Serotonin Regulates Performance Nonmonotonically in a Spatial Working Memory Network

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The executive functions of prefrontal cortex (PFC) are regulated by ascending monoaminergic systems (Robbins and Arnsten 2009). In particular, the dorsal PFC is associated with spatial working memory (SWM; Smith and Jonides 1999), linked to persistent neuronal activity (Goldman-Rakic 1995), and receives anatomical projections from the brainstem monoamine nuclei (Porrino and Goldman-Rakic 1982). Catecholamine regulation of SWM has been studied at mechanistic (Brozoski et al. 1979; Ramos et al. 2005; Wang et al. 2007, 2011) and computational levels (Durstewitz et al. 2000; Brunel and Wang 2001; Cohen et al. 2002). However, the role of serotonin (5-hydroxytryptamine, 5-HT) in SWM is unclear. Thus, while 5-HT is clearly associated with orbitofrontal cortex functions (Robbins 2000, 2005; Clarke et al. 2004; Robbins and Roberts 2007), its association with SWM is controversial, with positive (Luciana et al. 1998; Vollenweider et al. 1998; Wingen et al. 2007; Wittmann et al. 2007) and negative reports (Park et al. 1994; Luciana et al. 2001; Carter et al. 2005).

An indirect association between PFC 5-HT and SWM is suggested by the procognitive effects (Keefe et al. 2007; Terry et al. 2008) of some antipsychotic drugs targeting 5-HT receptors (Meltzer and Massey 2011), although this remains a controversial issue (Goldberg 2007). Several neuropsychological problems (Park and Holzman 1992; Dickinson et al. 2007; Zhang and Arsenault 2005; Zhang and Arsenault 2005) and computational levels (Durstewitz et al. 2000; Brunel and Wang 2001; Cohen et al. 2002) have suggested specific predictions regarding the expected behavioral effects of serotoninergic agents in 2 classic working-memory tasks. Our results underscore the relevance of identifying different error types in SWM tasks in order to reveal the association between neuromodulatory systems and SWM.

Keywords: computational model, neuromodulation, persistent activity, prefrontal cortex

Introduction

The prefrontal cortex (PFC) contains a dense network of serotoninergic [serotonin, 5-hydroxytryptamine (5-HT)] axons, and endogenous 5-HT markedly modulates PFC neuronal function via several postsynaptic receptors. The therapeutic action of atypical antipsychotic drugs, acting mainly via 5-HT receptors, also suggests a role for serotonin neurotransmission in cognitive functions. However, psychopharmacological studies have failed to find a consistent relationship between serotoninergic transmission and cognitive functions of the PFC, including spatial working memory (SWM). Here, we built a computational network model to investigate 5-HT modulation of SWM in the PFC. We found that 5-HT modulates network’s SWM performance nonmonotonically via 5-HT₁₅ and 5-HT₂₅ receptors, following an inverted U-shape. This relationship may contribute to blur the effects of serotoninergic agents in previous SWM group-based behavioral studies. Our simulations also showed that errors occurring at low and high 5-HT concentrations are due to different network dynamics instabilities, suggesting that these 2 conditions can be distinguished experimentally based on their distinct dependency on experimental variables. We inferred specific predictions regarding the expected behavioral effects of serotoninergic agents in 2 classic working-memory tasks. Our results underscore the relevance of identifying different error types in SWM tasks in order to reveal the association between neuromodulatory systems and SWM.

Materials and Methods

Computational Model

Model Neurons

The network model represents a local circuit responsible for the maintenance of information in working memory (WM), for example,
a circuit in dorsolateral PFC. To simulate the local recurrent cortical network, we used 2 populations of leaky integrate-and-fire neurons (Tuckwell 1988): Pyramidal cells (\(N_e = 1024\)) and interneurons (\(N_i = 256\)). For integrate-and-fire neurons, the membrane voltage \(V_m\) integrates incoming inputs (see equations below), and a spike is discharged each time \(V_m\) reaches a threshold value \(V_{th}\). Then, \(V_m\) is reset to \(V_{m0}\) and stays there for an absolute refractory period \(t_{ref}\) before continuing integrating inputs according to its equation.

Each pyramidal cell obeys the following dynamical equation:

\[
C_m \frac{dV_m}{dt} = -I_e - I_{syn,e} - I_{syn,i} - I_{ext,e} - I_{ext,i}
\]

where \(C_m\) is the capacitance, \(I_{ext,e}\) represents input from outside the network, and the leak current is \(I_e = g_l (V_m - V_l)\), with \(g_l\) and \(V_l\) being the conductance and reversal potential of leak channels. \(I_{syn,e}\) and \(I_{syn,i}\) are the recurrent synaptic inputs from presynaptic pyramidal cells and interneurons, respectively. Details of synaptic transmission are given below. \(I_{ext,i}\) is the input from outside the network. \(I_{ext,i}\) is the sum of the all the currents that are modulated by serotonin. The intrinsic parameters that characterize pyramidal cells are: \(C_m = 0.5\) nF, \(g_l = 27.4\) nS, \(V_l = -70\) mV, \(V_{m0} = -50\) mV, \(V_{ref} = -60\) mV, and \(t_{ref} = 2\) ms.

The membrane voltage of each interneuron obeys the equation:

\[
C_m \frac{dV_m}{dt} = -I_e - I_{syn,e} - I_{syn,i} - I_{ext,e} - I_{ext,i}
\]

where \(I_{ext,i}\) represents external inputs from outside the circuit, and the leak current, \(I_{ext,i}\), depends on 5-HT concentration (5-HT, see below). \(I_{syn,e}\) and \(I_{syn,i}\) are the recurrent synaptic inputs from presynaptic pyramidal cells and interneurons, respectively. For interneurons, \(C_m = 0.2\) nF, \(V_l = -70\) mV, \(V_{m0} = -50\) mV, \(V_{ref} = -60\) mV, and \(t_{ref} = 1\) ms.

All cells received random background excitatory inputs (\(I_{ext,e}\) in pyramidal cells and interneurons, respectively). This unspecific external input was modeled as uncorrelated Poisson spike trains to each neuron at a rate of \(v_{ext,e} = 1650\) Hz for pyramidal cells (or equivalently, 1000 presynaptic Poisson spike trains at 1.65 Hz) and \(v_{ext,i} = 1800\) Hz for interneurons. This input was exclusively mediated by \(\alpha\)-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPARs), with the maximum conductances \(g_{ext,e} = 5\) nS on pyramidal cells and \(g_{ext,i} = 1.8\) nS on interneurons.

### 5-HT Modulation

We included 5-HT receptors in our model, whose mechanisms have been characterized in prefrontal neurons in in vitro studies: 5-HT\(_{1A}\) and 5-HT\(_{2A}\) receptors on pyramidal cells and 5-HT\(_{2A}\) receptors on interneurons.

