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Corresponding Author	Family Name	**Boulougouris**
	Particle	
	Given Name	**Vasileios**
	Suffix	
	Division	Experimental Psychology Laboratory, Department of Psychiatry
	Organization	Athens University Medical School, Eginition Hospital
	Address	74, Vas. Sofias Ave., 11528, Athens, Greece
	Email	vboulougouris@googlemail.com
Author	Family Name	**Tsaltas**
	Particle	
	Given Name	**Eleftheria**
	Suffix	
	Division	Experimental Psychology Laboratory, Department of Psychiatry
	Organization	Athens University Medical School, Eginition Hospital
	Address	74, Vas. Sofias Ave., 11528, Athens, Greece
	Email	

Abstract	Disturbances in attentional processes and executive functioning are a common feature of several psychiatric afflictions such as schizophrenia, attention deficit/hyperactivity disorder, and obsessive–compulsive disorder (OCD). The use of animal models has been useful in defining various candidate neural systems, thus enabling us to translate basic laboratory science to the clinic and vice versa. This chapter provides a review on the contribution of the serotonergic system on the modulation of basic behavioral operations such as selective attention, vigilance, set shifting, and executive control focusing on the 5-HT_{2C} receptor subtype. Specifically, we have reviewed evidence emerging from several behavioral paradigms in experimental animals, each of which centers on a different aspect of the attentional and executive function. These paradigms include the five-choice serial reaction time task (5CSRTT), attentional set shifting, the spatial alternation, and the signal attenuation tasks. In each case, the types of operation that are measured by the given paradigm are defined, and the role of the ascending serotonergic system in the neurochemical modulation of its behavioral output is examined. In conclusion, reference is made to clinical implications for neurological and neuropsychiatric disorders that exhibit deficits in these cognitive tests.

Chapter 23
The Role of Serotonin on Attentional Processes and Executive Functioning: Focus on 5-HT$_{2C}$ Receptors

Eleftheria Tsaltas and Vasileios Boulougouris

23.1 Introduction

Attention refers to the processes determining an organism's receptivity to external or internal excitation and hence the probability that it will engage in the processing of that excitation (Parasuraman 1998). Although it is often related as a cognitive function, it is distinct in encompassing a multitude of manifestations that underlie and sustain the activity of the other cognitive and behavioral performance in several ways: through the selection and integration of sensory inputs, which is essential for efficient learning and remembering as well as for the organization of appropriate responses. Impaired attentional processing may therefore become manifested as inattention, distractibility, memory impairment, confusion, perseveration, or disinhibition. Recognition of the diversity of attention has led to the identification of three distinct fundamental qualities: selection, enabling the allocation of priority to certain informational elements to the exclusion of others; vigilance, referring to the capacity for attentional persistence over time; and control, which optimizes performance, for example, by inhibition of concurrent activities (Parasuraman 1998; Robbins 2002, 2005).

Attempts to uncover neural mechanisms through which brain serotonin systems influence attentional processes as well as other executive functions are complicated by the heterogeneity of the receptors through which serotonin acts. At least 14 distinct subtypes of serotonin (5-hydroxytryptamine, or 5-HT) receptors are expressed within the central nervous system (Barnes and Sharp 1999). They are highly diverse in respect to their structures, gene regulation, primary effect or mechanisms, regional and subcellular expression patterns and physiological actions. However, the multiplicity of 5-HT receptors provides an opportunity for a fine functional dissection of brain serotonin systems, one receptor at a time.

V. Boulougouris (✉)
Experimental Psychology Laboratory, Department of Psychiatry, Athens University Medical School, Eginition Hospital, 74, Vas. Sofias Ave., 11528 Athens, Greece
e-mail: vboulougouris@googlemail.com

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Progress in this area has been facilitated by the development of relatively selective pharmacological tools and by molecular genetic techniques enabling the generation of animals with planned 5-HT receptor gene mutations. In order to ascertain neuroanatomical and neurochemical specificity of experimental interventions, it is necessary to resort to the use of experimental animal models. This endeavor has been facilitated by the current availability of comparable cross-species tests of cognitive function. These enable the identification of common neural substrates that subserve similar functions across species, increasing the likelihood that the same cognitive functions are being studied in each species.

In this chapter, the contribution of the serotonergic system to basic operations such as vigilance, shifting, and executive control are surveyed with emphasis to a prominent central serotonin receptor subtype – the 5-HT_{2C} receptor. Following a brief description of the anatomy of 5-HT_{2A} and 5-HT_{2C} receptor, the survey is focused on evidence from experimental animals. It encompasses data generated by four different experimental conditions, each of which centers on a specific aspect of the attentional and executive function.

