Prefrontal Cortex Activation and Stopping Performance Underlie the Beneficial Effects of Atomoxetine on Response Inhibition in Healthy Volunteers and Those With Cocaine Use Disorder


ABSTRACT

BACKGROUND: Impaired response inhibition in individuals with cocaine use disorder (CUD) is hypothesized to depend on deficient noradrenergic signaling in corticostriatal networks. Remediation of noradrenergic neurotransmission with selective norepinephrine reuptake inhibitors such as atomoxetine may therefore have clinical utility to improve response inhibitory control in CUD.

METHODS: We carried out a randomized, double-blind, placebo-controlled, crossover study with 26 participants with CUD and 28 control volunteers investigating the neural substrates of stop-signal inhibitory control. The effects of a single dose of atomoxetine (40 mg) were compared with placebo on stop-signal reaction time performance and functional network connectivity using dynamic causal modeling.

RESULTS: We found that atomoxetine speeded Go response times in both control participants and those with CUD. Improvements in stopping efficiency on atomoxetine were conditional on baseline (placebo) stopping performance and were directly associated with increased inferior frontal gyrus activation. Further, stopping performance, task-based brain activation, and effective connectivity were similar in the 2 groups. Dynamic causal modeling of effective connectivity of multiple prefrontal and basal ganglia regions replicated and extended previous models of network function underlying inhibitory control to CUD and control volunteers and showed subtle effects of atomoxetine on prefrontal-basal ganglia interactions.

CONCLUSIONS: These findings demonstrate that atomoxetine improves response inhibition in a baseline-dependent manner in control participants and in those with CUD. Our results emphasize inferior frontal cortex function as a future treatment target owing to its key role in improving response inhibition in CUD.

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Cocaine use disorder (CUD) is exemplified by high levels of impulsivity and impaired response inhibition (1,2). Response inhibition is typically assessed using the stop-signal reaction time (SSRT) task (3–5), with prefrontal hypoactivity a feature of impaired inhibition in stimulant use disorder (6,7). The response inhibitory frontostriatal network includes the right inferior frontal gyrus (rIFG), dorsomedial prefrontal cortex (dmPFC), putamen, and subthalamic nucleus (STN) (8–11). Neurochemically, response inhibition encompasses dopaminergic and noradrenergic mechanisms operating at distinct cortical and subcortical sites (12,13). Norepinephrine in particular appears to have a preferential contribution to response inhibition in the PFC (12,14).

Given the prominence of response inhibition difficulties in the conceptualization of addiction models (7), pharmacological interventions of norepinephrine neurotransmission have been suggested as potentially improving executive inhibitory control in addiction, although its effects in CUD remain to be established (15–17). Atomoxetine is a well-tolerated selective pre-synaptic norepinephrine transporter blocker (18–20) prescribed for attention-deficit/hyperactivity disorder (ADHD), which is also characterized by impulsive behavior and poor response control (21). Acute administration of atomoxetine has been found to improve response inhibition in healthy volunteers and in adult patients with ADHD (14,22), and longer-term administration in ADHD has been associated with broader attentional control improvements (23). In addition, atomoxetine was found to upregulate rIFG during stopping in healthy volunteers (24). Furthermore, atomoxetine ameliorated attentional bias to drug-related cues in participants with CUD (25).

However, not all studies on atomoxetine have found performance improvements in stopping or concomitant brain correlates (26–29). A possible reason for this may be baseline-dependent individual differences, whereby only those with
worse stopping performance benefit from atomoxetine administration. Two studies on atomoxetine administration in older adults with Parkinson’s disease found that atomoxetine-related improvement in stopping was associated with baseline performance (30,31). In one of these studies, improvement of response inhibition by atomoxetine was also associated with increased rIFG activation (30). Moreover, these studies pointed to atomoxetine enhancing and even restoring abnormal connectivity within the stopping frontostriatal network (30,31).