Electrophysiological studies have shown that phasic 5-HT generally causes a reduction in the excitability of cortical neurons and occasionally a delayed excitability increase, reflected in discharge rate reductions and increases, respectively (Arana and Andrade 1991; Puig et al. 2005). The inhibitory response has been attributed to the activation of the 5-HT\(_{1A}\) receptor (Puig et al. 2005; Goodfellow et al. 2009), which is abundantly expressed in PFC pyramidal neurons (Santana et al. 2004). 5-HT\(_{1A}\) is a metabotropic receptor coupled to the \(G_{\alpha}\) family of heterotrimeric G-proteins that generate a hyperpolarization of pyramidal neurons by the activation of G-protein gated inwardly-rectifying K\(^+\) channels (Andrade et al. 1986; Béïque et al. 2001). Based on these experimental data, we simulated the action of the 5-HT\(_{1A}\) receptor in pyramidal prefrontal neurons by including a 5-HT\(_{1A}\)-modulated K\(^+\) current (\(I_{K1A}\)) in excitatory cells of our network (Fig. 1A).

In contrast to the hyperpolarizing/inhibitory effect of 5-HT\(_{1A}\) receptors, 5-HT\(_{2A}\) receptors mediate depolarizing/excitatory responses in pyramidal cortical neurons (Arana and Andrade 1991; Puig et al. 2005). The 5-HT\(_{2A}\) receptor acts through G-proteins of the \(G_{\beta\gamma}\) type to produce a complex cascade of physiological effects in prefrontal neurons. It increases intracellular Ca\(^{2+}\), it inhibits calcium-activated afterhyperpolarization currents (\(I_{KCa}\)) (Villalobos et al. 2005), and it activates an afterdepolarization current mediated by a calcium-dependent nonselective cation channel (\(I_{Can}\); Zhang andArsenault 2005; Fowler et al. 2007). 5-HT\(_{1A}\) and 5-HT\(_{2A}\) receptors are colocalized in pyramidal neurons of the PFC (Amargós-Bosch et al. 2004), so we included all their effects in the excitatory cells of our network model (Fig. 1A, see below). The 5-HT\(_{1A}\) receptor also acts in prefrontal interneurons (Fig. 1B) by increasing neuronal excitability (Puig et al. 2010; Weber and Andrade 2010), mediated by the inhibition of a potassium current (Deng et al. 2007; Ma et al. 2007). We incorporated this effect in inhibitory neurons of our network model, by having 5-HT\(_{2A}\) receptor activation decrease the conductance of their leak current (Fig. 1B).

The receptors kinetics were modeled by the following equations:

\[
\frac{dx_{1A}}{dt} = \frac{1}{\tau_{1A}} (x_{1A} - x_{1A}^{\text{eq}}) + \frac{1}{\tau_{1A}} \left( \alpha_{1A} \left( [\text{5-HT}] - x_{1A}^{\text{eq}} \right) - \beta_{1A} x_{1A} \right)
\]

\[
\frac{dx_{2A}}{dt} = \frac{1}{\tau_{2A}} (x_{2A} - x_{2A}^{\text{eq}}) + \frac{1}{\tau_{2A}} \left( \alpha_{2A} \left( [\text{5-HT}] - x_{2A}^{\text{eq}} \right) - \beta_{2A} x_{2A} \right)
\]

where \(x_{1A}\) and \(x_{2A}\) are the gating variables for the corresponding 5-HT receptors (\(0 < x_{1A}, x_{2A} < 1\)); [5-HT] is the serotonin concentration, which we take to be 10 nM in physiological conditions (Celada et al. 2001); \(\tau_{1A} = 30\) ms and \(\tau_{2A} = 120\) ms are the time constants of the receptors; and \(\alpha_{1A} = 1.8\) kHz/\(\mu\)M, \(\alpha_{2A} = 2.25\) kHz/\(\mu\)M, and \(\beta_{1A} = 11\) kHz/\(\mu\)M control the affinity of the receptors to 5-HT.

The 5-HT\(_{1A}\) receptor modulates a potassium current on pyramidal cells according to:

\[
I_{K1A} = g_{K1A} x_{1A} (V - V_K)
\]

where \(g_{K1A} = 29.7\) nS is the maximal conductance of the channel, and \(V_K = -70\) mV, the potassium reversal potential.

In pyramidal neurons, the 5-HT\(_{1A}\) receptor modulates the calcium-dependent potassium current (\(I_{KCa}\)) and the nonselective cationic current (\(I_{Can}\)) through changes in calcium dynamics. Serotonin-
modulated calcium dynamics in pyramidal cells obey:

\[
\frac{d[Ca^{2+}]}{dt} = \alpha_{Ca} \sum_{sp} \delta(t - t_{sp}) \frac{[Ca^{2+}]}{\tau_{Ca}} + \gamma_{5-HT} \delta_{2A}
\]

where \( \gamma_{5-HT} = 0.41 \) nM/ms controls calcium flow through 5-HT2A receptors, the [Ca\(^{2+}\)] influx per spike is \( \alpha_{Ca} = 0.1 \) \muM and \( \tau_{Ca} = 240 \) ms (Wang 1998; Tegnér et al. 2002).

This calcium dynamics affect \( I_{Ca} \) and \( I_{Can} \) via the following equations:

\[
I_{Ca} = g_{Ca}(1 - s_{2A}) \frac{[Ca^{2+}]}{[Ca^{2+}] + \beta_{Ca}} (V - V_{K})
\]

\[
I_{Can} = g_{Can} m_{Can} h_{Can} (V - V_{Can})
\]

\[
\frac{m_{Can}}{\alpha_{Can} [Ca^{2+}] + \beta_{Can}} = \frac{1}{\tau_{Can}}
\]

\[
h_{Can} = \frac{1}{1 + \exp\left(\frac{[Ca^{2+]} - \beta_{Can}}{\alpha_{Can}}\right)}
\]

where \( g_{Ca} = 703 \) nS, \( V_{K} = -70 \) mV, \( K_{0} = 30 \) \muM, \( g_{Can} = 36 \) nS, \( V_{Can} = -20 \) mV, \( \alpha_{Can} = 0.0056 \) ms\(^{-1}\) m\(^{-1}\), \( \beta_{Can} = 0.002 \) ms\(^{-1}\), \( a_{Can} = 3 \) \muM, \( \beta_{Can} = 5 \) \muM. Relative to previous formulations (Tegnér et al. 2002), we introduced the inactivation term \( h_{Can} \) to account for the inactivation of \( I_{Can} \) through protein kinase C at high [Ca\(^{2+}\)] (Venkatachalam et al. 1986; Lee et al. 1988). From the network activity at the end of the delay period, we computed a population vector estimation (Georgopoulos et al. 1986). All the connections were structured with \( J_{syn} = 4.4 \) nS (interneuron to interneuron). 