The first paradigm is the five-choice serial reaction time task, which provides a direct measure of sustained attention and bears good analogy to the human continuous performance test (CPT), a traditional index of human vigilance. The second paradigm is attentional set shifting and reversal learning, which has been used to decompose the types of processes engaged by tests of attentional flexibility such as the Wisconsin Card Sort Test (WCST). The third paradigm is the reinforced spatial alternation measuring memory, cognitive flexibility, as well as persistent behavior. Finally, the signal attenuation paradigm models certain components of executive control, including attention and inhibition. In each case, the types of operation that are measured by the given paradigm will be defined. Then, the role of the serotonergic systems in the neurochemical modulation of its behavioral output will be examined, focusing on the contribution of the 5-HT_{2C} receptor subtype. In conclusion, reference to clinical implications for neurological and neuropsychiatric disorders will be made.

23.2 5-HT Receptor Subtypes

The true complexity of the serotonergic system is revealed when it is considered that over 14 different types of 5-HT receptor, assigned to one of seven families (5-$HT_{1–7}$), have currently been identified and that the number is set to rise (Barnes and Sharp 1999; Hoyer et al. 2002). Investigation of the possibility that these different receptors mediate different functions within the 5-HT system has only begun more recently with the advent of selective pharmaceutical compounds that can distinguish between the different receptor subtypes, and this avenue of research is constantly growing with the continuous development of more selective agents. Given the increasing interest in the serotonergic system in relation to psychiatric disorders and the escalating number of drug targets available, a comprehensive

review of this work would be lengthy undertaking. Discussion that is more detailed will therefore be limited to 5-HT_{2A} and 5-HT_{2C} receptor subtypes, with the caveat that this is not a comprehensive delineation of the 5-HT receptors that may be implicated in the regulation of attentional processes and executive functions.

23.2.1 5-HT_{2A} Receptor Subtypes

There are currently three members of the 5-HT_2 receptor family (5-HT_{2A}, 5-HT_{2B}, 5-HT_{2C}) all of which are coupled positively to phospholipase C and mobilize intracellular calcium. Investigation of the function of individual members of the 5-HT_2 family has only proved possible quite recently with the development of selective 5-HT2A and 5-HT_{2C} receptor antagonists (5-HT_{2A} receptor antagonist: M100907, formerly MDL 100907; 5-HT_{2C} receptor antagonists: SB 242084 and RS 102221). However, there is still a need for more selective agonists, particularly at the 5-HT_{2A} receptor. Receptor autoradiography studies using tritiated ligands demonstrate high levels of 5-HT_{2A} receptors in many forebrain regions, and particularly in cortical areas, including frontal cortex, the nucleus accumbens, caudate nucleus, and HPC (Lopez-Gimenez et al. 1997; Pazos et al. 1985, 1987).

5-HT_{2A} receptors are located postsynaptically to serotonergic neurons and have been found on both γ-aminobutyric acid (GABA)-ergic interneurons as well as glutamatergic cortical pyramidal cells (Burnet et al. 1995; Francis et al. 1992; Morilak et al. 1993, 1994; Wright et al. 1995). Activation of the 5-HT_{2A} receptors depolarizes the cell membrane, potentially through a decrease in K^+ currents (Marek and Aghajanian 1995; Aghajanian and Marek 1997; Araneda and Andrade 1991). Although it has generally been reported that none of the more selective 5-HT_2 receptor agonists or antagonists alter levels of 5-HT (e.g., Gobert and Millan 1999; Gobert et al. 2000), it has been suggested that 5-HT_{2A} receptors are involved in a glutamatergic feedback loop originating from the prefrontal cortex (PFC) and terminating in the ~~DRN, therefore~~ stimulation of 5-HT_{2A} receptors in this region may have the capacity to alter 5-HT release throughout the forebrain (Martin-Ruiz et al. 2001).

23.2.2 5-HT_{2C} Receptor Subtypes

The 5-HT_{2C} receptor was originally classified as a member of the 5-HT1 family (5-HT_{1C}) (Pazos et al. 1987) but has been reclassified following more extensive investigation of its structure and function (Humphrey et al. 1993). Unlike the 5-HT_{2A} receptors, 5-HT_{2C} receptors are only found within the central nervous system (Palacios et al. 1990). However, 5-HT_{2C} receptors are widely distributed within the brain, and high levels are found in the cortex, limbic system, and basal ganglia. The majority of studies point to a predominantly postsynaptic location for 5-HT_{2C}

receptors, but 5-HT_{2C} receptor mRNA has been localized within the DRN, indicating that this receptor could be found at presynaptic sites as well.

