ARCHIVAL REPORT

# Methylphenidate But Not Atomoxetine or Citalopram Modulates Inhibitory Control and Response Time Variability

L. Sanjay Nandam, Robert Hester, Joe Wagner, Tarrant D.R. Cummins, Kelly Garner, Angela J. Dean, Bung Nyun Kim, Pradeep J. Nathan, Jason B. Mattingley, and Mark A. Bellgrove

**Background:** Response inhibition is a prototypical executive function of considerable clinical relevance to psychiatry. Nevertheless, our understanding of its pharmacological modulation remains incomplete.

**Methods:** We used a randomized, double-blind, placebo-controlled, crossover design to examine the effect of an acute dose of methylphenidate (MPH) (30 mg), atomoxetine (ATM) (60 mg), citalopram (CIT) (30 mg), and placebo (PLAC) (dextrose) on the stop signal inhibition task in 24 healthy, right-handed men 18–35 years of age. Participants performed the task under each of the four drug conditions across four consecutive sessions.

**Results:** Methylphenidate led to a reduction in both response time variability and stop-signal reaction time (SSRT), indicating enhanced response inhibition compared with all other drug conditions. Crucially, the enhancement of response inhibition by MPH occurred without concomitant changes in overall response speed, arguing against a simple enhancement of processing speed. We found no significant differences between ATM and PLAC, CIT and PLAC, or ATM and CIT for either response time variability or SSRT.

**Conclusions:** An acute dose of MPH but not ATM or CIT was able to improve SSRT and reduce response time variability in nonclinical participants. Improvements in response inhibition and response variability might underlie the reported clinical benefits of MPH in disorders such as attention-deficit/hyperactivity disorder.

**Key Words:** Atomoxetine, citalopram, methylphenidate, response inhibition, stop signal, variability

The processes that inhibit unwanted behavior and maintain consistent task performance are impaired in several psychiatric conditions, including schizophrenia (1), obsessive compulsive disorder (2), and attention-deficit/hyperactivity disorder (ADHD) (3). Significant controversy exists regarding their precise neurochemical basis, despite the relevance of response inhibition and variability to psychiatry and their potential for pharmacological treatment. Here we used a within-subjects design to examine the influence of an acute dose of methylphenidate (MPH), atomoxetine (ATM), citalopram (CIT), or PLAC on measures of inhibitory control and response variability.

Response inhibition has been studied in cognitive neuroscience with paradigms such as the stop-signal task. This task requires the countermanding or cancelation of a prepotent "go" response upon presentation of an infrequent "stop" signal. Stop-signal inhibition can be viewed as a race between two competing "go" and "stop" processes. By introducing a delay between the presentation of the go and any subsequent stop signal, one can bias the outcome of the race. When the theoretical assumptions underlying this race model are respected, an index of the speed of inhibition can be calculated, the stop-signal reaction time (SSRT) (4).

Reaction time tasks, including the stop-signal task, also allow measurement of behavioral variability, measured as the SD of reaction times to the go signal. Increased variability is thought to arise from both moment-to-moment fluctuations in attentional control and from more gradual drifts in performance that might result from diminished arousal (5,6).

Here we sought to determine the influence of three agents that are used in the management of ADHD (MPH, ATM) and obsessive compulsive disorder (CIT) on behavioral measures of response inhibition. A randomized, double-blind, placebo-controlled, crossover design was used to study the effects of an acute dose of MPH (30 mg), ATM (60 mg), CIT (30 mg), and PLAC (dextrose) on SSRT and behavioral variability in healthy subjects.

## Methods and Materials

### Participants

Twenty-four healthy right-handed, nonclinical Caucasian male participants, 18–35 years of age, were recruited. Additional details regarding the recruitment and screening procedures can be found in Supplement 1.

### Drug Administration

Participants were tested on the same day and time across 4 consecutive weeks in a double-blind manner. On each occasion a single blue gelatine capsule containing MPH 30 mg, ATM 60 mg, CIT 30 mg, or PLAC (dextrose) was ingested with water. Participants performed the stop-signal reaction time task from min +150 to +180 after drug administration. There was no significant drug × time interactions for either blood pressure or subjective side effect ratings (Supplement 1).

### Stop-Signal Paradigm

The SSRT was derived as the mean reaction time to go-stimuli (mean reaction time [MRT]) minus the stop signal delay for the 50%

From the University of Queensland (LSN, JW, TDRC, KG, AJD, BNK, JBM, MAB), Queensland Brain Institute and School of Psychology; Prince Charles Hospital (LSN), Brisbane; University of Melbourne (RH), Department of Psychology, Parkville; Monash University (PJN), School of Psychology, Psychiatry and Psychological Medicine, Clayton, Australia; Seoul National University (BNK), Division of Child and Adolescent Psychiatry, Department of Neuropsychiatry, College of Medicine, Seoul, Korea; and The University of Cambridge (PJN), Department of Psychiatry, Cambridge, United Kingdom.