Network Pyramidal cells and interneurons were spatially distributed on a ring simulating the cortical columnar organization, labeled by their preferred spatial location (\( \theta_{th} \) from \(-180^\circ\) to \(+180^\circ\)) (Fig. 1C). Connections between cells were spatially tuned, such that nearby cells were strongly connected, whereas distant cells had relatively weaker connections (Compte et al. 2000). The connection strength \( P_{syn,i} \) between cells \( i \) and \( j \) depends on the difference in preferred angle between the cells and is described by the equation \( P_{syn,i} = W(\theta_{i} - \theta_{j}) \) \( \gamma_{syn} \) where \( W(\theta_{i} - \theta_{j}) \) was the sum of a constant term plus a Gaussian: \( W(\theta_{i} - \theta_{j}) = f'(\theta_{i} - \theta_{j}) f''(\theta_{i} - \theta_{j}) \) \( \sigma \) depends on 2 parameters, \( f' \) and \( \sigma \), while \( f'' \) is determined from a normalization condition (Compte et al. 2000). All the connections were structured with the same \( \sigma(\theta_{i} - \theta_{j}) = \sigma_{GABA} = \sigma_{GABA} = 4.4^\circ \) but with different \( f' \) \( J_{syn} = 2 \), \( f_{2A} = 0.5 \), \( f_{3A} = 1.4 \), and \( f_{4A} = 1.9 \). Following the notations by Compte et al. (2000), the parameters defining the strengths of local connections in the network were as follows: \( G_{EE,AMPX} = 0.14 \) nS, \( G_{EE,\text{GABA}} = 0.72 \) nS, \( G_{EE,\text{GABA}} = 1.9 \) nS (pyramid to interneuron); \( G_{EE,\text{GABA}} = 7.8 \) nS (interneuron to pyramid); \( G_{EE,\text{GABA}} = 4.4 \) nS (interneuron to interneuron).

Simulations The chosen simulation protocol resembled behavioral protocols used in monkey SWM experiments (Funahashi et al. 1989; Williams et al. 2002). The trials consisted of 4 periods: Intertial period (3 s), cue (0.25 s), delay (3 s), and response. In the intertrial period, there were no external inputs to the network so it stayed in a spontaneous, unstructured firing state. In the cue period, a cue stimulus was applied (current injection) to neurons selective for directions around \( \theta_{i} \). A stimulus in the direction \( \theta_{i} \) was simulated as current injection to each excitatory neuron in the network (labeled by \( \theta_{i} \)) of intensity \( I_{1} = 1 \exp(\mu_{syn}(\cos(\theta_{i} - \theta_{i} - 1))) \). We typically used \( I_{1} = 0.235 \) nA and \( \mu_{syn} = 10 \). During the delay, no stimulus was presented and the network maintained the cue position in a stable pattern of network activation (activity bump). When focusing on the stability of this memory state, we represent only the last 0.75 s of the intertrial period (Figs 2A, 3A, and 4C,E). We also ran simulations of control trials where no external stimuli were applied (i.e. no cue stimulus). In these trials, we wanted to confirm the stability of the spontaneous, unstructured state for the duration of the trial, and we illustrate it with the first 4 s of network activity in Figures 2B and 4A.

The response period was not simulated explicitly, but a decoding algorithm was used to simulate behavioral responses during simulated tasks. The oculomotor delayed response task consisted in reporting the location of the cue stimulus after the delay period within a predefined tolerance window. To mimic a real experiment, we removed from the analysis the control trials used to test the stability of the spontaneous state (i.e. trials in which no cue was presented) since they do not correspond to a real behavioral condition in the context of the task. To obtain a behavioral response from our simulation trials, we computed a population vector estimation (Georgopoulos et al. 1986; Lee et al. 1988) from the network activity at the end of the delay period. Thus, if \( n_{i} \in \{1 \ldots N_{E}\} \) are the spike counts of all the excitatory neurons labeled by \( \theta_{i} \in \{1 \ldots N_{E}\} \) in a 50-ms window at the end of the delay period, the population vector was computed as the normalized sum of each neuron’s selectivity vector \( e^{\theta_{i}} \) (we use complex notation to operate with vectors in a compact manner) weighted by its spike count:

\[
P = \frac{\sum n_{i} e^{i \theta_{i}}}{\sum n_{i}}
\]

where \( \theta_{i} \) is the resultant population vector: \( P = C e^{i \theta_{i}} \). For each individual simulation trial, we took \( \theta_{i} \) as the decoded location memorized in the network activity before response initiation, the “behavioral response.” Correct trials were those trials for which \( |\theta_{i} - \theta_{i}^{*}| < 22.5^\circ \). In addition, \( C \) measures the signal-to-noise ratio of the population code contained in the network. Arbitrarily, we took a threshold of \( C > 0.5 \) as our criterion for a confident behavioral response.

From the network’s behavior characterized by the collection of \( \theta_{i} \) over 1000 network simulations, we estimated the probability of memorizing the item \( P_{i} \) and the precision of the memory \( \sigma_{i} \), as previously

Synapses Neurons received their recurrent excitatory inputs through AMPAR- and N-methyl-D-aspartate receptor (NMDAR)-mediated transmission and their inhibitory inputs through \( \gamma \)-aminobutyric acid receptors type A (GABA\(_{A}\)Rs). These conductance-based synaptic responses were calibrated by the experimentally measured dynamics of synaptic currents. Thus, postsynaptic currents were modeled according to \( I_{syn} = g_{syn} x(V_{m} - V_{syn}) \), where \( g_{syn} \) is a synaptic conductance, \( x \) is a synaptic gating variable, and \( V_{syn} \) is the synaptic reversal potential (\( V_{syn} = 0 \) for excitatory synapses and \( V_{syn} = -70 \) mV for inhibitory synapses). AMPAR and GABA\(_{A}\) synaptic gating variables were modeled as an instantaneous jump of magnitude 1 when a spike occurred in the presynaptic neuron, followed by an exponential decay with time constant 2 ms for AMPA and 10 ms for GABA\(_{A}\). The NMDA conductance was voltage-dependent, with \( g_{syn} \) multiplied by \( 1/(1 + [Mg^{2+}]^{0.062} V_{m}/5.79) \), \( [Mg^{2+}] = 1.0 \) mM. The NMDA channel kinetics were modeled by the following equations:

\[
\frac{ds}{dt} = -\frac{1}{\tau_{s}} s + \alpha_{s}(1 - s), \quad \frac{dx}{dt} = \frac{1}{\tau_{x}} x + \sum_{t} \delta(t - t_{i})
\]

where \( s \) is the gating variable, \( x \) a synaptic variable proportion to the neurotransmitter concentration in the synapse, \( t_{i} \) the presynaptic spike times, \( \tau_{s} = 100 \) ms the decay time of NMDA currents, \( \tau_{x} = 2 \) ms controls the rise time of NMDAR channels, and \( \alpha_{s} = 0.5 \) kHz controls the saturation properties of NMDAR channels at high presynaptic firing frequencies. Parameters for synaptic transmission were taken from Compte et al. (2000).
described (Zhang and Luck 2008). We calculated the fraction of trial responses $\theta_k$ from $-180^\circ$ to $180^\circ$ in bins of $\Delta\theta = 5^\circ$, that is, the probability of report $P_k$. We then fitted $P_k$ with a Von Mises distribution:

$$P_k = \frac{1 - P_m}{360} + P_m \frac{e^{k_{\text{cos}}(b_k - b_0)} \Delta\theta}{I_0(k)} \frac{1}{360}$$

where $k > 0$ is a shape parameter known as the concentration (effectively equivalent to the inverse of the standard deviation) and $I_0(k)$ is the modified Bessel function of order 0. From the fit we extracted the parameters $P_m$ and $k$, with which we calculated the width at half-height of the curve ($\sigma$) as a measure of the precision of the encoded memory.