In common with the 5-HT_{2A} receptor, activation of the 5-HT_{2C} receptor also appears to depolarize the cell membrane (Rick et al. 1995; Sheldon and Aghajanian 1991), although as with the majority of data regarding the 5-HT_{2A} receptor, much has been inferred through observations that 5-HT-induced increases in activity are not blocked by a range of other 5-HT-receptor specific antagonists. Hopefully, the fact that there is now a commercially available 5-HT_{2C} receptor agonist, WAY 161503, will enable clarification of both the physiological and behavioral effects of 5-HT_{2C} receptor stimulation.

23.3 5-HT and the Five-Choice Serial Reaction Time Task (5CSRTT)

The 5CSRTT is an animal test widely used with rodents providing substantial validity as a direct measure of different components of attention (for details see Boulougouris and Tsaltas 2008; Carli et al. 1983). In brief, animals are trained to detect the location of a brief visual stimulus presented pseudorandomly in one of the five apertures over a large number of trials. The performance measures include choice accuracy, omissions, premature responses (responses made before the target stimulus), perseverative responses (additional nose pokes made postpresentation of the stimulus in any nose-poke aperture), perseverative panel pushes (additional responses made at the food magazine before or after food retrieval), correct response latency, and food collection latency.

Optimal performance on this apparently simple task requires the integration of several cognitive processes. Sustained attention to the goal area for the duration of the intertrial interval (ITI) is necessary in order not to miss the target, while divided attention across all five exposed holes is essential in order to scan the entire visual array. Other processes measured by this task include sensor, motor or motivational processes, decision making, and inhibitory control (for details see Boulougouris and Tsaltas 2008). Apart ~~for~~ aspects of attention and impulse control, the task is also capable of dissociating performance elements which usually covary, although they probably rely on processes that are under control of different neural mechanisms.

Neurochemically speaking, apart from the involvement of the dopaminergic system in the modulation of the 5CSRTT (discussed in Boulougouris and Tsaltas 2008), the serotonergic system is also heavily implicated. The 5CSRTT is demonstrably sensitive to serotonergic manipulations: Global, 5,7-dihydroxytryptamine (5,7-DHT) lesion-induced 5-HT depletion consistently appears to spare response accuracy, while it increases impulsivity as reflected by increased premature responding and decreased omissions as well as correct response latency (Harrison et al. 1997; Winstanley et al. 2003a, 2004; Koskinen et al. 2000). However, systemic administration of the 5-HT_{1A} receptor agonist 8-hydroxy-2-(di-*n*-propylamino)tetraline

(8-OH-DPAT), which also decreases 5-HT release (Bonvento et al. 1992; Hajos et al. 1999; Celada et al. 2001), does not affect impulsive responding and improves attentional performance (Winstanley et al. 2003a). At higher doses, the selective 5-HT1A receptor agonist 8-OH-DPAT reportedly increased impulsivity, possibly by activating presynaptic 5-HT_{1A} receptors (Carli and Samanin 2000). There is an incongruence, then, between the effects of chronic lesion-induced global 5-HT decreases and [AU3] the effects of acute global decreases such as those affected by systemic administration of a 5-HT_{1A} receptor agonist.

The apparent inconsistency is compounded by the observation that systemic and ~~infusions~~ of the 5-HT_{2A} receptor antagonist M100907 in the prefrontal cortex (PFC) decrease impulsive responding (Winstanley et al. 2003a). Moreover, infusions of M100907 in the medial prefrontal cortex (mPFC) counteracted the loss of executive control [impulsivity induced by the competitive *N*-methyl-D-aspartate (NMDA) receptor antagonist 3-(R)-2-carboxypiperazin-4-propyl-1-phosphonic acid (CPP)], while 8-OH-DPAT decreased compulsive perseveration (Carli et al. 2006). Thus, an antagonist of the 5-HT system effectively produces effects opposite of those of global decrease in 5-HT transmission. This paradox, along with the observation that 2,5-dimethoxy-4-iodoamphetamine (DOI), a 5-$HT_{2A/2C}$ agonist does increase premature responding, probably through activation of the 5-HT_{2A} receptor (Koskinen et al. 2000), suggests dissociable behavioral contribution of 5-HT receptor subtypes in the 5CSRTT.