In the current study, we investigated the effects of atomoxetine on inhibitory performance and associated brain function in participants with CUD and in healthy control participants. We used pharmacological functional magnetic resonance imaging (fMRI) of the stop-signal task (6,32), expecting participants with CUD to show performance impairments that could be remediated by atomoxetine. We hypothesized that changes in frontostriatal regions subserving stopping would underlie any beneficial effects of atomoxetine. We further aimed to identify effects of atomoxetine on effective connectivity of the stopping network. To this end, we built on previous dynamic causal modeling (DCM) of the stop-signal connectivity of the stopping network. To this end, we built on previous dynamic causal modeling (DCM) of the stop-signal network. To this end, we built on previous dynamic causal modeling (DCM) of the stop-signal network.

**METHODS AND MATERIALS**

**Participants**

A starting sample of 28 healthy participants and 28 individuals who satisfied DSM-IV-TR (33) criteria for cocaine dependence, here referred to as CUD, were recruited from drug treatment services by advertisement and word of mouth. Two patients with CUD did not complete the task in the scanner and thus were excluded. Healthy control participants were recruited from the Cambridge BioResource volunteer panel (http://www.cambridgebioresource.org.uk) and had no current or past psychiatric disorders. All participants were screened using the Mini-International Neuropsychiatric Interview (34) and had no current or past psychiatric disorder, or metabolic disorder, 2) were taking any stimulants for the treatment of ADHD. Cocaine dependence was verified using the Structured Clinical Interview for DSM-IV (35). Fifteen patients with CUD also met the DSM-IV criteria for opioid dependence; 10 of these were taking methadone or buprenorphine as part of their maintenance therapy. Ten patients with CUD also met criteria for tetrahydrocannabinol dependence. Participants were excluded if they 1) had a history of neurologic disorder, head or brain injury, psychotic disorder, or metabolic disorder, 2) were taking any medication that would interact with atomoxetine such as aripiprazole or bupropion, 3) were pregnant, 4) had MR incompatibilities, or 5) had been involved in a clinical trial within the past 6 months. Urine screens verified recent cocaine use in all patients with CUD and were drug negative for all control participants. An additional 5 patients with CUD were excluded from each session owing to limited task compliance and race model violations (6), resulting in 8 patients with CUD being precluded from analyses incorporating both sessions (Table S1).

**Experimental Procedure and Design**

The study followed a randomized, double-blind, placebo-controlled, crossover, balanced design. All participants provided written informed consent, which received ethical approval from National Ethics Committee (12/EE/0519; principal investigator, K.D. Ersche). Participants received orally either 40 mg atomoxetine or a placebo of identical appearance, consistent with previous studies (24,30). At least 7 days separated the sessions for each participant, which included a neuropsychological battery and brain imaging (25). Blood samples for plasma were collected 150 minutes after administration (mean 366 ng/mL, standard deviation 200 ng/mL) following established pharmacokinetics immediately after scanning (36,37). Participants underwent structural and functional MRI scanning where they performed the stop-signal task. Generalized linear models (GLM) on SSRT and Go reaction time (RT) were conducted with subject-level random effects (equivalent to mixed-effect analyses of variance) to explore the main effects of group (cocaine vs. control), drug (atomoxetine vs. placebo), and the group-by-drug interaction (nlme and car packages in RStudio [version 3.4.1]). Age and atomoxetine plasma levels were included as covariates. Regression weights with their respective t and p values are reported. After the GLM analyses described below, predictors of performance changes due to atomoxetine were explored. Analysis of covariance models (aov package in RStudio [version 3.4.1]) were fitted to explain the variability in atomoxetine-dependent changes in SSRT and in Go RT.

**MRI Acquisition.** MRI data were acquired using a Siemens Trio 3T scanner (Siemens AG). Functional images used a whole-brain echo planar image sequence (repetition time, 2000 ms; echo time, 30 ms; flip angle, 78°; 32 slices with 3-mm slice thickness and a 0.75-mm gap; matrix = 64 × 64; field of view, 192 × 192 mm; 3 × 3-mm in-plane resolution; number of volumes ranging between 278 and 305). High resolution T1-weighted gradient echo images were acquired for registration purposes (176 sequential slices of 1-mm thickness; repetition time, 2300 ms; echo time, 2.98 ms; flip angle, 9°; field of view, 240 × 256 mm).