In all these SWM simulations, we assumed a diffuse, temporally constant action of 5-HT on the network’s mechanisms (“tonic 5-HT”). The fact that dorsal raphe neurons typically fire tonically (Jacobs and Fernald 1991) and project diffusively onto PFC suggests that a tonic release of 5-HT is the plausible scenario during waking (but see Fernald et al. 1996), in particular during cognitive function. Our tonic 5-HT simulations thus used a constant value of [5-HT] for all neurons in the network and through all periods of the task. However, we also simulated in Figure 3 a phasic action of 5-HT (“phasic 5-HT”), where [5-HT] rose and fell ([5-HT]=80 nM) sharply over a brief interval (50 ms) to compare with available PFC electrophysiological studies during dorsal raphe electrical stimulation in vivo (Puig et al. 2005).

We also simulated a delayed match-to-sample (DMS) task (Fig. 9A). Each trial began with a fixation period (3 s), then a cue stimulus was presented at location $\theta_0$ (0.25 s), and after a delay period of 1, 2, or 3 s a probe appeared at location $\theta_p$. The task consisted in reporting if the probe matched the location of the stimulus or not and then indicate the confidence level for the response. There were 16 possible locations for the cue (squares in Fig. 9A). Given the symmetry of our network, we fixed $\theta_k$ at 0° and varied the location of the probe $\theta_p$ in different trials. In 50% of the trials, the probe matched the cue location ($\theta_p = \theta_0$) and the rest were nonmatch trials, where the probe was located at one of the other possible locations with equal probability. The comparison and response process was not simulated biophysically. Instead, we used the same decoding algorithm as before to extract the report location ($\theta_k$) and the confidence level of the response ($C$, confident trial if $C > 0.5$) and for each trial we calculated the probability of a “match” response ($P_m$) using the sigmoid function (Engel and Wang 2011; Wei et al. 2012):

$$P_m = a \frac{1}{1 + e^{-(b_1 - b_0) \Delta\theta}}$$

where $a = 0.8214$, $b_0 = -0.8243$, $b_1 = 23.57^\circ$, and $\Delta\theta = 6.32^\circ$. We ran 500 match trials and computed the fraction of correct match trials ($P_{m}$ hits) as $P_{m} = \sum_{i=1}^{500} P_{m_i}/500$ and the fraction of incorrect match trials ($P_{m}$ misses) as $P_{m} = 1 - P_{m}$. Over 500 nonmatch trials, we calculated the fraction of correct nonmatch trials ($P_{nv}$, correct rejections) as $P_{nv} = \sum_{i=1}^{500} (1 - P_{m_i})/500$ and the fraction of incorrect nonmatch trials ($P_{nv}$, false alarms) as $P_{nv} = 1 - P_{nv}$. We also classified the responses considering the confidence level of the decision and computing together the match and nonmatch trials as in Mayer and Park (2012). The types of responses were: true memories (correct confident), correct nonconfident, false alarms (incorrect confident), and incorrect nonconfident.

### Parameter Optimization Algorithm

We designed an unbiased, automated optimization procedure to find the parameters of suitable PFC networks (Ardid et al. 2010). This procedure consisted in randomly initializing 21 free parameters within a prespecified range of values (Supplementary Table 1), for each of 50 networks, henceforth called particles. From the 21 free parameters, 15 are independent of 5-HT modulation ($J_{\text{min}}$; $J_{\text{EE,AMPA}}$; $g_{\text{EE,AMPA}}$; $g_{\text{GLU,AMPA}}$; $g_{\text{GLU,NMDA}}$; $g_{\text{GLU,AMPA}}$; $J_{\text{EE}}$; $J_{\text{EE,AMPA}}$; $J_{\text{EE,NMDA}}$; $J_{\text{EE,AMPA}}$; $J_{\text{EE,NMDA}}$; $\nu_{\text{EE}}$; and $\nu_{\text{EE}}$) and the other 6 are related with 5-HT ($J_{\text{5-HT}}$; $g_{\text{K1A}}$; $g_{\text{K Ca2+}}$; $g_{\text{K Ca2+}}$; $g_{\text{K1A}}$; and $g_{\text{K Ca2+}}$). Such networks were simulated to evaluate the stability and quantitative details of their spontaneous and memory states. Evaluation was performed with predefined fitness functions that rated the degree of accomplishment of specified target behaviors for each model (particle). The predefined fitness functions evaluate: (1) Maximal and minimal firing rates; (2) the difference between maximal and minimal firing rate for simulations when a brief external stimulus was presented (memory state) and for simulations in which no external stimulus was applied (spontaneous state); (3) homogeneity among repeated simulations (stability of solutions); (4) similar behavior throughout the simulation (stability of solutions); (5) different behavior when a external stimulus was presented (memory state) compared with the spontaneous state; and (6) correlations among neurons (to discard highly synchronous solutions). Based on the overall rating of each particle, and the history of best rating for each particle and for the collection of particles (swarm), a particle swarm optimization algorithm (Kennedy and Eberhart 2001) updated the parameters of each particle in the swarm. This procedure was repeated iteratively until the swarm converged to a network that accomplished the required functional output (typically within 50 iterations). Such swarm simulations were computationally intensive (10 000 computer processing hours each) and required specialized grid computing management software [Grid SuperScalar (Sirvent et al. 2006)]. We ran several swarm simulations and from the resulting set of optimized networks we selected a sample of 20 different PFC networks with similar functional output but very different parameters (Supplementary Fig. 1): Parameter values in each of these 20 network solutions covered a minimum of 50% of the allowed range for each parameter in the optimization procedure, and the mean coefficient of variation of parameter values was 0.47 ± 0.18 (mean ± standard deviation). This highly diverse implementation of SWM function in 20 different networks was used to identify the conclusions that were not only specific of one network implementation, but also general to our family of solutions, and to test the effects of interindividual differences in group-based behavioral studies (Fig. 7). We selected one network to illustrate the results in our figures and to provide specific parameter values in Materials and Methods section.

### Numerical Integration

The integration method used was a second-order Runge-Kutta algorithm with a time step of $\Delta t = 0.02$ ms. The custom code for the simulations was written in C++.

### Results

To investigate how 5-HT modulates SWM function, we used a network model of a PFC neuronal microcircuit for SWM (Compte et al. 2000), in which we incorporated the mechanisms of 5-HT neuromodulation in PFC (see Materials and Methods). 5-HT$_{1A}$ and 5-HT$_{2A}$ receptors on pyramidal cells (Fig. 1A) and 5-HT$_{2A}$ receptors on interneurons (Fig. 1B, Materials and Methods) were included.