Indeed, evidence suggests that the 5-HT_{2A} and 5-HT_{2C} receptors have opposing neurochemical effects. 5-HT_{2C} receptor activation inhibits dopamine release, whereas 5-HT_{2A} activation enhances dopamine release (Di Matteo et al. 2000, 2001; Millan et al. 1998). Antagonism of 5-HT_{2C} and 5-HT_{2A} receptors has opposite effects on some behavioral effects of cocaine (Fletcher et al. 2002). Furthermore, it has been demonstrated that 5-HT_{2C} and 5-HT_{2A} receptors also have contrasting and dissociable behavioral contribution on impulsivity in the 5CSRTT. The selective 5-HT_{2C} antagonist SB 242084 increases premature responding and decreases correct response latency (Winstanley et al. 2004; Higgins et al. 2003) (Fig. 23.1a). This premature responding increase has recently been shown to be mediated by the nucleus accumbens (NAc) (Robinson et al. 2008) (Fig. 23.1c). When the antagonist was administered systemically to 5,7-DHT-lesioned animals, the increase in premature responding emerged over and above the similar effects of the 5,7-DHT lesion (Winstanley et al. 2004). In contrast, the selective 5-HT_{2A} antagonist M100907 had no effect on response latency and actually reduced premature responding, an effect mediated by the NAc (Robinson et al. 2008). The effect of M100907 (administered systemically) was abolished by 5,7-DHT lesions (Winstanley et al. 2004). This dissociation challenges the hypothesis that general decreases in 5-HT neurotransmission increase impulsivity. Furthermore, the fact that antagonism of the 5-HT_{2C} receptor produces a behavioral profile closer to 5,7-DHT lesions than any other receptor so far tested including the 5-HT_{2A} receptor suggests that the 5-HT_{2C} receptor is central in the serotonergic regulation of behavioral inhibition.

Compulsivity, another form of inhibition deficit, is also accessible by the 5CSRTT via the measure of repeated responding at the holes (perseverative

responding), offering a putative index of compulsivity. Winstanley et al. (2004) demonstrated that 5,7-DHT lesions increased perseverative as well as impulsive responding, a finding consistent with increased perseverative errors during reversal in the marmoset after localized 5-HT depletion within the PFC (Clarke et al. 2004) and after orbitofrontal cortex (OFC) damage (Jones and Mishkin 1972; Rogers et al. 1999; Schoenbaum et al. 2002; Chudasama and Robbins 2003; Chudasama et al. 2003). Neither 5-HT_{2A} antagonism (M100907) nor 5-HT_{2C} antagonism (SB 242084) appears to affect perseverative responses (Winstanley et al. 2003a, 2004; Higgins et al. 2003; Chudasama and Robbins 2003; Chudasama et al. 2003). These data suggest that different kinds of motor disinhibition differ in their neurobiological bases, as impulsivity and compulsivity appear to be differentially regulated by the 5-HT system.

