Supporting Information

Crockett et al. 10.1073/pnas.1009396107

SI Materials and Methods

Ultimatum Game. During each trial, participants viewed sequentially a photograph of the proposer (1,500 ms), the amount of the stake (1,500 ms), and the amount of the offer (4,000 ms). Participants responded to each offer by pressing one of two buttons (labeled "accept" and "reject") while the offer was on the screen. In our previous study, the effects of the serotonin manipulation were strongest at the beginning of the task (M.J.C., unpublished observations), so in the current experiment, we used a shorter version of the task to minimize repetition and demands on participants. To enhance the credibility of the UG task, participants were told that they were part of a large ongoing study in which they would be playing the role of responder with volunteers who had submitted their offers previously. In addition, they were told they would have the opportunity to play the role of proposer with volunteers who would participate in the future, if they would allow their photograph to be taken and used in future sessions, and submit proposals for 12 different stake sizes. In reality, there were no actual proposers. Before the game started, the experimenter required a verbal confirmation that the participant understood the game. Participants were told that they would receive the financial outcomes from two trials that would be randomly selected at the end of the game. At debriefing, we asked whether participants believed the offers were made by the pictured proposers and that they and the proposers would be paid based on their choices. Two participants were excluded based on their negative responses to these questions.

Trait Empathy Measure. We assessed trait empathy by using global scores on the Interpersonal Reactivity Index (1), a 28-item self-report questionnaire (Cronbach's $\alpha = 0.76$). To examine interactions between trait empathy, drug treatment, and our behavioral measures, we performed a median split to divide our subject pool into high and low empathy groups. High and low empathy groups did not significantly differ in age ($t = 0.334$, $P = 0.741$), level of education ($t = -1.665$, $P = 0.11$), IQ as measured by the National Adult Reading Test ($t = 0.286$, $P = 0.77$), or serotonin transporter genotype ($\chi^2 = 0.686$, $P = 0.408$). However, high and low empathy groups did differ according to gender ($\chi^2 = 4.196$, $P = 0.041$). The female:male ratio was higher in the high empathy group than the low empathy group, although raw empathy scores were not significantly different between genders ($t = 1.680$, $P = 0.107$). We therefore controlled for gender when examining the impact of empathy.

Measures of Executive Function. To test the effects of the drugs on general aspects of executive function, we used two tasks: The rapid visual information processing (RVP) task, and the go/no-go task. The RVP task is a test of attentional vigilance with a working memory component, taken from the Cambridge Neuropsychological Test Automated Battery (CANTAB) (www.camcog.com). On this test, volunteers observed a continuous series of single digits appearing on-screen, and were asked to make a simple motor response whenever a target sequence occurred (e.g., "2" followed by "4" followed by "6"). Measures included target sensitivity (an index of the ability to discriminate signal from noise, range 0–1), response bias (a measure of the tendency to respond regardless of whether a target is present, range −1 to +1), and response latency.

The go/no-go task is a standard measure of motor response inhibition. Stimuli were 5 × 5 checkerboards composed of random configurations of blue and yellow squares. For half of the participants, "go" stimuli had a majority of blue squares and a minority of yellow squares; "no-go" stimuli had a majority of yellow squares and a minority of blue squares. For the other half of the participants, the go stimuli were yellow-dominant and the no-go stimuli were blue-dominant. During the task, stimuli were presented serially against a black background, for an average duration of 900 ms. Participants were instructed to press a key as quickly as possible in response to go stimuli but to avoid responding to no-go stimuli. In total, there were 28 no-go trials and 28 go trials. Average reaction times for correct go responses, proportion correct go responses (hits), and proportion incorrect no-go responses (commission errors) were recorded.

For the RVIP task, we analyzed target sensitivity, response bias and response latency measures, with drug and session as within-subjects factors. For the go/no-go task, we analyzed commission error rates, average go reaction times, and proportion of correct go responses, with drug and session as within-subjects factors.

Data Analysis. In within-subject designs, the appropriate index of variation is not the SEMs but the SE of the difference of the means (SED), which is used when one is interested in the relationship between variables rather than the variables themselves. The SED is therefore used in the figures as an index of variation. The SED is calculated by using the formula provided in Cochran and Cox (2):

$$\mathrm{SED} = \sqrt{[(2 \times \mathrm{MSe})/n]}$$

MSe = mean square for the error, or residual, term, and n = number of observations made.