### A Network Model for SWM

The neuronal connectivity within the network model is structured, so that simulations can produce neuronal activity consistent with neuronal prefrontal data acquired during performance of SWM tasks (Compte et al. 2000). After a brief presentation of a stimulus (250 ms of localized external current input, see Materials and Methods), memory was maintained in a localized bump of neuronal activity (the cluster of neighboring cells with raised activity) that supported itself through the strong connections between neighboring E cells (bump attractor, Fig. 2A). This tuned persistent activity state can be stably maintained by the network and corresponds to the “memory state.” Crucially, the network has another stable —yet qualitatively different—network state, where all neurons fire at a low firing rate in an unstructured network activity
The Model Replicates Prefrontal Physiology in SWM and 5-HT Stimulation Studies

The network operation described above, with both a stable spontaneous state and a stable memory state, was the target regime for our network in a physiological concentration of 5-HT (5-HT) set at 10 nM. We used an optimization procedure (see Materials and Methods) to identify combinations of parameters that yielded such stable network states with physiologically reasonable firing rates, when all the serotonergic mechanisms described above were included in the network of Compte et al. (2000). Several networks (n = 20) were consistent with this operational mode (Supplementary Fig. 1). We used simulations from one of these networks to illustrate our results in the figures, and we used simulations from all other models to confirm that the results were general to this class of models and not specific to one particular realization. Memory states are characterized by elevated persistent activity after stimulus presentation (Fig. 3B), which remains restricted to a selective neuronal subpopulation (Fig. 3A). Increasing values of tonic [5-HT] in our simulations resulted in a monotonic reduction in the maximal firing rate of memory states (Fig. 3C), consistent with a general suppressive action of 5-HT on network responses.

The parameters of our simulations were set by requiring network simulations to display the 2 stable states of Figure 2. As an independent control, we tested in these models the effect of a phasic application of 5-HT (see Materials and Methods) to all model neurons (arrow in Fig. 3D). Network activity immediately decreased below baseline firing rates, followed by a slower excitation phase (Fig. 3D,E). This activity pattern matches the physiological responses of PFC pyramidal neurons to the electrical stimulation of raphe neurons in the rat (Puig et al. 2005; Fig. 3F). The initial rate of suppression is mediated by the 5-HT1A receptor, which has a faster dynamics, and it is followed by an overshoot over baseline firing rate due to the excitatory and slower effect of the 5-HT2A receptor. These responses to phasic 5-HT stimulation were consistent across our population of 20 different PFC networks.

5-HT Affects Network Dynamics Markedly

Following the construction and calibration of our network model for 5-HT modulation of SWM (Figs 1–3), we evaluated how 5-HT affected the SWM function of our circuit by testing the stability of our network’s dynamical states in repeated simulation trials.

We first analyzed the spontaneous state in terms of stability. In simulations lacking external stimuli, network activity should remain in a low and homogeneous activity for the duration of the simulation (Fig. 4A, top). However, in some trials, a spontaneous bump of activity formed and remained stable (Fig. 4A, bottom). We found that the probability of appearance of these spontaneous (false) memories depended on the tonic [5-HT] (Fig. 4B). An increase in tonic [5-HT] resulted in a more stable spontaneous state, while a reduction of 20% in tonic [5-HT] (light gray line) caused 35% of the trials to develop a spontaneous bump of activity after 4 s of simulation.

We also found that the stability of the memory state was strongly affected by tonic [5-HT]. Stable memory states, maintained by excitatory reverberation, are the substrate of SWM function in our network (Fig. 4C, top). In some cases,
however, network activity failed to reverberate through the length of the delay period and collapsed to the state of spontaneous activity (Fig. 4C, bottom). The mean duration of stable memory states was found to depend on tonic [5-HT] (Fig. 4D). When tonic [5-HT] was increased by 20%, virtually all memory states destabilized as in Figure 4C (bottom) after 3 s of delay period. Thus, 5-HT modulations that increased the stability of the spontaneous state (Fig. 4B) caused destabilization of the memory state (Fig. 4D) and vice versa.

The memory state can also lose stability in a different way: the activity bump can drift away from the original cued location due to random fluctuations in neuronal inputs (Fig. 4E) (Compte et al. 2000). We quantified this memory precision loss by computing the variance over 100 simulation trials of the estimated instant location of the bump using a population vector decoder. The population vector computes a probability distribution for the centers of activity in a window of 50 ms at each location. The nature of these modulations, however, was network simulations and analyzed the data as in psychophysics experiments. We first simulated a task protocol that resembles closely behavioral protocols in oculomotor delayed response tasks used in SWM studies, with an intertrial period (3 s), a cue period (0.25 s), and a delay period (1, 2, or 3 s) before behavioral response (see Materials and Methods).

For each simulation trial, we obtained a “behavioral response” by extracting a population vector read-out of the angle $\theta_R$ encoded in network activity in a window of 50 ms at the end of the delay period (see Materials and Methods). Thus, for each simulation trial with a cue stimulus presented at $\theta_c$ (given the circular symmetry of the model we used $\theta_c = 0^\circ$), we can extract the decoded angle $\theta_R$ after a delay of 1, 2, and 3 s. We ran 1000 trials of this task simulation, and we computed the distribution of reported angles $\theta_R$ (Fig. 5A), for 5 different values of tonic [5-HT]. The distribution of behavioral reports depended on [5-HT] (Fig. 5A), and we characterized this dependency by extracting the probability that the cue stimulus was in memory ($P_m$, shaded yellow area in Fig. 5A) and a measure of the precision of the memory ($1/\sigma$, $\sigma$ being the width at half height in Fig. 5A) from Von Mises fits to the “behavioral” data, as typically done in psychophysics studies (Zhang and Luck 2008 and see Materials and Methods). We found that $\sigma$ increased with delay length, but it remained roughly constant with [5-HT] except for the longer delays, when it increased markedly with [5-HT] (Fig. 5B).

Thus, the precision of the memory ($1/\sigma$) decreased with the delay, but it was not strongly affected by [5-HT] manipulations except for long delays and high [5-HT]. In contrast, the probability of memory maintenance $P_m$ presented an inverted U-shape with [5-HT] (Fig. 5B). This indicates that both increases and reductions in [5-HT] induced responses to random locations due to the inability to maintain the cue location. The nature of these modulations, however, was

Nonmonotonic Behavioral Effects of 5-HT

From these analyses, we concluded that tonic [5-HT] has a profound effect in the stability of the attractor states of a SWM computational network based on the reverberatory hypothesis for persistent activity. This is in sharp contrast to the lack of conclusive behavioral effects of serotonergic drugs in SWM tasks (see Introduction). To address this discrepancy directly, we decoded behavioral responses from many successive behavioral reports and analyzed them to determine the precision and stability of the memory state.
different for [5-HT] reductions and for [5-HT] increases: The decrease in $P_m$ for reduced [5-HT] was not sensitive to delay duration, while the decrease in $P_m$ for increased [5-HT] depended strongly on delay length (Fig. 5B).

The different dependency of $P_m$ with delay reflects the different destabilization of network activity induced by [5-HT] increases (destabilized memory states, Fig. 4C,D) and by [5-HT] reductions (destabilized spontaneous state, Fig. 4A,B). We reasoned that these 2 types of memory failures would also be reflected in the confidence of behavioral responses: Unstable memory states would lead to the lack of structured network activity and thus to nonconfident reports, while unstable spontaneous states would result in spurious memory states formed at random locations and they would generate confident but wrong responses. We tested this explicitly in our network simulations: From each simulation trial, we extracted not only the read-out of the memorized location $\theta_R$, but also a measure of confidence $C_R$ in the response from the same population vector analysis computed from network activity at the end of the delay (see Materials and Methods). This measure quantifies the quality of the selectivity in the neuronal network at the end of the delay. Thus, for each simulation trial with stimulus presentation at location $\theta_s$, we obtained the full network dynamics over the course of the trial, and 2 different behavioral measures: The decoded stimulus location $\theta_R$ and the confidence in the response $C_R$.