**Stop-Signal Task.** On Go trials, participants were required to respond with left or right key presses to corresponding left or right arrow stimuli (100 ms) (6). On Stop trials, a stop signal subsequently appeared (an orange upward arrow, 300 ms), and participants had to cancel their planned response. Left and right arrows were counterbalanced and intermixed, and the delay between Go and Stop stimuli was adjusted in 50 ms steps from an initial value of 250 ms to achieve 50% successful stopping (38). The task included 48 Stop trials and 240 Go trials in one block, with Stop trials repeating at a later time if participants responded before stop-signal onset. Intertrial intervals varied randomly between 900 and 1100 ms (39). Participants were instructed to respond as quickly as possible and not to delay responding. Key task outcome measures included

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mean RT on Go trials and the SSRT calculated using the integration method with replacement of Go omissions (32). Participants who did not meet the assumptions of the race were excluded (6). ΔSSRT was calculated as the difference between SSRT on atomoxetine and SSRT on placebo.

Finally, as part of clinical assessments, participants completed the Beck Depression Inventory-II, the National Adult Reading Test, an estimate of verbal intelligence, the Obsessive Compulsive Drug Use Scale, Alcohol Use Disorders Identification Test, and the Barratt Impulsivity Scale-11 (40–45).

**MRI Data Processing and Analyses**

**Preprocessing.** fMRI data processing was carried out using FEAT (version 6.00, part of FSL (FMRIb’s Software Library) (http://www.fmrib.ox.ac.uk/fsl). The first 5 volumes were discarded to achieve steady-state equilibrium. Registration to structural and standard space images was carried out using FLIRT (46–48) and FNIRT (49,50). Preprocessing included motion correction using MCFLIRT (1); nonbrain removal using BET (51); spatial smoothing using a Gaussian kernel of full width at half maximum 5 mm and grand-mean intensity normalization; and high-pass temporal filtering (100 s). First-level analysis (52) included 4 regressors of interest: successful Stops, failed Stops, successful Go, and error Go responses (all other Go trials) convolved with double-gamma hemodynamic response function. Temporal derivatives were also included for each of the regressors. Successful Stops were contrasted with successful Go responses (stopping contrast). Twenty-four movement parameters were included as covariates of no interest along with a prewhitening step.

**GLM Analyses.** Two GLMs, one for the placebo and one for the atomoxetine drug condition, used one-sample whole-brain t tests to identify significant Stop-related group mean activations in the control and cocaine groups using FEAT FLAME-1 analysis (53). Conjunction analysis tested for overlap between the groups (easycthresh_conj.sh). An additional GLM included the difference maps of parameter estimate contrasts for placebo and atomoxetine. Here, one-sample t tests of theatomoxetine versus placebo difference maps were used to evaluate drug effects across subjects, and a group-by-drug interaction was tested using independent sample t tests (CUD vs. control) (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Randomise/UserGuide).

We also sought to assess whether behavioral effects of atomoxetine were conditional on individual differences in brain activation. To test for associations between drug-related changes in task performance and brain activity, the difference between atomoxetine and placebo in SSRT (ΔSSRT) was added as a covariate to the atomoxetine versus placebo difference GLM. Based on previous findings (24,30), an IFG region of interest (ROI) was applied using the Harvard-Oxford atlas. As significant improvement in Go RT was noted, a parallel yet exploratory analysis was conducted with the difference between drug conditions in Go RT (ΔGoRT) added as a covariate to the Go > Stop drug difference GLM with primary motor cortex (M1) serving as an ROI (primary motor cortex from the Juelich Atlas). For all analyses, images were thresholded using threshold-free cluster enhancement in randomise with 5000 permutations ($p > 2.3$, $p < .05$). Demeaned order of drug versus placebo sessions was included as a second-level covariate of no interest in all GLMs. Group mean activations and placebo-atomoxetine GLMs were conducted using a whole-brain mask, while the ΔSSRT and ΔGoRT analyses were conducted within the IFG and M1 masks, respectively.