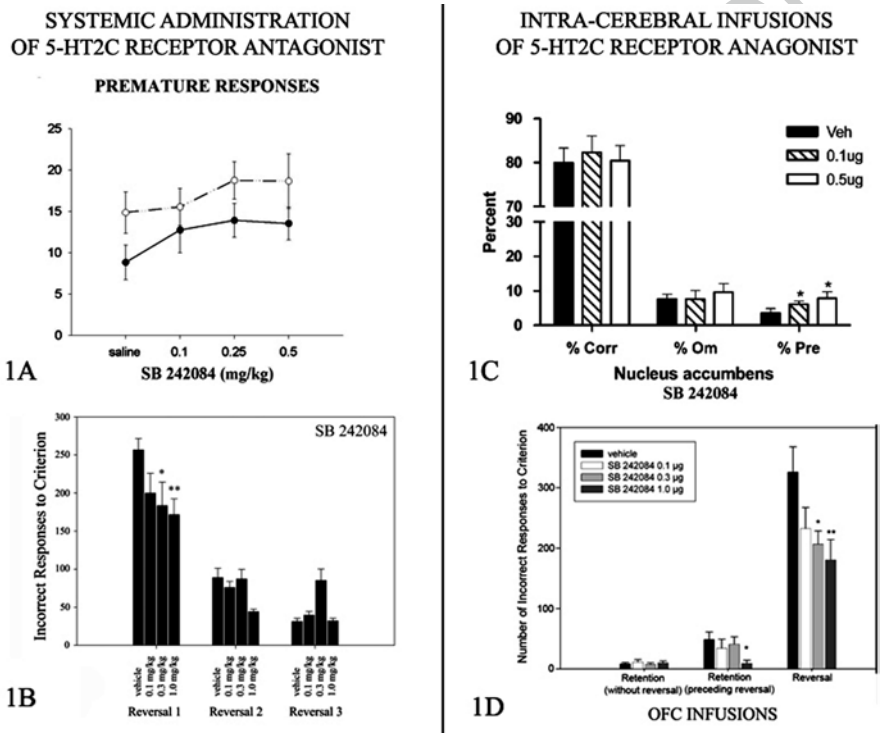

Fig. 23.1 (**a**) Effects of systemic administration of the 5-HT_{2C} receptor antagonist SB 242084 on the percentage of premature responses performed during the 5CSRTT in ICV 5,7-DHT-lesioned animals and sham-operated controls (Reproduced from Winstanley et al. 2004. With permission). (**b**) Effects of systemic administration of SB 242084 on incorrect responses during spatial reversal learning (Adapted from Boulougouris et al. 2008). (**c**) Effects of intra-NAc infusions of SB 242084 on the percent correct, omissions, and premature responses during the 5CSRTT (Reproduced from Robinson et al. 2008. With permission). (**d**) Effects of intra-OFC infusions of SB 242084 on incorrect responses during spatial reversal learning (Adapted from Boulougouris and Robbins 2010) [AU4] [AU5]

23.4 5-HT and Reversal Learning

Tests such as the WCST, which index cognitive flexibility, in fact address several similar yet distinct forms of attentional shifts. For example, if we consider discrimination learning based on compound stimuli involving two perceptual dimensions (e.g., shapes and lines), where exemplars of these dimensions occur in combination with one another on successive trials, one exemplar of one particular dimension being correct (e.g., vertical but not skewed line correct), then (1) when the relevant stimulus dimension (i.e., lines) stays constant but novel stimuli are used (e.g., straight but not curly line correct), this is an intradimensional (ID) shift; (2) when an exemplar from the previously irrelevant dimension (shapes) becomes correct (square but not triangle), then an extradimensional (ED) shift is demanded; finally (3) when the stimuli remain the same, but the previously correct exemplar is now incorrect (triangle but not square), then we refer to *reversal learning*, a shift which can occur either at the compound discrimination learning stage or after the ID or ED shift.

Different tests of attentional flexibility involving ID or ED shifts and reversal are used translationally. Such procedures by necessity engage other processes besides switching attention (e.g., ability to utilize feedback denoting that a shift is necessary, ability to overcome "learned irrelevance" of a previously nonoperative perceptual dimension). However, the precise nature of any failure to make a required shift can be further analyzed (see, e.g., Owen et al. 1993).

Accumulating evidence implicated the serotonergic system in reversal learning but not in attentional shifting. Selective 5-HT depletion in the marmoset had no effect on ED or serial ID shifting, but it produced a large deficit in reversal learning due to perseverative responding to the previously rewarded object (Clarke et al. 2004, 2008, 2005, 2007).

In human volunteers, transient depletion of central 5-HT by the tryptophan depletion technique produced effects on discrimination learning that were especially evident in reversal learning (Park et al. 1994). Another study (Rogers et al. 1999) also reported that tryptophan depletion led to relatively selective effects on human reversal learning (but see also reference Talbot et al. 2006) with no effect on ED shifting. Evers et al. (2005) showed that behavioral reversal was accompanied by significant signal change in the right ventrolateral and dorsomedial PFC of healthy volunteers performing a probabilistic reversal task. Tryptophan depletion enhanced reversal-related signal change in the dorsomedial PFC only, affecting the blood oxygen level-dependent (BOLD) signal specifically associated with negative feedback. These data indicate that the 5-HT system has a modulatory role in reversal learning specifically.

On the receptor level, recent evidence suggests that different 5-HT receptor subtypes have distinct roles in the modulation of reversal learning. Boulougouris et al. (2008) established a double dissociation in the role of 5-HT_{2C} and 5-HT_{2A} receptor subtypes in serial spatial reversal learning. Specifically, systemic administration of the 5-HT_{2C} receptor antagonist SB 242084 facilitated spatial reversal learning in a dose-dependent manner (Fig. 23.1b). Selective infusions into the

orbitofrontal cortex (OFC) of SB 242084 also promoted reversal learning, whereas infusions in the mPFC or nucleus accumbens did not. The facilitation of reversal learning therefore appears to be mediated by 5-HT_{2C} receptors within the OFC (Boulougouris and Robbins 2010) (Fig. 23.1d). In contrast, systemic treatment with the 5-HT_{2A} receptor antagonist M100907 dose-dependently impaired reversal learning, on the first reversal of the series in particular. This deficit emerged as increased perseveration of the previously correct response, reproducing the effects observed after selective orbitofrontal 5,7-DHT lesions (Clarke et al. 2004, 2005, 2007) as well as orbitofrontal cortical lesions in rats and nonhuman primates (Chudasama and Robbins 2003; Dias et al. 1996; Boulougouris et al. 2007).

