Supporting Information

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SI Results

To exclude potentially confounding effects related to positron emission tomography (PET) data, further exploratory analyses were carried out. There was no significant association between radiochemical variables (specific activity, mass of unlabeled compound, injected dose) and serotonin-1A receptor (5-HT_{1A}) binding potentials (BP_{ND}) in any of the reported regions ($r < 0.34$, rho < 0.32, $P > 0.05$). Inclusion of these radiochemical variables in the regression model did not change our findings. Similarly, correcting the dorsal raphe nucleus 5-HT_{1A} binding for partial volume effects with PMOD 3.3 (1) did not change the observed results. Of note, after correction, there was an additional negative association between the dorsal raphe BP_{ND} and the resting-state default mode network (DMN) in the rostral anterior cingulate cortex ($P < 0.001$, uncorrected), which, however, did not withstand correction for multiple comparisons. Taken together, we cannot conclude that the reported findings are simply driven by radiochemical variables or partial volume effects.

SI Materials and Methods

Subjects. To rule out physical, psychiatric, and neurological disorders, all subjects underwent standard medical examinations, electrocardiogram, routine laboratory tests, and the Structural Clinical Interview (SCID) for Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV). Further exclusion criteria were past or current substance abuse, intake of psychotropic medication, implants or steel grafts, pregnancy [tested with a urine human chorionic gonadotropin pregnancy test at the screening visit and before the functional magnetic resonance imaging (fMRI) and PET scans], hormonal treatment, and intake of oral contraceptives. Subjects provided written informed consent after detailed explanation of the study protocol and received reimbursement for their participation.

Positron Emission Tomography. PET measurements were carried out with a GE Advance scanner (General Electric Medical Systems), starting with a 5-min tissue attenuation scan (retractable ^{68}Ge ring source). This was followed by a 3D dynamic emission measurement and synchronous injection of the radioligand [*carbonyl*-^{11}C]WAY-100635 (mean injected dose ± SD = 381 ± 31.9 MBq, specific activity = 183.2 ± 147.1 MBq/nmol, mass of unlabeled compound = 3 ± 4.4 μg). Scans lasted for 90 min (30 frames: 15 × 1 min, 15 × 5 min) and reconstructed images comprised a spatial resolution of 4.36 mm full-width at half-maximum at the center of the field of view (matrix 128 × 128, 35 slices).

PET scans were corrected for head motion (quality = 1) and normalized (affine regularization = average-sized template) to the stereotactic space defined by the Montreal Neurological Institute (MNI) using SPM8 with default settings for remaining parameters (Wellcome Trust Centre for Neuroimaging; http://www.fil.ion.ucl.ac.uk/spm). To ensure optimal spatial overlap between PET and fMRI image modalities, the normalization was carried out via the corresponding T1-weighted MRI. Hence, structural MRI scans were normalized using the standard segmentation option of SPM8, and the obtained transformation matrix was applied to the coregistered PET frames.

Functional Magnetic Resonance Imaging. Single-shot gradient-recalled echo-planar imaging sequences were used [echo time (TE) = 40 ms, repetition time (TR) = 1,000 ms, matrix size = 96 × 64] yielding 14 axial slices aligned to the anterior commissure-posterior commissure (AC-PC) line (5-mm thickness + 1-mm slice gap). Within the resting-state scan, subjects were instructed to relax in the scanner, stay awake with eyes open (low-level illumination, no fixation cross-hair), and "allow thoughts to come and go freely."

Tower of London Task. Within the Tower of London paradigm, two sets of colored balls on pegs were displayed together with two possible answers (one correct). Participants were required to (mentally) rearrange the starting set to match the target configuration and hence to finally determine the minimum number of moves to solve the task. The correct answer was then chosen from two given possibilities with a corresponding button press. Stimuli were chosen randomly from a pool of 50 image sets of varying difficulty (two to eight moves). This is feasible for obtaining variation in the individual levels of activation, which in turn is required to assess a reasonable association with 5-HT_{1A} receptor binding. Baseline condition was defined with a fixation cross-hair, shown at the beginning and end of the task (each 20 s) as well as between stimuli (12 s).

1. Rousset OG, Ma Y, Evans AC (1998) Correction for partial volume effects in PET: Principle and validation. *J Nucl Med* 39:904–911.