**DCM Analyses.** To examine the most likely network identified by group mean GLM maps and to inspect the directed connectivity in that network, dynamic causal models (54,55) were built and tested in each group and drug condition in SPM12 (https://www.fil.ion.ucl.ac.uk/spm/software/spm12/). We examined the effective connectivity between well-known nodes of the stopping network that included the IFG, dorsal anterior cingulate cortex (dACC), M1, and STN, building on previous DCM findings (9). We extended the network underlying action initiation and inhibition by adding the putamen, a key node of the indirect corticobasal ganglia pathway (56,57). The addition of the putamen allowed for the assessment of striatal contributions to response inhibition via the indirect pathway (58) by explicitly modeling its connections with cortical regions such as the dACC and IFG as well as subcortical regions such as the STN.

Full details of the DCM analyses are provided in the Supplement. Briefly, the dynamic causal models allowed us to compare 1) fixed connections between the network nodes (DCM.a), 2) modulatory effects of the task (successful Stop > Go contrast) on these connections (DCM.b), 3) inputs that drive network activity (Go stimulus presentation on all trials), and 4) nonlinear modulatory effects of one node on connectivity between other nodes (DCM.d). A set of 33 models guided by a priori hypotheses (2) were generated. Six linear models and 5 nonlinear models were initially defined to test for linear (DCM.a) and nonlinear (DCM.d) effects. All models included connections from dACC and from STN to M1, connections from dACC to putamen, and from putamen to STN. Among the nonlinear models, models A, B, and C included interactive effects by the IFG, and models D and E included interactive effects by the putamen. The set of 11 models was tested for task modulatory effects (successful Stop vs. Go) at the IFG, the dACC, and the putamen, resulting in $3 \times 11 = 33$ models. Bayesian model selection (3) determined the winning models separately in each group in each drug condition. Subject-specific connectivity values from the DCM.a and DCM.b matrices were then extracted for the most likely model for each group-by-drug condition using Bayesian model averaging. The resulting connectivity values from the most likely group model were subsequently subjected to the same subject-level random effects analysis approach as the behavioral performance measures.

**RESULTS**

Demographic and Behavioral Results

Demographic, clinical, and personality measures are reported in Table 1. The participants were well matched in terms of their sex, education level, and pattern of alcohol use as reflected by
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Table 1. Demographic and Psychological Assessment Data for Final Control and CUD Groups

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Control</th>
<th>CUD</th>
<th>Group Statistic (t Value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, Female/Male</td>
<td>1:27</td>
<td>0:18</td>
<td>–</td>
</tr>
<tr>
<td>Age, Years</td>
<td>44.7 (7.4)</td>
<td>38.8 (6.5)</td>
<td>2.80*</td>
</tr>
<tr>
<td>Education, Years</td>
<td>12.8 (2.8)</td>
<td>11.7 (2.2)</td>
<td>1.46</td>
</tr>
<tr>
<td>Verbal Intelligence (NART)</td>
<td>115.3 (6.7)</td>
<td>104.4 (8.8)</td>
<td>4.44*</td>
</tr>
<tr>
<td>Impulsivity (BIS-11 Total)</td>
<td>58.4 (6.8)</td>
<td>74.3 (7.9)</td>
<td>–6.94*</td>
</tr>
<tr>
<td>Depression (BDI-II Total)</td>
<td>3.0 (4.4)</td>
<td>16.9 (8.6)</td>
<td>–6.31*</td>
</tr>
<tr>
<td>Alcohol Use (AUDIT)</td>
<td>3.9 (2.1)</td>
<td>5.6 (6.5)</td>
<td>–1.07</td>
</tr>
<tr>
<td>Compulsive Drug Use (OCDSUS)</td>
<td>–</td>
<td>24.4 (8.6)</td>
<td>–</td>
</tr>
<tr>
<td>Duration of Cocaine Use, Years</td>
<td>–</td>
<td>16.0 (5.6)</td>
<td>–</td>
</tr>
<tr>
<td>Plasma Atomoxetine, ng/mL</td>
<td>293.5 (191.8)</td>
<td>478.4 (159.4)</td>
<td>–3.48*</td>
</tr>
</tbody>
</table>

Data are presented as n or mean (SD). Control versus CUD independent-samples t statistics are shown.