At the neuronal level, correct trials are characterized by stimulus-triggered localized network activity that is maintained around the same location robustly through the delay (Fig. 6A). Error trials are more heterogeneous. In some cases, network activity may fail to maintain the excitatory reverberation through the length of the delay period (bottom), losing the memory state. Population firing profiles, averaged over the last 500 ms of the delay period, are shown on the right. (D) For 5 levels of [5-HT] (gray scale): Fraction of trials, from a total of 100 simulation trials per [5-HT] condition, where the memory state lost stability as the delay progressed. (E) Same as C, for 2 simulation trials with random diffusion of the memory bump in the delay period. Notice the deviation in bump location from the beginning (dashed gray line on the right) to the end of the delay (solid black line on the right). (F) For 5 levels of [5-HT] (gray scale): Variance in the center location of the bump over repeated (100 trials) simulations with an identical cue (0°). Memory precision degrades with delay duration, but it is not strongly affected by [5-HT].
almost all trials yielded correct responses (Fig. 6D). However, when the tonic 5-HT level was either increased or decreased, errors became more frequent (Fig. 6D). The curve relating [5-HT] to behavioral performance thus had again a delay-dependent inverted U-shape, with optimal performance for our reference [5-HT]. This inverted U-curve was a general property of our population of 20 different network realizations (Fig. 7A), and it is therefore a consistent prediction emanating from our modeling effort.

When we classified error trials based on the confidence of the response as detailed above, we found that errors in the low [5-HT] network were only high-confidence errors (Fig. 6F), while performance decrease for high [5-HT] was due to low-confidence errors (Fig. 6E). This provides a specific prediction that can be addressed experimentally: Despite similar overall performance in a SWM task for high and low [5-HT], the type of error trials as evaluated by the confidence declared by participants in their responses should reveal a monotonic behavioral effect of 5-HT modulation.

The nonmonotonic effect of [5-HT] on performance but monotonic prediction of error types (Fig. 6, solid black curves) was a general feature of the population of 20 PFC networks used to test the generality of our findings (Fig. 7A). Although [5-HT] had a significant effect both on the fraction of high- and low-confidence errors compared with the fraction of correct trials across our networks (multinomial logistic model, \( P < 0.05 \)), the linear effect of [5-HT] on the fraction of correct trials did not subsist a population analysis (binomial logistic mixed model, \( P > 0.05 \), Fig. 7B). This analysis shows that the profound behavioral effects of 5-HT in our network simulations are generally confounded in group-based analyses of our network models due to the nonmonotonicity of the
SWM performance curve (Fig. 6D) and the variance of such relationship across network models (Fig. 7A). Only distinguishing error types based on declared response confidence unveils a monotonic behavioral effect consistently in our population of networks (Fig. 7B).

**Role of 5-HT1A and 5-HT2A Receptors in SWM**

Our model also allowed us to evaluate the relative roles of 5-HT1A and 5-HT2A receptors in the behavioral effects of 5-HT modulation. We ran simulations keeping constant the activation of one receptor, while modifying the activation of the other one, in order to mimic the effects of agonists or antagonists of this receptor. Behavioral analyses parallel to the ones described above for these simulations are plotted in Figures 5C and 6E,F. Regarding the distribution of behavioral reports (Fig. 5C), varying independently the activation of 5-HT1A had the same tendency than [5-HT], both for σ and Pinv. 5-HT2A activation, in contrast, had the opposite behavior: Pinv decreased independently of delay length for 5-HT1A agonism, and it decreased in a delay-dependent manner for 5-HT2A antagonism. Memory precision was roughly constant, but decreased slightly for the lowest levels of 5-HT2A activation. When we studied the confidence in error responses, the behavioral modulations following 5-HT1A receptor stimulation mimicked also in this case the effects of [5-HT]: Low-confidence errors for 5-HT1A activation together with high-confidence errors for 5-HT1A receptor blockade. In contrast, 5-HT2A receptor activation showed the opposite effects (Fig. 6E,F).

The parallelism between 5-HT1A receptor-mediated actions and tonic [5-HT] changes in both analyses indicates that this receptor is mainly driving the “behavioral” effects observed in the network upon [5-HT] modulations. This was consistently observed in our population of 20 different PFC network instantiations (Supplementary Fig. 2). However, qualitative changes in behavioral performance induced by modulations of the 5-HT2A receptor were more heterogeneous across our 20 network models, typically showing weaker and often inverse effects compared to the 5-HT1A receptor (Supplementary Fig. S2).

The effect of tonic 5-HT could be attributed mostly to its action via 5-HT1A receptors, which activate a potassium conductance in pyramidal neurons. This suggests that the "behavioral" effects of 5-HT in the SWM network can be interpreted in terms of changes in stability of the memory and spontaneous states caused by a change in neuronal polarization. We confirmed explicitly that the hyperpolarization induced by 5-HT1A receptors was more important than the change in membrane conductance by computing the percentage change in either one during the operation of neurons in our task. During the delay period of the task, the 5-HT-induced change in effective membrane threshold was between 3 and 5 times (depending on whether the neuron tested was encoding—or not—the memorized item) bigger than the change in effective membrane conductance. We can thus interpret the behavioral modulations observed in Figure 6 primarily as excitability changes in the neuronal input–output curve of Figure 2C. When [5-HT] is decreased, neurons become slightly depolarized and the neuronal response curve is shifted to the left (Fig. 8, left). This produces an effect in the stability of the stable states, which can be gauged from the distance of each state to the unstable point (the middle intersection of the 2 curves, black cross). The memory state becomes more stable and the spontaneous state less stable (Fig. 8, left), so that the probability of emergence of spontaneous bumps (Fig. 6C) increases, resulting in high-confidence errors. Spontaneous bumps that emerge before cue presentation persists through the delay, so that these high-confidence errors do not change as a function of delay length. For high [5-HT], the opposite occurs. Neurons are slightly hyperpolarized, and the rightward shift in the neuronal input–output curve (Fig. 8, right)
produces an increase in the distance between the spontaneous state and the unstable point and, therefore, an increase in the stability of the spontaneous state of the network. Simultaneously, the memory state loses stability easily and collapses to the spontaneous state (Fig. 6B), resulting in low-confidence errors. These errors will be more frequent as the delay is extended, since the destabilization of the memory state will occur in more and more trials as the delay length increases. This graphical interpretation is thus able to explain conceptually why “monotonic” changes in neuronal excitability due to 5-HT1A receptor activation modulate SWM behavior nonmonotonically in our network model, causing different types of errors and different dependence with delay length depending on whether it is increased or decreased relative to optimal performance.