The finding that the enhancement of spatial reversal learning via 5-HT_{2C} receptor blockade is actually mediated by the OFC is apparently at odds with the above-mentioned lesion studies. This is not the only instance where contrasting effects between 5-HT depletion and 5-HT receptor antagonism have been reported. For example, recent studies showed no effect of 5-HT depletion on the delayed discounting task (Winstanley et al. 2003b), while the 5-HT_{1A} receptor agonist 8-OH-DPAT (shown to turn off 5-HT release at autoreceptors) produces impulsive choice (Winstanley et al. 2005). Therefore, although the discrepancy could be attributed to task differences between lesion and antagonist studies (e.g., differences in the modalities of the reversal learning task used here and by Roberts and colleagues: object versus spatial response reversal), such explanations would appear rather superficial. A more interesting hypothesis is that the discrepancy between the lesion and antagonist studies may reflect incomplete 5-HT depletion from OFC resulting in 5-HT_{2C} receptor supersensitivity (as may occur in OCD) (Graf et al. 2003; Yamauchi et al. 2004). This possibility could perhaps be investigated through infusions of 5-HT_{2C} and 5-HT_{2A} receptor antagonists on 5-HT depleted animals.

These findings are of considerable theoretical and clinical importance. At a theoretical level, the opposing effects of 5-HT_{2A} and 5-HT_{2C} antagonism on perseverative responding in spatial reversal learning task (increase and decrease, respectively) contrast with the also reverse effects of these agents on impulsive responding in the 5CSRTT (see Sect. 23.3 on 5CSRTT). Specifically, intra-PFC 5-HT_{2A} antagonism [AU6] decreases impulsive responding (Winstanley et al. 2003a; Higgins et al. 2003), whereas 5-HT_{2C} antagonism increases it (Winstanley et al. 2004). These observations are relevant to the concept of an impulsivity–compulsivity spectrum in obsessive–compulsive spectrum disorders (Hollander and Rosen 2000). At a clinical level, these data also bear on the issue of whether 5-HT_{2C} receptor antagonists might be expected to be useful in the treatment of human obsessive–compulsive disorder (OCD).

23.5 5-HT and the Reinforced Spatial Alternation Task

The reinforced spatial alternation task is a behavioral procedure used in animals to measure memory, executive functions, as well as persistent behavior (Tsaltas et al. 2005; Rawlins and Olton 1982; Rawlins and Tsaltas 1983; Givens and Olton 1995).

Each alternation trial includes two runs through the T-maze, with both food cups baited. The animal is placed on the start point with its back toward the closed guillotine door. In the first run (forced, information run), one arm of the maze is blocked. As soon as the animal reaches the goal and eats the reinforcer, it is moved on the start point, the obstacle is removed, and the second run (free direction choice run) begins. The choice run is completed when all paws of the animal are in the lateral arm. Thereafter, change in choice is prevented. Choice of the arm opposite to the preceding forced arm is rewarded and of the same resulted in nonreward. [AU7]

A model of compulsive behavior based on a spontaneous behavioral persistence tendency in the framework of spatial reward alternation in the T-maze was recently developed by Tsaltas et al. (2005). This model's focal behavioral criterion is directional persistence. It has been established that this model responds isomorphically with clinical compulsive behavior to a number of serotonergic manipulations, while it is not influenced by nonserotoninergic antidepressants or benzodiazepines. Specifically, it has been demonstrated that meta-chlorophenylpiperazine (mCPP), a nonspecific 5-HT_{2C} agonist, -induced directional persistence is blocked by chronic treatment with the selective serotonin reuptake inhibitor (SSRI) fluoxetine but not with diazepam (benzodiazepine, anxiolytic) or desipramine (tricyclic antidepressant); these data support the reliability and predictive validity of the model's target behavior. Moreover, the focal obsessive behavior of the model has been demonstrated to (1) be controlled by 5-HT_{2C} and not by 5-HT_{1D} receptors, since the specific 5-HT_{1D} agonist naratriptan had no effect on mCPP-induced persistence (Tsaltas et al. 2005), (2) exhibit cross-tolerance between SSRI fluoxetine and the nonspecific serotonin agonist mCPP, suggesting a possible common path of action of the two substances, and (3) be sensitive to the administration of the agonist of the dopaminergic D_2/D_3 receptors of quinpirole, supporting the hypothesis of the serotonin–dopamine interaction and contributing to its construct validity (Kontis et al. 2008).