*P < .01.
**P < .001.

the Alcohol Use Disorders Identification Test score. Patients with CUD were younger and had a lower verbal IQ and significantly higher levels of depressed mood on the Beck Depression Inventory-II.

Stopping performance is summarized in Table 2. For SSRT, there was no main effect of atomoxetine compared with placebo (β = 12.6, SE = 9.4, t44 = 1.3, p = .180) or CUD compared with control subjects (β = 5.3, SE = 14.7, t42 = 0.4, p = .717), nor was there a significant interaction (β = -17.3, SE = 12.0, t42 = 1.4, p = .151) while controlling for age (β = 1.9, SE = 0.9, t44 = 2.1, p = .038) and plasma atomoxetine levels (p = .388). For Go RT, there was a significant main effect of drug condition, as atomoxetine speeded responding compared with placebo (β = 28.5, SE = 11.0, t44 = 2.6, p = .009), with no main effect of group (β = -27.2, SE = 19.3, t42 = -1.4, p = .159) or significant interaction (β = -17.5, SE = 14.1, t44 = -1.2, p = .215).

fMRI Results

Whole-brain group mean activations were found in the IFG, dACC, medial frontal gyrus, and parietal and visual areas for the stopping contrast. Conjunction analysis revealed widespread overlap in the above areas activated by both cocaine and control groups in both drug conditions (Figure 1). On placebo, no significant group differences were observed using a whole-brain mask. On atomoxetine, patients with CUD showed significantly greater activation than control subjects in the dACC (peak Montreal Neurological Institute coordinates [-6, 16, 52], zmax = 3.89, p = .002). There were no significant drug effects in either group, nor was there an interaction between group and drug.

In sum, participants with CUD and control participants showed robust and largely consistent activations in the key nodes of the stopping network regardless of drug condition. Thus, associations with drug-dependent performance differences (ΔSSRT) were assessed across the entire sample. At the whole-brain level, no results survived threshold-free cluster enhancement multiple comparison correction. Using the bilateral IFG mask, we identified a robust cluster of right IFG activation that was associated with improved SSRT performance on atomoxetine (Figure 2A, B). This finding was in line with our hypothesis that frontostriatal activation would be associated with atomoxetine-induced stopping improvements.

Analyses for the Go > Stop contrast revealed group mean activations in the left precentral gyrus (M1), contralateral to the right-handed task response, as would be expected (Figure S1). Associations with drug-dependent performance differences (ΔGo RT) showed that within the primary motor cortex (M1) ROI, increased activation in a robust cluster was associated with improved Go RT performance on atomoxetine across all participants (Figure 2C, D).

Predictors of Changes in Performance Induced by Atomoxetine

To determine the factors predicting changes in performance after atomoxetine administration, mixed-effect GLM (aov package) assessed the contribution of placebo performance (baseline), plasma atomoxetine, and change in rIFG activation on SSRT improvements on atomoxetine. The rIFG region was defined based on the voxelwise fMRI results in which ΔSSRT was included as covariate of interest. The full model explained a significant amount of variance in ΔSSRT in all participants (R² = 0.64, F4,41 = 18.33, p = 1.1 × 10⁻⁴).

ΔSSRT = β1 × SSRTplacebo + β2 × [Δ rIFG activation] + β3 × [plasma Atx] + order

Stopping improvement on atomoxetine was predicted by worse baseline stopping performance (β = -0.32, t42 = -3.8, p = 4.6 × 10⁻³), greater activation of rIFG (Figure 2B) (β = -0.19, t42 = -5.1, p = 9.5 × 10⁻⁴), and higher levels of plasma atomoxetine (β = -0.05, t42 = -2.3, p = .025). No significant effects of order were found (p = .268).

