Atomoxetine Modulates Right Inferior Frontal Activation During Inhibitory Control: A Pharmacological Functional Magnetic Resonance Imaging Study

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Background: Atomoxetine, a selective noradrenaline reuptake inhibitor (SNRI) licensed for the treatment of attention-deficit/hyperactivity disorder (ADHD), has been shown to improve response inhibition in animals, healthy volunteers, and adult patients. However, the mechanisms by which atomoxetine improves inhibitory control have yet to be determined.

Methods: The effects of atomoxetine (40 mg) were measured with a stop-signal functional magnetic resonance imaging (fMRI) paradigm in 19 healthy volunteers, in a within-subject, double-blind, placebo-controlled design.

Results: Atomoxetine improved inhibitory control and increased activation in the right inferior frontal gyrus when volunteers attempted to inhibit their responses (irrespective of success). Plasma levels of drug correlated significantly with right inferior frontal gyrus activation only during successful inhibition.

Conclusions: These results show that atomoxetine exerts its beneficial effects on inhibitory control via modulation of right inferior frontal function, with implications for understanding and treating inhibitory dysfunction of ADHD and other disorders.

Key Words: Atomoxetine, cognition, fMRI, impulsiveness, impulsivity, inhibition, neuromodulation, noradrenaline, SSRT, stop-signal

Atomoxetine is a highly selective noradrenaline reuptake inhibitor (SNRI) and represents the only nonstimulant pharmacotherapy currently licensed for attention-deficit/hyperactivity disorder (ADHD) in the United States and Europe (1–3). In animals, atomoxetine has been shown to increase free levels of noradrenaline and dopamine in the cortex, without significant effects on subcortical dopamine levels (4). Thus, atomoxetine has a distinct mode of action from the psychostimulant drugs and might proffer clinical advantages over stimulants in some patients, such as reduced likelihood of motor tics and reduced addictive potential (4–6).

It has been proposed that the beneficial effects of atomoxetine (and other licensed medications) on ADHD symptomatology stem from the augmentation of cognitive functions dependent on the integrity of the frontal cortex (1,7–17). Impulsivity is a defining feature of ADHD and has been associated with poor inhibitory control, which can be modeled in the laboratory with stop-signal tasks. Such paradigms require volunteers to suppress pre-potent motor responses that are triggered by a high frequency of go signals, whenever a rare and unpredictable stop-signal occurs (18–20). Stop-signal tasks provide a sensitive estimate of the time taken by the brain to internally suppress motor responses (18–20) and have been shown to be sensitive to motor impulsivity associated with ADHD (21–23). Lesion and functional imaging studies have shown that inhibitory control is dependent, at least in part, on the function and integrity of the inferior frontal gyrus (19,24–29). Drugs with demonstrable efficacy in the treatment of ADHD, including atomoxetine, methylphenidate, and the anti-narcoleptic drug modafinil, have been shown to improve response inhibition on stop-signal paradigms in rats, healthy volunteers, and patients with ADHD (30–36) (for review see 37).

Pharmacological manipulation in combination with fMRI (38) represents a technique for investigating the brain mechanisms by which psychotropic medications are able to exert their beneficial effects on cognition and, by extension, aspects of psychiatric symptomatology (39–41). The individually adjusted fMRI stop-signal task measures the ability to inhibit pre-potent and triggered motor responses when a go signal is shortly followed by a stop signal (18–20). The time interval between go and stop signal is altered according to each subject's performance, making sure that each subject succeeds and fails to 50% of the stop trials. Each subject is therefore working at the edge of his/her own inhibitory capacity, providing homogenous difficulty levels between subjects (19,25). Inhibitory control on this task has been shown to activate the right inferior prefrontal cortex (19,23,25,27).

In this study, we assessed the effects of a single dose (40 mg) of atomoxetine on neural circuitry during inhibitory control with the stop-signal fMRI task (19,23,25). Twenty healthy volunteers

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received atomoxetine and placebo in a within-subject double-blind placebo-controlled design. It was hypothesized that atomoxetine would modulate the frontal cortex (specifically, the right inferior frontal gyrus [RIFG]) during inhibitory control and would shorten stop-signal reaction times behaviorally.