The initial finding implicating the 5-HT_{2C} receptor in the mediation of persistent behavior in this model was further investigated with the use of specific 5-HT_{2A} and 5-HT_{2C} receptor antagonists, M100907 and SB 242084, respectively. Systemic blockade of the 5-HT_{2C}, but not the 5-HT_{2A}, receptor offered protection against the mCPP-induced directional persistence, thus strengthening 5-HT_{2C} receptor involvement in compulsive behavior (Papakosta submitted) (Fig. 23.2). It should be noted that the above findings constitute new evidence in the understanding of OCD etiopathogenesis, as well as other psychiatric afflictions where inflexible behavior is a feature.

23.6 5-HT and the Signal Attenuation Task

Another sophisticated task used to measure both attention and inhibitory control is that of "signal attenuation." The signal attenuation model, developed by Joel et al. (Joel and Avisar 2001; Joel et al. 2001, 2005a, b), is based on the hypothesis that compulsive behavior results from deficient feedback associated with the completion

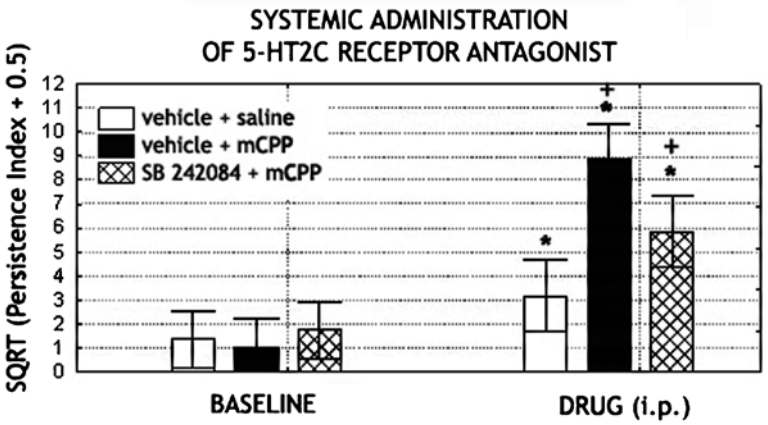

Fig. 23.2 Effects of systemic administration of the 5-HT_{2C} receptor antagonist SB 242084. on mCPP-induced directional persistence in the reinforced spatial alternation task in the T-maze (Adapted from Papakosta~~, submitted~~) [AU8]

of goal-directed responses: Normal functioning of such feedback prevents pointless repetitions of responses once their goal has been attained. The goal-directed behavior of this model is instrumental lever pressing for food. The feedback for a successful response is a compound stimulus of light and tone. The "feedback deficit" assumed to underlie compulsive behavior is induced in the model by means of attenuation of the "signaling property" of this compound stimulus (repeated presentation without food and without lever-press opportunity). The behavioral control condition for this attenuation process is called *regular extinction*, and it is an identical training and testing sequence, apart from the omission of the stimulus devaluation stage. The effects of signal attenuation on lever-press responding are assessed under extinction conditions through comparisons to the effects of regular extinction. Regular extinction and, to a lesser extent, extinction after signal attenuation both produce excessive lever presses (ELP), followed by magazine entry (ELP completed, or ELP-C) extinction after signal attenuation additionally produces ELP not followed by magazine entry (ELP uncompleted, or ELP-U). According to the authors, ELP-C reflects rats' responses to nonreward, while ELP-U reflects response to the encounter of an attenuated signal and constitutes the model's focal behavior (compulsive lever pressing).

It has been demonstrated that the model is sensitive to serotonergic manipulations since administration of SSRIs (paroxetine and fluvoxamine) had an "anticompulsive" effect on "compulsive" lever pressing (Joel et al. 2004; Joel and Doljansky 2003). Although there are no studies investigating the contribution of distinct 5-HT receptor subtypes, it has been recently reported that the 5-HT_{2C}, but not the 5-HT_{2A}, receptor subtype is implicated in inhibitory control. Specifically, 5-HT_{2C} receptor blockade following administration of the selective 5-HT_{2C} receptor antagonist RS 102221 reduced compulsivelever pressing, an effect mediated within the orbitofrontal cortex (Flaisher-Grinberg et al. 2008) (Fig. 23.3).