A separate exploratory parallel model was fitted to explain atomoxetine-dependent Go RT improvement. M1 was defined...
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based on the voxelwise fMRI results where ΔGo RT was included as a covariate.

\[
\Delta \text{GoRT} = \beta_1 \times \text{GoRT}_{\text{placebo}} + \beta_2 \times [\Delta \text{M1 activation}] + \beta_3 \times [\text{plasma Atx}] + \text{order}
\]

The full model explained a significant amount of variance in ΔGo RT in all participants \((R^2 = 0.48, F_{1,44} = 9.59, p = 1.4 \times 10^{-5})\). Baseline Go RT predicted greater improvement with atomoxetine, with slower responders benefiting more from atomoxetine \((\beta = -0.22, t_{40} = -2.25, p = 0.030)\). Increases in M1 activation were also associated with faster response execution \((\text{Figure 2D})\) \((\beta = -0.34, t_{40} = -3.8, p = 4.4 \times 10^{-4})\). No significant effects of plasma atomoxetine were found \((\beta = -0.01, t_{40} = -4, p = .663)\). No significant effects of order were found \((p = .151)\).

**DCM Results**

Overall, DCM connectivity analyses were consistent between the groups and largely replicated previous findings regarding the effective connectivity underlying stopping, although the putamen was not included in previous models \((9)\). Bayesian model selection \((\text{Figure 3A})\) \((\text{Figure S2})\) indicated the same winning model for both groups on placebo \((\text{nonlinear C})\). In addition, the winning model was the same for both groups on atomoxetine \((\text{linear D})\). On placebo, the winning model included nonlinear modulation of the hyperdirect dACC-STN connection by the IFG \((\text{Figure 3B})\). In contrast, on atomoxetine, this nonlinear modulatory connection was replaced with a fixed connection between the IFG and putamen. Looking at task modulation \((\text{the red arrow in Figure 3B})\), stopping modulated the IFG in control subjects on placebo \((\text{nonlinear C})\). Stopping modulated putamen blood oxygen level-dependent activity in individuals with CUD, regardless of drug condition. This observation is consistent with the expectation that the putamen plays a key role in the stopping network \((8–11)\) and further refines our hypothesis of a frontostriatal network incorporating the IFG and putamen in modulating stopping performance.

The excitatory and inhibitory connectivity patterns as revealed by the Bayesian model averaging in the control subjects on placebo replicated previous findings with an inhibitory connection from STN to M1 and an excitatory connection between dorsomedial PFC and STN as well as excitatory modulation of this connection by the IFG \((9)\). Extending these results, we show that the putamen provides inhibitory inputs to the STN. To investigate further, mixed-effect models assessed the parameters obtained in the Bayesian model averaging, with no results surviving Bonferroni multiple comparison correction \((\text{see the Supplement for further details})\). Overall, our dynamic causal models replicate and extend an effective connectivity model of prefrontal-basal ganglia interactions in both control and CUD groups and show subtle effects of atomoxetine on the interactions between the IFG and the putamen in both groups.

**DISCUSSION**

This study investigated the mechanisms underlying the effects of atomoxetine on inhibitory control in participants with CUD and healthy participants. Atomoxetine led to faster response execution across the two groups. While atomoxetine had no significant effects on stopping latency at group level \([\text{in keeping with some previous studies of the effects of atomoxetine on the SSRT task (28,29)]}\), we found baseline-dependent improvements in stopping on atomoxetine. These activations encompassed key established nodes of the stopping network including rIFG and dmPFC in addition to striatal and parietal regions \((39)\). Additional connectivity analyses pointed to the same winning model of network architecture in both groups on placebo. The architecture, connections, and weights are consistent with those previously found in a cohort of 16 healthy young adults \((9)\). We extended the connectivity model for response inhibition by introducing and showing the contributions of the putamen which again was consistent across the 2 groups. Importantly, we also investigated the effect of atomoxetine on effective connectivity. Specifically, whereas on placebo the rIFG modulated the hyperdirect frontostriatal pathway from the dmPFC to the STN, atomoxetine led to the rIFG modulating the indirect pathway by interacting with the putamen. This change in the network architecture with atomoxetine was found in both groups independently. Taken together, task performance and neural activations point to similar