Methods and Materials

Recruitment and Study Design

Twenty healthy male right-handed volunteers were recruited via media advertisements in East Anglia, United Kingdom, and undertook a baseline screening session before enrolment, comprising: a medical interview to screen for inclusion/exclusion criteria and depressive mood (Montgomery-Asberg Depression Rating Scale [MADRS]) (42), completion of the National Adult Reading Test (NART) of verbal IQ (43), and familiarization with the stop-signal task. Exclusion criteria were current or recent (past week) intake of any medication, prior diagnosis and/or treatment of depression or other axis-I psychiatric disorders on the basis of verbal history, history of head injury or neurologic disorder, contra-indications for atomoxetine (e.g., history of renal impairment [http://www.bnf.org]), contra-indications for fMRI (e.g., metallic implants, non-corrected visual impairments), IQ $<$ 90 (43), or MADRS score $>$ 10 (significant dysphoria) (42). Participants were excluded if they had ever been treated for alcohol addiction or currently consumed $>$ 30 U of alcohol/week; if they reported significant prior use of illicit substances (more than thrice lifetime use of any illicit substance); and if they smoked (excepting occasional social use). During the baseline screening session, volunteers were given verbal instructions as to the aims of the stop-signal task, whilst being shown the task on a laptop screen by the experimenter. Volunteers then undertook brief practice on the laptop task, until it was evident to the experimenter that the volunteer was responding appropriately to directional arrows and attempting to inhibit responses after stop cues. No more than 20 practice trials were required for volunteers to learn to perform the task in this study.

The study was approved by the Cambridge Research Ethics Committee (CamREC no. 06/Q108/131) and was exempted from clinical trials status by the Medicine and Healthcare Regulatory Agency (MHRA) of the United Kingdom. All participants provided written informed consent and met the aforementioned criteria. The final sample comprised 19 healthy volunteers, because the scanner data for one subject were excluded due to failure of the stop-signal tracking algorithm (probability of inhibition was over 90%). The remaining sample were of age (mean ± SD) 28.95 ± 7.24 years, range 19–46, and with verbal IQ 115.42 ± 5.57, range 105–122. The MADRS total scores were .79 ± 1.93, of range 0–8.

The effects of atomoxetine on neural substrates of inhibitory control were assessed in a within-subject, double-blind, crossover, randomized, placebo-controlled design, with participants visiting on two occasions at least 5 days apart. Volunteers were requested to abstain from caffeine during the study days. On one occasion they ingested a single capsule containing 40 mg atomoxetine and on the other (randomized order) a capsule of identical appearance containing lactose placebo. The 40-mg dose of atomoxetine was selected to be in the typical clinical range for the treatment of ADHD in adults (http://www.bnf.org), whilst minimizing the risk of nausea/vomiting that increases with escalating doses (32,33).

On each visit, after swallowing an active/placebo capsule with water, volunteers relaxed for 1.5 hours in a quiet waiting room, before undertaking brain scans (detailed in following text). The timing of neuroimaging was based on previous physiological and behavioral findings with the drug (32,44) and pharmacokinetic data, which indicate that peak plasma levels occur approximately 1–2 hours after oral ingestion (45). To measure plasma drug levels (to confirm randomization and for correlational analyses) 8-mL blood samples were collected from subjects immediately before and then after exiting the scanner.

The stop-signal event-related fMRI paradigm has been described and validated in detail elsewhere (19,23,25). The in-scanner task was undertaken in a single block comprising 290 total trials including 60 stop trials, which were presented pseudo-randomly. Volunteers made speeded motor responses with their right-hand, by pressing a left or right button on the button-box, depending on the direction of arrows appearing on-screen. The inter-trial interval (ITI) for go trials was jittered randomly between 1600 and 2000 msec. On 20% of trials, an up-facing arrow appeared a variable delay after the go stimulus, signalling to volunteers that they should try to withhold the motor response that was already triggered by the go signal. The initial go-stop delay was 290 msec, and this was incremented or decremented by 50 msec between trials, depending on the average percentage of inhibition on previous stop trials that was re-calculated after each stop trial. The algorithm hence provided equal numbers of successful and failed trials over the task as a whole (19,23,25). Mean probability of inhibition was 54 ± 1% during active treatment and 52 ± 4% during placebo (no significant difference, paired *t* test, $p > .10$), showing that the algorithm worked well. The actual dynamic range of go-stop delays generated by the task in this study was 50–1200 msec.