The SED is the denominator for Student's t test and also provides a visual method of comparing mean values in graphical depictions of within-subject designs.

For the self-report mood assessment, we analyzed the difference scores (pretest – baseline) of positive and negative affect scales, and the nauseous, drowsy, hostile, energetic and attentive visual analog scales.

SI Results

Executive Function. We examined performance on two standard measures of executive function: the rapid visual information processing (RVP) test, which evaluates sustained attention and working memory; and the go/no-go task, which measures motor response inhibition. Atomoxetine, but not citalopram, improved executive function as assessed by these measures (Fig. S1). We found significant main effects of drug ($P = 0.004$) and session ($P < 0.001$) on target sensitivity in the RVP task. Target sensitivity was significantly improved on session 2 compared with session 1 ($P = 0.034$) and on session 3 compared with session 2 ($P = 0.04$). Atomoxetine improved target sensitivity, relative to both citalopram ($P = 0.026$) and placebo ($P = 0.002$). There was also a significant effect of testing session on response latency ($P = 0.006$). Responses were faster on session 2, relative to session 1 ($P = 0.001$). We also found a significant main effect of drug ($P = 0.031$) on commission error rates in the go/no-go task. Atomoxetine reduced commission error rates, relative to citalopram ($P = 0.009$). There were no significant effects of drug, session, or their interaction on go reaction times or proportion correct go responses (all $P > 0.216$).

Self-Report Mood. There were no significant effects of drug or session on changes from baseline to pretest on self-reported positive affect, negative affect, drowsiness, hostility, energy, or attention (all

$P > 0.167$). However, there was a significant effect of drug on self-reported nausea ($P = 0.016$). Compared with the placebo condition, participants reported greater increases in nausea from baseline to pretest on both citalopram ($P = 0.04$) and atomoxetine ($P = 0.001$). Citalopram and atomoxetine did not differ significantly with respect to induced nausea ratings ($P = 0.144$).

To examine the possibility that our observed behavioral effects were due to nausea rather than changes in serotonergic neurotransmission, we repeated the above analyses including self-reported changes in nausea as a covariate. For the UG, the drug × fairness interaction remained significant ($P = 0.024$), and the three-way interaction between drug, fairness, and nausea was not significant ($P = 0.148$).

For the moral judgment task, the drug × scenario type interaction remained significant ($P < 0.001$), but we also observed a significant three-way interaction between drug, scenario type, and nausea ($P < 0.001$). To examine this interaction, we conducted a number of follow-up analyses. First, we examined correlations between self-reported nausea and acceptability judgments, broken down by drug and scenario type. Only one significant correlation was observed: Subjects reporting greater nausea on citalopram were more likely to rate personal avoidable harms as acceptable ($r = 0.481$, $P = 0.017$). We also examined the relationship between drug-induced nausea and drug effects on moral judgment by correlating nausea ratings with drug effects (relative to placebo) for each scenario type. The only significant correlation was between citalopram-induced nausea and the effect of citalopram on judgment of personal avoidable harms ($r = -0.406$, $P = 0.04$); subjects showing the greatest effect of citalopram on moral judgment (relative to placebo) were those reporting the lowest nausea. Because the effect of citalopram on moral judgment went in the opposite direction of the observed nausea effects (i.e., citalopram caused fewer acceptability judgments, whereas nausea was associated with more acceptability judgments), it is unlikely that the reported behavioral effects of citalopram are simply due to nausea; if anything, the effects of nausea made it more difficult to detect effects of citalopram.

Confirmation of Double-Blind Procedure. At debriefing on the final session, we asked participants to indicate if they had any suspicion about the order of drug administration by using a Likert scale ranging from −3 (not at all suspicious) to +3 (completely suspicious); a rating of zero indicates a neutral suspicion level. Participants were also asked to write down which drug they believe they received on each day. On average, participants' suspicion ratings were not significantly above neutral (mean = 0.208, SE = 0.458). Only two participants correctly guessed the order of drug administration.