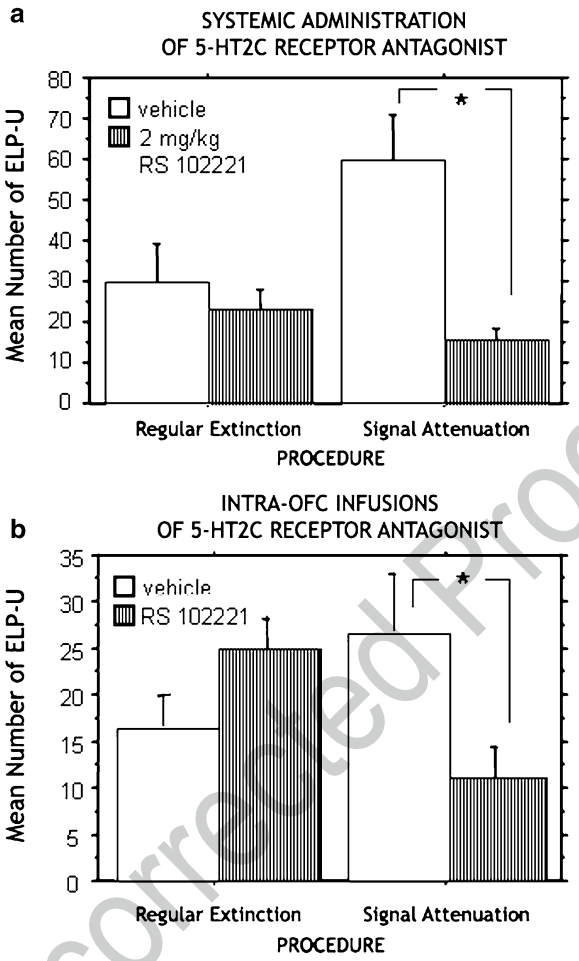

Fig. 23.3 (**a**) Effects of systemic administration of the 5-HT_{2C} receptor antagonist RS 102221 on excessive uncompleted lever presses (ELP-U) in the posttraining signal attenuation and regular extinction procedures. (**b**) Effects of intra-OFC infusions of RS 102221 on the same behavioral measure in both procedures (Adapted from Flaisher-Grinberg et al. 2008)

[AU9]

23.7 5-HT_2 Receptors and Clinical Implications

Studies on the involvement of 5-HT_2 receptors in attentional processes and executive control may be relevant to various neuropsychiatric disorders. The evidence emerging from studies in the 5CSRTT suggests that serotonergic modulation in the mPFC and the NAc can increase attentional selectivity and decrease impulsivity via 5-HT_{1A} and 5-HT_{2A} receptors. These findings bear clinical relevance, given that some atypical antipsychotics have 5-HT_{2A} receptor antagonist actions that may potentially contribute to a procognitive effect in

schizophrenia (Meltzer et al. 2003). The opposing effects of 5-HT_{2A} and 5-HT_{2C} receptor antagonism on premature responding in the 5CSRTT (Winstanley et al. 2004) indicate that selective 5-HT_{2A} receptor antagonists and/or 5-HT_{2C} receptor agonists may have beneficial effects in psychiatric disorders where coexisting impulsivity is often present, including attention deficit hyperactivity disorder, schizophrenia, and substance abuse.

Finally, the Boulougouris et al. (2008) data may be useful in relieving reversal deficits such as those noted in Huntington disease. In fact, they may deserve consideration as a means of controlling compulsivity in the context of OCD. The latter is strengthened by the anticompulsive effect of 5-HT_{2C} receptor antagonism on the reinforced spatial alternation and signal attenuation tasks.

23.8 Conclusions

This survey provides an integrative account of the contribution of serotonin, with emphasis on the 5-HT_{2C} receptor subtype, to specific aspects of attentional processes and executive functioning as they emerge from experimental animal work. Four tasks allowing translational study have been used to that purpose:

1. The 5CSRTT, an analogue of the human CPT, is designed to measure several attentional operations with an emphasis on sustained attention or vigilance.
2. Attentional set shifting including reversal, intra- and intradimensional shifts, as the human WCST, tap attentional flexibility, that is the ability of humans and animals to develop and maintain higher-order rules, and shift attention according to changing reward contingencies.
3. The reinforced spatial alternation assesses working memory and other executive functions as well as persistent behavior.
4. Finally, the signal attenuation task addresses the issue of behavioral control by means of inhibition of activities that no longer serve environmental demands.

Taken together, the findings detailed above highlight the specificity of influences that the serotonin system has on overall prefrontal executive control, acting to promote distinct components of prefrontal processing in a context-dependent manner. Future directions must focus toward the definition of the specific aspects of attentional functions in which the serotonergic system is acting to influence prefrontal processing.

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