Data Acquisition

Volunteers were scanned at the Wolfson Brain Imaging Centre (WBIC), University of Cambridge, Addenbrooke's Site, Cambridge, United Kingdom, with a 3-T Siemens Tim Trio scanner. During presentation of the paradigm, 227 contiguous blood-oxygen-level dependent (BOLD)–sensitive three-dimensional (3D) volume images were acquired with a repetition time of 2 sec (i.e., one scan occurred every 2 sec during the stop-signal task). The first 10 volumes were discarded to avoid T1 equilibrium effects. Each image volume comprised 32 slices of 4-mm thickness, with in-plane resolution of 3 × 3 mm, orientated parallel to the anterior commissure–posterior commissure line. Siemens standard Echo-planar Imaging (EPI) sequence was used, with flip angle 78°, echo time (TE) 30 msec, in a contiguous descending sequence. The field of view was 192 × 192 mm, with matrix 64 × 64, echo spacing .51 msec, and bandwidth 2232 Hz/Px.

Plasma Atomoxetine Level Analysis

Plasma levels of atomoxetine were analyzed in all obtained pre- and post-scan active treatment samples, with a high performance liquid chromatographic method with diode array detection on Agilent 1100 series chromatographic system (Agilent Technologies GmbH, Waldbronn, Germany). Blood samples were unobtainable from one volunteer due to difficult veins, thus a total of 18 × 2 samples were available. Separation of atomoxetine and mianserine (internal standard) was performed on an Agilent Zorbax Eclipse XDB C8 reversed phase column after sample preparation by liquid/liquid extraction. Detection wavelength was 218 nm, and the limit of quantitation was 2.0 μg/L. The calibration function was linear within a range from 2 to 500

μg/L (coefficient of correlation .995). Intra- and inter-day coefficients of variation were below 8.0%.

The chromatography method was validated for atomoxetine, but the selectivity for its two major metabolites (4-hydroxyatomoxetine and N-desmethylatomoxetine) was not characterized, due to lack of availability of reference compounds. However, there were no interfering peaks observed in the chromatography at the retention times of atomoxetine or internal standard in drug-free human plasma control subjects or in samples from study volunteers. Even under steady state conditions, the plasma concentrations of the metabolites relative to atomoxetine range between 1% and 5% in extensive Caucasian metabolizers of cytochrome CYP2D6 (46). Therefore this should not have substantially influenced the measured data, especially in the case of single-dose administration. Because the plasma concentration of the metabolites peaked within a median of 2.5 to 3.5 hours, chromatographic coelution was only expected to occur in the post-scan samples. Overall there were no cases of suspected overlapping peaks, and the peak height of the internal standard within all analyses ranged between 95% and 103% of expected value.

Behavioral Data Analysis

Behavioral data were analyzed with paired *t* tests, to compare performance during the active and placebo conditions. Measures of interest were the mean reaction times for go trials and stop-signal reaction times (estimated by taking the mean go-stop gap across the whole task [i.e., approximately the gap for which inhibition was successful on 50% of stop trials] and subtracting this from the mean reaction time on go trials) (19). Significance was set to $p < .025$ (i.e., $p < .05$ Bonferroni corrected for two comparisons).

Imaging Data Analysis

Imaging data were pre-processed with the general recipe aa batch system (version 2.0) (http://imaging.mrc-cbu.cam.ac.uk/imaging/AutomaticAnalysisManualReference). Images were motion– and slice-time acquisition–corrected, co-registered to structural magnetization prepared rapid gradient echo scans (obtained at first visit), normalized to the Montreal Neurological Institute (MNI) echo-planar template, and smoothed with an 8-mm full width half maximum Gaussian kernel with the Statistical Parametric Mapping (SPM) 5 software package (www.fil.ion.ucl.ac.uk/spm).

Separate fixed effects analyses were carried out on each participant's data with general linear models. Two orthogonal regressors were generated by convolving timing parameters representing the onset and duration of (1) successful and (2) failed inhibition trials, with a function representing the canonical hemodynamic response. Six additional regressors were included in the model to account for subject movement (that is, translations and rotations around orthogonal axes). Go trials occurred too frequently to estimate orthogonally from the constant term of the linear model and so were not included in the model. Our two regressors of interest therefore estimated the variance in the BOLD signal that was additional to routine response to the go signal (i.e., the go trials formed an implicit baseline). Overall brain activation maps for all subjects (irrespective of drug condition) for successful and failed inhibition were generated in SPM (analysis of variance [ANOVA], within-subject factor of regressor type; $p < .001$ uncorrected).