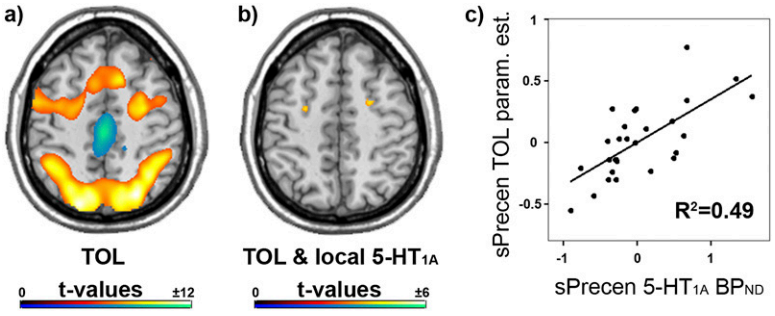

Fig. S1. (*A*) Task-specific activations induced by the Tower of London paradigm within the supplementary motor area, superior precentral gyri (sPrecen), and intraparietal sulci [$P < 0.05$, family-wise error (FWE)-corrected]. (*B*) Modulations of local 5-HT_{1A} receptor BP_{ND} were found in the superior precentral gyrus bilaterally ($P < 0.001$, $k = 120$ mm^3). (*C*) The scatter plot shows the association for the cluster in the left hemisphere given in *B*. Note that variables are mean-centered after adjustment for nuisance covariates, which introduces negative values into the plot (see Table S2 for actual BP_{ND} values). $z = 49$ mm MNI stereotactic space.

Table S1. Modulations of serotonin-1A receptor binding on the default mode network

Condition	Region		MNI coordinates (mm)			Peak		Cluster Size (mm^3)
	AAL	BA	*x*	*y*	*z*	*t* value	R^2	
Resting state								
5-HT_{1A} local								
Task-negative	RSC	29/30	2	−44	12	6.49*†‡	0.64	704
	Angular	39	−48	−66	36	−6.39*†‡	0.62	464
	dmPFC	9	−10	52	38	−4.44*	0.45	128
	PCC	23	2	−46	28	−4.35*	0.44	152
	dlPFC	9	−28	20	58	−4.27*	0.44	128
Task-positive	Insula	48	50	8	−14	4.67*‡	0.48	400
5-HT_{1A} auto								
Task-negative	PCC	23	2	−50	30	5.31*‡	0.55	440
	Angular	39	−48	−66	36	5.38*	0.55	184
Tower of London								
5-HT_{1A} local								
Task-negative	RSC	29/30	6	−44	20	−5.26*†‡	0.55	160
Task-positive	Sup precen	6	−26	−6	42	4.82*‡	0.50	336
			24	−2	46	4.77*	0.49	144

The task-positive and task-negative network parts are evaluated separately for inhibitory effects of both local heteroreceptors (5-HT_{1A} local) and dorsal raphe nucleus autoreceptors (5-HT_{1A} auto). The DMN was obtained using resting-state fMRI and the Tower of London paradigm. *$P < 0.001$, uncorrected (voxel) with $k = 120$ mm^3 (cluster). $P < 0.05$, FWE-corrected at †voxel or ‡cluster level. AAL, automated anatomical labeling; BA, Brodmann area; dmPFC/dlPFC, dorsal medial/lateral prefrontal cortex; PCC, posterior cingulate cortex; RSC, retrosplenial cortex; Sup precen, superior precentral gyrus.

Table S2. Serotonin-1A receptor binding potentials for regions showing significant associations with the default mode network

Region	5-HT_{1A} BP_{ND}
5-HT_{1A} auto	
DRN	1.85 ± 0.5
5-HT_{1A} local	
RSC	1.42 ± 0.44
PCC	3.91 ± 0.93
dmPFC	3.46 ± 0.95
dlPFC	3.38 ± 0.93
Insula	4.59 ± 1.42
Sup precen	1.09 ± 0.44
Angular	3.09 ± 0.9

Data are given as mean ± SD separately for dorsal raphe nucleus autoreceptor (DRN, 5-HT_{1A} auto) and local heteroreceptor binding (5-HT_{1A} local). See Fig. 1*A* for visualization and Table S1 for associations with the DMN. dmPFC/dlPFC, dorsal medial/lateral prefrontal cortex; DRN, dorsal raphe nucleus; PCC, posterior cingulate cortex; RSC, retrosplenial cortex; Sup precen, superior precentral gyrus.