<table>
<thead>
<tr>
<th>Measure</th>
<th>Control</th>
<th>CUD</th>
<th>Group Effect</th>
<th>Atomoxetine Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ptc</td>
<td>Atx</td>
<td>Ptc</td>
<td>Atx</td>
</tr>
<tr>
<td>SSRT, ms</td>
<td>218 (46)</td>
<td>222 (43)</td>
<td>224 (47)</td>
<td>211 (39)</td>
</tr>
<tr>
<td>Go RT, ms</td>
<td>414 (57)</td>
<td>403 (55b)</td>
<td>449 (63)</td>
<td>420 (62)</td>
</tr>
<tr>
<td>P (Go Response</td>
<td>Stop)</td>
<td>0.486</td>
<td>0.492</td>
<td>0.466</td>
</tr>
<tr>
<td>SSTef</td>
<td>171.4</td>
<td>192.7</td>
<td>159.9</td>
<td>183.1</td>
</tr>
<tr>
<td>P (Go Omisions)</td>
<td>0.009</td>
<td>0.007</td>
<td>0.05</td>
<td>0.05</td>
</tr>
<tr>
<td>P (Go Errors)</td>
<td>0.029</td>
<td>0.032</td>
<td>0.05</td>
<td>0.05</td>
</tr>
<tr>
<td>Go RT (Failed Stop)</td>
<td>371.4</td>
<td>363.9</td>
<td>388.5</td>
<td>366.8</td>
</tr>
</tbody>
</table>

Data are presented as mean or mean (SD). Atx, atomoxetine; CUD, cocaine use disorder; Ptc, placebo; RT, reaction time; SSD, stop-signal delay; SSRT, stop-signal reaction time.

\(^{a}p < .05\)

\(^{a}p < .01\)
mechanisms of action for atomoxetine across participants with CUD and control participants.

**Individual Differences in Atomoxetine Effects**

Importantly, atomoxetine improved stopping performance in a baseline-dependent manner independent from diagnosis, in keeping with findings from a much older cohort of healthy volunteers and patients with Parkinson’s disease (30,31). Thus, poorer inhibitors benefited the most from atomoxetine compared with placebo. Moreover, this was accompanied by increased rIFG activation such that the greatest improvement in stopping latency was associated with greater upregulation of this region. Higher levels of atomoxetine as detected in the blood were also positively correlated with greater brain activation in the rIFG during successful stopping (24). These results are consistent with the inverted-U modulation by norepinephrine of PFC-mediated cognitive control (59–61).

They are reminiscent of findings found not only with atomoxetine but also with methylphenidate, which acts on both the noradrenergic and dopaminergic systems, in accordance with the broader literature of optimal catecholamine levels.
determining optimal performance (62–64). This also points to the likely utility of placebo inhibitory performance (baseline) in predicting subsequent effects of atomoxetine on cognitive control across individuals. Larger studies may be more adequately powered to detect group-level benefits to patients with CUD driven by those who showed increased rIFG activation and improved stopping performance.

Unexpectedly, atomoxetine also improved response execution compared with placebo. These improvements were found in a baseline-dependent manner, independent from diagnosis. Moreover, faster responding with atomoxetine was positively associated with enhanced activation in primary motor cortex, which is typically activated with response execution (8). Atomoxetine is known to improve attention, but acute administration does not typically promote general response speeding (26,65). Faster response latencies with atomoxetine compared with placebo in the stop-signal task were also reported in ADHD boys (28), suggesting that speeding may occur in some situations. The effects on response speeding indicate that atomoxetine facilitated compliance without any concomitant negative effects on stopping, as instructions emphasized to respond as fast as possible and avoid slowing.