The neural effects of drug treatment and regressor (contrast) type (successful and failed inhibition) during the stop-signal task were analyzed with permutation-based methods with the Cambridge Brain Activation software (CAMBA v2.1.0, http://www-bmu.psychiatry.cam.ac.uk/software/) as described in detail elsewhere (47). Response estimations were entered into a repeated-measures analysis of variance model with drug condition and contrast type as within-subject factors. We used cluster-level statistical analysis that has previously been shown to give good type I error control (39,47–50). A voxel-level threshold was initially set at $p < .05$ to maximize sensitivity and to avoid type II errors. Voxels representing statistics above this threshold were aggregated into contiguous 3D clusters, and cluster-statistics were calculated for each by summing the supra-threshold values they contained. The null distribution for cluster-statistics was sampled by repeating these steps on maps of main effect, and interactions were calculated after appropriate permutation of subjects amongst treatments. Type I errors were controlled by setting the p values for clusters such that, under the null-hypothesis, the number of expected clusters was < 1.

Relationships between plasma atomoxetine levels (mean of pre- and post-scan samples) and brain activation during the active treatment condition were investigated in a separate CAMBA analysis. On the basis of the aforementioned analysis, a mask was generated of the neural regions that were significantly modulated by atomoxetine (main effect of atomoxetine). A correlational analysis was then conducted with CAMBA, with regressor type and plasma atomoxetine levels as within-subject factors, restricting the processing to within the mask to maximize sensitivity. Again, cluster-level thresholds were adjusted such that the expected number of false positive clusters for each whole brain map of interest was < 1.

Results

Atomoxetine was generally very well tolerated at the 40-mg dose, with no participants reporting adverse events during the study. Plasma levels of atomoxetine (average of pre- and post-scan values) were 224.00 ± 105.55 ng/mL, range 89.80–529.65, during active treatment and confirmed correct randomization. There were no significant differences between the active and placebo conditions in mean reaction times for go trials (atomoxetine: mean 482.92 ± 136.47 msec, placebo: 466.26 ± 106.10 msec, $p > .10$). Atomoxetine was associated with significantly shorter stop-signal reaction times than under placebo (atomoxetine: 249.03 ± 78.24 msec, placebo: 278.26 ± 79.79 msec, $p < .025$ [i.e., $p < .05$ Bonferroni corrected]).

Overall, both successful and failed inhibition were associated with activation in distributed neural networks, including the RIFG (Figure 1 in Supplement 1; see Tables 1 and 2 in Supplement 1 for peak activation co-ordinates). Repeated measures ANOVA analysis in CAMBA demonstrated a significant main effect of atomoxetine on brain activation after inhibition signals in a single right-hemispheric cluster (1848 voxels). This cluster exhibited peak coordinates in the inferior frontal gyrus [Brodmann areas [BAs] 44, 45; x = 48, y = 4, z = 12, MNI space] and reached caudally into superior temporal cortex (BA 22) and ventrally into the insula. There was significantly greater activation in this cluster during atomoxetine treatment compared with placebo (Figure 1). There were no significant brain regions in which there was a significant interaction between drug treatment (active/placebo) and contrast type (successful/failed inhibition). There was a significant effect of contrast type (successful/failed inhibition) due to significantly greater activation when subjects failed to suppress responses (Figure 2 in Supplement 1); this

