microdialysis has demonstrated that the 5-HT₆ 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-HT₆ 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-HT₆ receptor antagonism on monoamines are less consistent, showing either an increase in DA and NE levels with SB271046¹¹⁶ or a lack of effect on monoamines with the

same compound.¹¹⁵ The literature consistently reports that facilitation of cholinergic transmission contributes to the procognitive effects of 5-HT₆ receptor antagonism. Two studies have demonstrated that 5-HT₆ 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-HT₆ 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-HT₆ receptors improves cortical performance in different learning and memory paradigms^{119–121} and a few 5-HT₆ receptor antagonists are in clinical development for cognitive disorders, most notably for Alzheimer's disease.^{122,123} 5-HT₆ 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-HT₆ 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-HT₇ Receptors. 5-HT₇ 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 interneurons¹²⁶ 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-HT₇ 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-HT₇ receptors on GABAergic interneurons in the frontal cortex; however, 5-HT₇ receptors have been identified on GABAergic cells in other brain regions, such as in cerebellar purkinje cells. 5-HT₇ 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-HT₇ receptor antagonism induces inhibition of 5-HT efflux indirectly via activation of GABA_A receptors.¹³⁰ In other words, activation of 5-HT₇ 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-HT₇ receptor antagonists would decrease 5-HT efflux.¹³⁰ Yet further work is needed to ascertain the mechanisms by which 5-HT₇ receptors produce these effects.

Nevertheless, 5-HT₇ receptors seem to play an important role in cognition. Selective 5-HT₇ 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-HT₇ 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-HT₇ 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-HT₇ 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-HT₇ 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-HT₆ 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-HT₃, 5-HT₇, 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-HT₃ 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

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-HT₃, and 5-HT₄ 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, (\pm)-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 tryptophan depletion; cAMP, cyclic adenosine monophosphate; BRL46470, endo-*N*-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-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-propoxyprolo[3,2-*b*]pyridine; CPP, 3-(2-carboxypiperazin-4-yl)propyl-1-phosphonic acid; DA, dopamine; DOI, (\pm)-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; MMS, 1-[4-(4-chinolin-2-yl-piperazin-1-yl)-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]carbomoyl]-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

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