Delayed Match-to-Sample Task
DMS tasks have been broadly used to assess SWM function and its neural correlates both in human (Ungerleider et al. 1998; Curtis et al. 2004; Pessoa and Ungerleider 2004; Lee et al. 2008) and animal studies (Miller et al. 1996; Romo et al. 1999; Zaksas and Pasternak 2006). We therefore derived specific predictions for this task from our network simulations. We simulated this task with a fixed period (3 s); a presentation of a stimulus in 1 of the 16 possible locations ($\theta_0$) (0.25 s); a delay of 1, 2, or 3 s; and a presentation of a probe ($\theta_p$) in the same (match trials) or in a different (nonmatch trials) location than the stimulus (Fig. 9A). We ran 1000 simulations of the task for the 5 different values of tonic [5-HT] having an equal proportion of match and nonmatch trials (500 of each type for each [5-HT] level). For each simulation trial, we obtained the encoded angle ($\theta_h$) at the end of the delay and the confidence in this estimation $C_{R_h}$ (as we did in the previous section). We then used a psychometric function (see Materials and Methods) from which we extracted the probability to respond match ($P_m$) in the ith trial given the response $\theta_h - \theta_0$. $P_m$ thus gives the probability of correct response in match trials ($\theta_h - \theta_0 = 0$) and the probability of incorrect response in nonmatch trials ($|\theta_h - \theta_0| > 0$). Averaging these probabilities over trials we obtained the fraction of correct trials as a function of [5-HT] for different delays (Fig. 9B). As we showed previously for the delayed response task (Fig. 6D), the behavioral performance in the DMS task also had an inverted U-shape dependence with [5-HT]. We also obtained delay-independent modulation by [5-HT] when [5-HT] was decreased relative to the optimum, and a strong dependency with delay for higher [5-HT] relative to the optimum (Fig. 9B).

We then analyzed separately match and nonmatch trials. We found that the dependence with [5-HT] was stronger in the hit rate (match correct trials) and in the miss rate (match incorrect trials), while correct rejections (nonmatch correct trials) and false alarms (nonmatch incorrect trials) were comparatively much less dependent on [5-HT] (Fig. 9C). Following our analyses for the delayed response task (Fig. 6), we then used the confidence level of the response to make additional predictions in the DMS task. We subclassified correct and incorrect trials based on the confidence of the decoding process at the end of the delay (see above). Then, we plot in Figure 9D the fraction of trials for the 4 possible responses: True memories (correct confident), correct not confident, false memories (incorrect confident), and incorrect not confident. True memories (correct confident) had an inverted U-shape dependence on [5-HT] (Fig. 9D), as it was also the case for hits (Fig. 9C) or fraction of correct responses (Fig. 9B), while [5-HT] had a monotonic effect in the fraction of false
memories, and nonconfident responses (Fig. 9D). Thus, similar to the delayed response task, also in the DMS task unambiguous, monotonic dependencies with [5-HT] can be obtained by considering the confidence of behavioral responses.

Discussion

We used a cortical network model proposed previously for SWM (Compte et al. 2000) to address the modulatory control of WM function by serotonin. Our model indicates that serotonin plays a role in stabilizing spontaneous and memory states in SWM, mainly through its action on inhibitory 5-HT$_{1A}$ receptors. Increasing levels of tonic [5-HT] compromised SWM by reducing the duration of mnemonic activity, while it favored SWM by suppressing unwanted “false” memories. These 2 effects resulted in an inverted U-shaped relationship of SWM performance with [5-HT] in both simulated delayed response and DMS tasks. Such nonmonotonic dependencies could be disambiguated based on the behavioral confidence declared in error trials, or considering the dependencies with delay duration.

Our findings indicate that a nonmonotonic dependence of behavioral accuracy with [5-HT] could be a factor in interpreting psychopharmacological studies of the role of 5-HT on SWM. Studies manipulating tryptophan levels, and thus serotonin synthesis, in healthy participants failed to find the effects of 5-HT on SWM (Park et al. 1994; Luciana et al. 2001). In contrast, selective serotonin reuptake inhibitors (SSRIs) and compounds with high affinity for 5-HT$_{2A}$ receptors, such as psilocin, mildly impair SWM performance (Luciana et al. 1998; Vollenweider et al. 1998; Wingen et al. 2007; Wittmann et al. 2007). Our network simulations suggest that individual differences in nonmonotonic variation of SWM performance with [5-HT] may compromise the detection of behavioral effects in group-based behavioral studies. Instead, when considering low-confidence and high-confidence errors separately, the relationships become monotonic and easier to document experimentally. Previous studies have also emphasized the importance of making this distinction in humans performing WM tasks (Pessoa and Ungerleider 2004; Rademaker et al. 2012), and in the context of SWM deficits in schizophrenia (Lee et al. 2008; Mayer and Park 2012). Recent SWM paradigms for monkeys are also measuring this metacognitive component (Middlebrooks and Sommer 2011, 2012; Tanaka and Funahashi 2012).

The behavioral effects observed in biophysical networks were readily understood in a simpler graphical interpretation relating neuronal responses to network feedback, where 5-HT affected neuronal excitability (Fig. 8). This interpretation would apply to any neuromodulator affecting cellular excitability, such as dopamine and norepinephrine, which are known to affect nonmonotonically WM performance (Goldman-Rakic et al. 2000; Arnsten and Li 2005; Cools and D’Esposito 2011). The different sensitivity of the various receptors for these neuromodulators and their presence in pyramidal neurons and GABAergic interneurons may explain some of this inverted U-shape dependency (Arnsten and Li 2005; Santana et al. 2009). In addition, our modeling indicates that the network structure supporting persistent activity may

Figure 9. 5-HT modulates the pattern of behavioral responses in the DMS task. (A) Schematic diagram of the simulated DMS task. After 3 s of fixation, a stimulus is presented in 1 of 16 possible locations. After a delay of 1, 2, or 3 s, a probe is presented and subjects have to indicate whether the position of the question mark matches the target position and their confidence in the decision. (B) Fraction of total correct trials for a delay of 1 (light gray line), 2 (dark gray line), and 3 s (black line). (C) For a delay of 3 s, fraction of hits (correct responses for match trials, black solid line) and correct rejections (correct nonmatch trials, gray solid line). Fraction of incorrect responses (dashed lines), which can be misses (in match trials, black line) or false alarms (in nonmatch trials, gray line). (D) For a delay of 3 s, fraction of trials with different responses considering the confidence in the response (Fig. 5): True memories (black line, correct confident trials), correct nonconfident trials (dashed line), false memories (semi-dashed line, incorrect confident trials), and incorrect nonconfident trials (dotted line).
also contribute. Indeed, in our simulations, monotonic effects of receptor activations (Fig. 3C) result in nonmonotonic effects in SWM performance (Figs 5C, 6D, and 9), due to the network’s nonlinear dynamics (see also Brunel and Wang 2001). Interestingly, rodent experiments with D1 receptor manipulations report subtle differences in the nature of errors at either side of the inverted U-curve, with random responses to insufficient and perseverative responses to excessive D1 receptor activation, respectively (Zahrt et al. 1997; Floresco and Phillips 2001; Seamas and Yang 2004). In our model, this would be consistent with an effective depolarizing effect of D1 receptor activation (Fig. 8), promoting a transition from unstable memory states for hypoactive D1 receptors (random responses or low-confidence errors, Fig. 6B) to unstable spontaneous states for hyperactive D1 receptors (perseverative responses or high-confidence errors, Fig. 6C).

Likewise, the convergent effect of different neuromodulatory systems on cellular excitability (and thus on network performance) must be taken into account when interpreting the behavioral effects of specific drugs. Hence, selective 5-HT1A receptor agonists and some SSRIs are known to stimulate catecholamine release in PFC (Tanda et al. 1994; Hajós-Korcsó and Sharp 1996; Díaz-Mataix et al. 2005). This effect is not only due to unspecific actions of these agents, but also to the functional connectivity of PFC with the brainstem monoamine nuclei (Groenewegen and Uylings 2000), which result in the distal activation of ascending catecholamine systems (Jodo and Aston-Jones 1997; Díaz-Mataix et al. 2005). Overall, this could result in competing effects through the various ascending pathways on the resulting behavioral effects according to our network model.