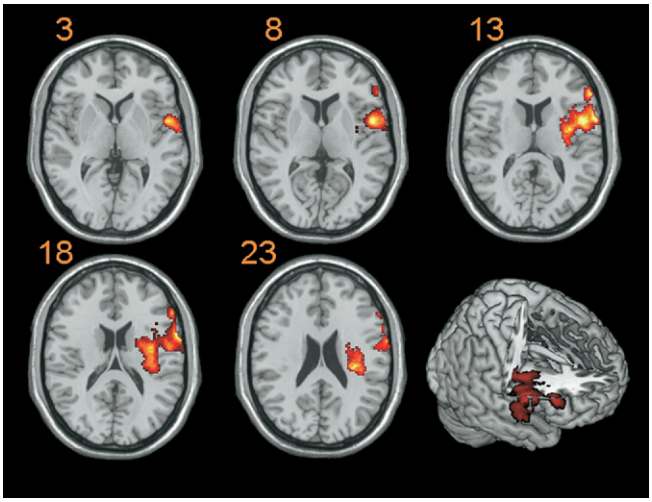

Figure 1. Main effect of atomoxetine. Atomoxetine increased brain activation during inhibitory control in a cluster (yellow/red in online version) including the right inferior frontal gyrus and temporal regions. Data are presented from the CAMBA analysis (< 1 false positive clusters/map; analysis of variance, within-subject factors of drug condition [active/placebo] and contrast type [successful/failed]). Numbers refer to *z* coordinates of the Montreal Neurological Institute standard anatomical space.

occurred predominantly in regions sub-serving motor generation, such as the bilateral supplemental motor cortices, bilateral cerebellum, and bilateral putamen.

Subsequent analysis indicated a significant interaction between atomoxetine plasma levels and regressor type (successful and failed inhibition) in the activation cluster of RIFG (BA 44) reaching into superior temporal cortex (BA 22) (peak coordinate [x = 56, y = 12, z = 6], 80 voxels). As can be seen in Figure 2, this was due to a significant positive correlation between plasma levels of atomoxetine and BOLD responses in this cluster during successful inhibition (Pearson's r = .603, $p = .008$) but not during failed inhibition (Pearson's r = .140, $p = .579$).

Discussion

This healthy volunteer pharmacological fMRI study demonstrated that atomoxetine improved the speed of inhibitory control and increased BOLD responses in an activation cluster at the inferior prefrontal/superior temporal junction, when volunteers attempted to inhibit their motor responses, whether they succeeded or not. The magnitude of BOLD responses correlated significantly with plasma levels of atomoxetine during successful inhibition only, such that higher levels of drug were associated with greater brain activation.

Our finding of an improvement in the main indicator of inhibitory performance, the stop-signal reaction time, is consistent with behavioral studies showing that single-dose administration of atomoxetine improved inhibitory control in healthy volunteers (32), adults with ADHD (33), and rats (36,51). We found that, in line with previous imaging studies on the stop-signal task, inhibitory control was mediated by a fronto-striatal neural network, including inferior prefrontal cortex, anterior cingulate, and the caudate (19,23,25). However, atomoxetine specifically affected activation of the right inferior frontal and adjacent superior temporal gyri, reaching deep into the insula. The right inferior fronto-temporal junction is the cortical part of a fronto-striatal neural network of top-down inhibitory control (19,23–25,28). Response inhibition tasks typically activate several brain regions, some of them thought to mediate other basic functions necessary for inhibitory performance, such as anterior cingulate for response conflict resolution and parietal regions for visual-spatial attention to stop signals (19). The right inferior prefrontal cortex is the key region that has been associated with the main indicator of inhibitory capacity in this task (stop-signal reaction time) in imaging, lesion, and transcranial stimulation studies (20,23,28,29,52). Our finding of increased activation in this region after atomoxetine administration together with improved inhibitory speed is consistent with the hypothesis that atomoxetine's beneficial effects on inhibitory performance are due to catecholaminergic enhancement of key fronto-temporal cortical areas. There was a significant effect of atomoxetine on brain activation across both successful and failed inhibition trials. Thus, the IFG might be necessary but not sufficient for success on stop trials; alternatively, there might be a critical threshold of right inferior frontal activation necessary to facilitate inhibition that is modulated by noradrenaline.

The effects of atomoxetine during fMRI have received scant investigation to date. Friedman *et al.* (53) explored the effects of chronic atomoxetine treatment (40 mg/day for 4-weeks, then 80 mg/day for 4 weeks) versus placebo in a parallel-group, randomized non-blinded study of eight patients with schizophrenia, who were already treated with antipsychotic drugs. Atomoxetine (administered to five participants) was associated with increased