Effective Connectivity Underlying Response Inhibition and Execution
Some of the network connectivity findings are relevant to a general understanding of response inhibition, with others being more specific to its basis in CUD. Present results in control subjects on placebo provide an important replication and extension of previous DCM findings (9), particularly as such replications are uncommon. Despite some methodological differences, not only was the same winning architecture found, but also, there was notable agreement as to the effective connectivity between regions. Specifically, dACC projections to M1 and STN were excitatory, while putamen (PUT) to the STN and STN to M1 projections were inhibitory (66). Positive modulation of the hyperdirect pathway by rIFG allows for top-down control over response cancelation. Present

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**Figure 3.** (A) Fixed connections and driving inputs of dynamic causal models comprising the model space. Six linear models and 5 nonlinear models were initially defined. The modulatory effects of stopping at 1) inferior frontal gyrus (IFG), 2) dorsal anterior cingulate cortex (dACC), and 3) putamen (PUT) resulted in $3 \times 11 = 33$ models. The winning models as revealed by Bayesian model selection are highlighted for the cocaine use disorder group (in red) and for the control group (in blue). Black arrows show driving inputs to the dACC and IFG. Modulatory inputs varied in their location. (B) Results of Bayesian model averaging for control and cocaine use disorder groups on placebo and atomoxetine. Average parameter estimates for the control and cocaine groups in placebo and atomoxetine conditions in winning dynamic causal modeling model (nonlinear model D on placebo and linear model C on atomoxetine). Bolded connections were significantly different from 0 (one-sample t tests, uncorrected for multiple comparisons). Autoinhibitory and autoexcitatory connections for IFG, PUT, subthalamic nucleus (STN), and motor cortex (M1) are not shown. Task modulation locations are highlighted using dotted red arrows, and driving inputs to the dACC and IFG are shown in black arrows.
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Conclusions and Limitations

This study points to baseline-dependent improvements in response inhibition with atomoxetine administration along with concomitant rIFG upregulation in a cohort of patients with CUD and in healthy volunteers. Patients with CUD did not demonstrate impaired stopping or reduced PFC activation compared with control subjects, contrary to expectations (1,6,7,12). However, patients with CUD showed significantly more omissions on Go trials, suggesting a degree of hesitancy manifesting from proactive inhibition (73) being used in this group in view of increased impulsivity (6,74). Some of the participants were also dependent on opioids and cannabis in addition to cocaine. The stop-signal task is a sensitive measure of response inhibition in stimulant use disorder, with impaired stopping in both clinical and preclinical studies (75–77). Notably, our participants were active cocaine users, and acute cocaine administration has been shown to improve response inhibition (77,78). Alternatively, lack of case-control differences in response inhibition may be due to the low power of our sample or differences between the behavioral and the fMRI versions of the stop-signal task, as some previous studies of patients with CUD also report no significant differences in behavioral performance (79–82), suggesting that the evidence for SSRT impairments in patients with CUD is inconsistent (76). Therefore, atomoxetine might prove more beneficial in drug abstinence CUD patients in recovery, strengthening response inhibition and preventing relapse. Furthermore, it is possible that participants who chose to undertake a lengthy pharmacological study with multiple visits and perform the task adequately in the scanner exhibit good executive control. In accordance with this notion, alcohol use was not increased in this cohort, although they reported high levels of trait impulsivity and chronic and compulsive drug use. The two groups were also not matched on demographic characteristics, although age was added as a covariate. In principle, atomoxetine may alter the hemodynamic response to neural activity, obscuring or confounding any differences detected by fMRI, although there is some evidence to counteract this (83). The spatial resolution of fMRI methods restricts precision in regions such as the putamen and STN. To mitigate this, we followed previous methods where possible (9) and used established anatomical masks. The present study used a dose of 40 mg of atomoxetine, which is the standard starting therapeutic dose (14). While greater improvements may have been detected with a larger dose, dosage was guided by safety and tolerability considerations.

The results emphasize the nature of response inhibition functioning as existing along a continuum, with considerable overlap between patients with CUD and healthy volunteers in the underlying neural network, determining the overall effects that atomoxetine has on its nodes and connectivity. Future studies may explore whether this is the case for other forms of impulsive behaviors such as premature responding also found to be abnormal in stimulant-dependent individuals (74), given the improvements with atomoxetine found in rodent studies (84). The findings also underscore the importance of individual differences within the patients with CUD in responding to atomoxetine, as those with worse response control are expected to benefit more from atomoxetine. More generally, the association between rIFG upregulation and successful stopping underscoring the effects of atomoxetine in the present sample supports the development of new interventions that can robustly upregulate rIFG activation in chronic cocaine users.

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