We used an optimization approach to determine network parameters compatible with qualitative aspects of SWM function (see Materials and Methods). This approach allowed us to identify several, parametrically diverse network implementations and to test the generality of our findings (Supplementary Fig. 1). However, such optimization search could question the significance of the inverted U-curve, raising the possibility that the curve be a mere consequence of such optimization. This seems unlikely in view that: (1) Tonic 5-HT was not included as one optimized parameter; (2) nonmonotonic behavior was not required: Some linear manipulations of network parameters led to monotonous changes in performance; and (3) our graphic interpretation in Figure 8 revealed that the inverted U-shape dependency resulted from network structure and dynamics, not from particular network instantiations.

We focused on the 2 most abundant 5-HT receptors in PFC (5-HT1A and 5-HT2A) whose effects on pyramidal neurons have been extensively characterized (see Materials and Methods). We also included the actions of 5-HT2A receptors on GABAergic interneurons, but not those of 5-HT1A receptors for lack of in vitro electrophysiological descriptions on these neurons. Our simulations showed that the effects of 5-HT on SWM in the model were primarily mediated by 5-HT1A receptors. This dominant inhibitory effect of 5-HT1A receptors agrees with rodent electrophysiological data (Puig et al. 2005), despite the abundant presence of 5-HT2A receptors in PFC and their colocalization with 5-HT1A receptors (Amargós-Bosch et al. 2004; Santana et al. 2004). The reason for this preferential inhibitory effect are not fully understood and may include (1) the indirect ionic nature of 5-HT1A receptors (coupled to G-protein gated inwardly-rectifying K+ channels), with stronger actions on neuronal excitability than 5-HT2A receptors, and (2) their localization in the axon hillock, where they directly control the generation of action potentials (DeFelipe et al. 2001; Cruz et al. 2004). In our modeling, an additional reason for the dominant effect of 5-HT1A receptors is the fact that the afterhyperpolarization current I_{KCa}, a site of 5-HT2A modulation, is known to hinder correct SWM in these networks (Hansel and Sompolinsky 1998; Laing and Longtin 2001), and it will be therefore penalized during parameter optimization or compensated for with the opposing I_{KCa} current, thereby resulting in a small global effect of the mechanisms modulated by 5-HT2A receptors. Experimentally, pyramidal neurons in hypercoupled subcircuits of the PFC show a remarkable lack of accommodating responses to current injections (Wang et al. 2006), compatible with a weak or compensated action of afterhyperpolarization currents such as I_{KCa}.

A limitation of the present study is that other receptors present in PFC, such as 5-HT3 (Puig et al. 2004) or 5-HT2C (Pompeiano et al. 1994), were not included since in vitro characterizations were not available. However, these receptors could be implicated in SWM since (1) recent reports support a role for 5-HT2C receptors in cognitive processes (Boulougouris et al. 2008; Boulougouris and Robbins 2010) and (2) these receptors are expressed by a substantial percentage of pyramidal and GABAAergic neurons in various PFC areas (Santana and Artigas 2012). Despite this limitation, several elements support the validity of our conclusions. First, our graphic interpretation in Figure 8 implies that the specific mechanisms by which 5-HT changes neuronal excitability are not critical. Secondly, responses to phasic [5-HT] in the network (Fig. 3E) were consistent with the observation that endogenous 5-HT modulates PFC pyramidal neuron activity mainly via 5-HT1A-mediated inhibitions (66% of the cases), followed by 5-HT2A-mediated excitations (Puig et al. 2005), suggesting that the fundamental excitability modulations by 5-HT in PFC were effectively accounted for in our model. Finally, the presence of 5-HT3 receptors—a Na+ channel—in GABAAergic interneurons could add an additional complexity, but these receptors are located in outer layers (mainly I-II) (Puig et al. 2004) and thus have little impact on the local current activity simulated in our network model.

Our modeling cannot make strong predictions regarding behavioral effects of 5-HT2A modulations. This was due to the fact that multiple, opposing mechanisms could be recruited by 5-HT2A receptor activation, and a different combination of these mechanisms was present in our 20 different network realizations. For the majority of networks 5-HT2A agonists increased high-confidence errors (Fig. 6F), but for a few networks they increased low-confidence responses. Indirectly, the fact that many 5-HT2A agonists are hallucinogens (Nichols 2004) suggests that high-confidence errors might characterize this condition, consistent with the “false memories” that emerge for high 5-HT2A receptor activation in Figure 6C.

Our computational study makes experimentally testable predictions, which will require further studies. First, performance in a SWM task, whether delayed response or DMS task, should show an inverted U-shape dependence with tonic [5-HT] (Figs 6D and 7), which could be pharmacologically modulated with SSRI or tryptophan load/depletion. Secondly, participants should declare high confidence in errors under
acutely tryptophan depletion (Figs 6F and 9D) and low confident errors should be abundant under tryptophan loading or SSRI treatment (Figs 6E and 9D). Thirdly, despite similar overall WM performance, prefrontal functional magnetic resonance imaging activations should be significantly enhanced in the error trials of tryptophan-depleted relative to SSRI-treated or tryptophan-loaded subjects, revealing their different neuronal substrate (Fig. 6B,C; Pessoa and Ungerleider 2004; Lee et al. 2008).Fourthly, 5-HT1A antagonists (agonists) should have similar behavioral effects than tryptophan depletion (loading), revealing the dominant role of 5-HT1A receptors in serotonin-modulated SWM (Figs 5C and 6E,F, and Supplementary Fig. 2).Fifthly, fitting the distribution of direct reports in a delayed response task, we should observe that serotoninergic manipulations affect more strongly the uniform component (Pn) than the Gaussian component (σ), indicating that errors are mostly due to random responses rather than degraded precision (Fig. 5B).Sixthly, all effects observed under tryptophan loading or SSRI treatment should be delayed dependent since errors are due to memory loss during the delay. In contrast, under tryptophan depletion, errors are mostly caused by spontaneous memories before cue presentation and are therefore delay-independent (Figs 5B, 6D, and 9B).Seventhly, performance in a DMS task should show an inverted U-shape for hits when [5-HT] is modulated pharmacologically, mostly due to the modulation of misses since the fractions of correct rejections and false alarms would remain fairly constant (Fig. 9C).Eighthly, when classifying trials based on declared response confidence, the rate of confident error trials (false memories) should be higher (lower) under tryptophan depletion (loading), and the reverse trend should be observed for nonconfident error trials (Fig. 9D).Finally, at the neurophysiological level, microinjection of serotoninergic drugs in the PFC should alter behavioral WM performance nonmonotonically (Fig. 6D), but it should modulate monotonically the average firing rate during delay periods of correct trials (Fig. 3C), thus demonstrating that the nonmonotonicity is generated beyond the cellular level.

Supplementary Material
Supplementary material can be found at: http://www.cercor.oxfordjournals.org/.

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Notes
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References