SI Discussion

Acute doses of reuptake inhibitors such as citalopram reduce neurotransmitter reuptake shortly after administration (3), but at low doses the resulting effects on neurotransmission may be countered by negative feedback of neurotransmitter release via presynaptic autoreceptors (4). For this reason, we chose a dose of citalopram at the higher end of established treatment guidelines. In this study, we found that citalopram influences social behavior in the UG in the opposite direction from tryptophan depletion (5), which lowers 5-HT synthesis (6). This result suggests that our chosen dose of citalopram enhanced 5-HT neurotransmission in our volunteers. The enhanced executive performance we observed on atomoxetine is consistent with a functional MRI study showing significant enhancement of inhibitory control by atomoxetine in conjunction with a dose-dependent boosting of the BOLD signal in the inferior prefrontal cortex (7) and other evidence that cortical noradrenaline participates in executive control (8).

1. Davis MH (1980) A multidimensional approach to individual differences in empathy. *JSAS Catalog Sel Doc Psych* 10:85.
2. Cochran WG, Cox GM (1957) Experimental Designs. *Wiley, New York*, 2nd Ed.
3. Bymaster FP, et al. (2002) Fluoxetine, but not other selective serotonin uptake inhibitors, increases norepinephrine and dopamine extracellular levels in prefrontal cortex. *Psychopharmacology (Berl)* 160:353–361.
4. Blier P, Piñeyro G, el Mansari M, Bergeron R, de Montigny C (1998) Role of somatodendritic 5-HT autoreceptors in modulating 5-HT neurotransmission. *Ann N Y Acad Sci* 861:204–216.
5. Crockett MJ, Clark L, Tabibnia G, Lieberman MD, Robbins TW (2008) Serotonin modulates behavioral reactions to unfairness. *Science* 320:1739.
6. Nishizawa S, et al. (1997) Differences between males and females in rates of serotonin synthesis in human brain. *Proc Natl Acad Sci USA* 94:5308–5313.
7. Chamberlain SR, et al. (2009) Atomoxetine modulates right inferior frontal activation during inhibitory control: A pharmacological functional magnetic resonance imaging study. *Biol Psychiatry* 65:550–555.
8. Robbins TW, Arnsten AF (2009) The neuropsychopharmacology of fronto-executive function: Monoaminergic modulation. *Annu Rev Neurosci* 32:267–287.

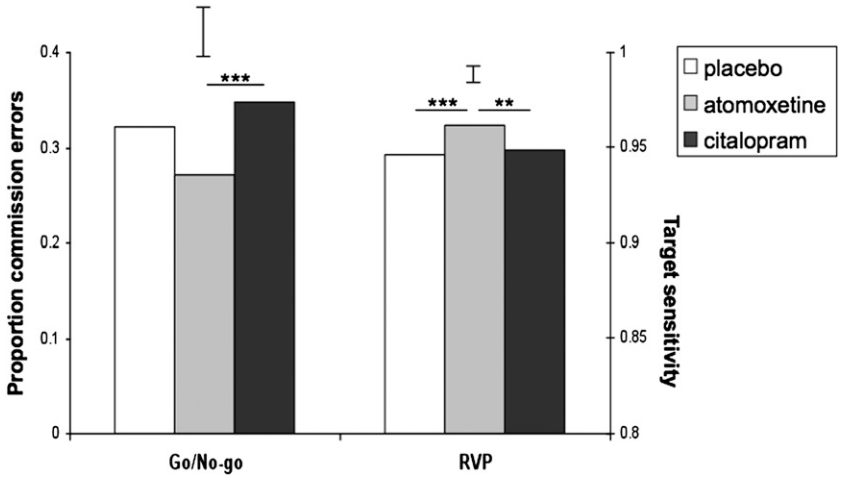

Fig. S1. Effects of citalopram and atomoxetine on executive function atomoxetine (NA) enhanced executive function in the go/no-go task (reduced commission error rates), relative to citalopram (5-HT); in the Rapid Visual Information Processing (RVP) task (enhanced target sensitivity), relative to both citalopram and placebo. $^{**}P \leq 0.05$; $^{***}P \leq 0.01$. Error bars represent twice the SE of the difference of means.