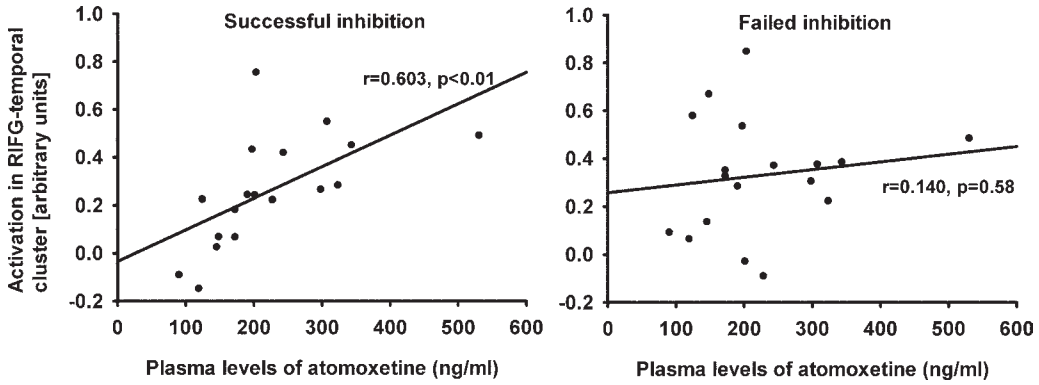

Figure 2. Scatter plots showing plasma atomoxetine levels against mean RIFG activation during successful and failed inhibition. The CAMBA analysis indicated a significant interaction between plasma levels of drug and regressor (successful and failed inhibition) in the RIFG–temporal cluster. Post hoc correlational analysis showed that this was attributable to a significant positive correlation between plasma drug levels and blood-oxygen-level dependent responses during successful (left) but not failed (right) inhibition. RIFG, right inferior frontal gyrus.

activation after treatment in the left dorsolateral prefrontal and posterior cingulate cortices under increasing working memory load conditions versus placebo (administered to three participants). The other study, which used anaesthetized rats, found that acute atomoxetine treatment (2 mg/kg) was associated with increased BOLD responses in the right ventral orbitofrontal cortex and widespread negative responses elsewhere (n = 10 atomoxetine, n = 9 placebo) (54).

This is the first study to explore the effects of atomoxetine on brain activation during inhibitory control. Strengths of this study include the use of a double-blind, placebo-controlled within-subject design and permutational analysis of fMRI data to maximize sensitivity to detect drug effects. Nonetheless, several limitations should be considered. We enrolled healthy male right-handed volunteers to maximize sample homogeneity, which might limit the extent to which these findings can be generalized to other populations. This study examined the effects of a single dose of 40 mg atomoxetine and did not directly evaluate dose-dependent effects, although we did assess the relationship between plasma drug levels and the magnitude of BOLD signal change. In the correctional analysis restricted to those brain regions affected by atomoxetine overall, there was a significant correlation between plasma levels of atomoxetine and RIFG activation during successful inhibition but not failed inhibition. We did not identify a significant drug × contrast type (successful vs. failed inhibition) interaction in the more conservative whole brain analysis. Although higher doses of atomoxetine might have increased power to detect whole-brain interaction effects, we used a 40-mg dose in this study to minimize the chance of adverse events (notably emesis, with potential safety implications in-scanner). Lastly, the beneficial clinical effects of atomoxetine (significant reductions in symptom severity on clinical rating scales) are thought to require several weeks to manifest in the treatment of ADHD. Single-dose healthy volunteer studies, such as the current one, provide important insights into the early beneficial effects of atomoxetine on brain function in the absence of potential imaging confounds arising from long-term treatment (e.g., reductions in depressive mood, given atomoxetine's anti-depressive effects) (17). However, follow-up studies are required in ADHD patients to evaluate the effects of short and long-term treatment on neural substrates of inhibitory control and other cognitive domains.

In conclusion, the findings of this study have important implications for inhibitory pathologies, notably ADHD (55–60). The right inferior prefrontal cortex is a key area of dysfunction in ADHD during inhibitory performance (21,23), and the current findings therefore provide important neurofunctional evidence relating to the mechanisms of action of atomoxetine and support the prescription of this drug in ADHD. Impaired inhibitory control has been reported in other manifestations of impulsivity, including trichotillomania (an impulse control disorder on DSM characterized by repetitive hair pulling) (61) and substance misuse (e.g., cannabis, cocaine, amphetamine) (62). On the basis of the current study it would be valuable to investigate the therapeutic potential of pharmacotherapies with noradrenergic properties in such patient groups afflicted by inhibitory problems and/or RIFG dysfunction.

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Supplementary material cited in this article is available online.

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