Address correspondence to Mark Bellgrove, Ph.D., Queensland Brain Institute, The University of Queensland, 4072 Brisbane, Australia. E-mail: m.bellgrove@uq.edu.au.

Received Jun 30, 2010; revised Nov 8, 2010; accepted Nov 8, 2010.

0006-3223/$36.00
doi:10.1016/j.biopsych.2010.11.014

**Table 1.** Mean SSRT and MRT and Stop-Signal Accuracy as a Function of Drug Condition

| | MPH | | ATM | | CIT | | PLAC | |
|---|---|---|---|---|---|---|---|---|
| | M | SD | M | SD | M | SD | M | SD |
| SSRT (msec) | 252 | 30 | 264 | 26 | 272 | 34 | 275 | 39 |
| MRT (msec) | 392 | 56 | 399 | 54 | 401 | 63 | 400 | 51 |
| % stop | 48 | 3 | 48 | 3 | 46 | 7 | 45 | 9 |
| SD of MRT | 64 | 13.6 | 74 | 14.8 | 78 | 17.6 | 79 | 23.8 |
| ICV | .16 | .03 | .18 | .03 | .19 | .04 | .19 | .04 |

Methylphenidate 30 mg (MPH); atomoxetine 60 mg (ATM); citalopram 30 mg (CIT); placebo (PLAC). SSRT, stop-signal reaction time (msec); MRT, mean correct "go" reaction time (msec); % stop, percentage of successful inhibitions on stop trials; ICV, intra-individual coefficient of variation (SD of MRT/MRT).

inhibition threshold (SSRT = MRT − stop-signal delay) (4). The intraindividual coefficient of variation [ICV: SD Go RT/MRT] was also calculated, which provides a measure of response variability, adjusted for the influence of response speed (5).

## Results

There was a significant effect of drug condition on SSRT [$F(3,66) = 5.83$, $p < .01$]. Methylphenidate led to a reduction in SSRTs, indicating enhanced response inhibition compared with all other drug conditions. Post hoc least significant difference tests revealed significant differences between MPH and PLAC ($p < .001$; $d = .65$) and MPH and CIT ($p < .01$; $d = .62$) and between MPH and ATM ($p = .05$, $d = .42$) (Table 1). There were no significant differences between ATM and PLAC ($p = .1$; $d = .32$) or between ATM and CIT ($p = .2$; $d = .26$).

Crucially, the selective enhancement of response inhibition by MPH occurred without concomitant changes in response speed, because there was no main effect of drug condition on MRT [$F(3,66) = .54$, $p = .65$]. This suggests that MPH was able to specifically improve action cancelation without simply increasing overall motor speed. A conservative reanalysis of the SSRT data with MRT as a covariate confirmed the significant effect of drug condition on SSRT [$p = .002$]. There was no main effect of drug condition on stop-signal accuracy [$F(3,66) = 1.35$, $p = .27$] (Table 1).

Significant main effects of drug condition were found for the intraindividual coefficient of variation [$F(3,66) = 5.76$, $p = .001$]. Methylphenidate led to a reduction in response time variability that was significantly different from all other conditions (all $p$ values $<$ .05, corrected) (Table 1). No other drug comparisons of variability were significant.

Because MPH enhanced both SSRT and response time variability, we sought to understand the relationship between these variables with correlation. No significant correlations were found between SSRT and response time variability in any of the drug conditions, suggesting that these processes are largely independent (MPH: $r = .08, p > .05$; ATM: $r = .02, p > .05$; CIT: $r = .27, p > .05$; PLAC: $r = .32, p > .05$).

## Discussion

This study demonstrated that clinically relevant doses of MPH were able to reduce SSRT and behavioral variability without concomitant changes in response speed or accuracy of responding. The inability of CIT to facilitate action cancelation is consistent with other human studies (7). However, the failure to confirm a beneficial effect of ATM compared with PLAC on SSRT contrasts with other work in humans and rodents (7–9). Our results challenge the view that stimulant medications act to solely speed motoric processes without specific effects on action cancelation (10).

Methylphenidate is a widely used stimulant medication for the treatment of ADHD, with clinical response rates of approximately 70%. Although MPH is often viewed as a dopaminergic agent, its pharmacology suggests effects on both dopamine (DA) and noradrenaline (NA). Within the striatum, MPH acts to inhibit the reuptake of DA by blockade of the dopamine transporter (DAT) (11). The increase in DA occasioned by DAT blockade likely modulates activity within the circuits of the basal ganglia, particularly via D2 and D1 receptors within the indirect and direct pathways, respectively. However, MPH increases both DA and NA at doses that enhance prefrontally dependent executive functions such as working memory (12). This effect is likely mediated via blockade of the noradrenaline transporter (NET), because DAT is sparse in prefrontal cortex (13). At the receptor level, the cognitive enhancing effects of MPH in rat prefrontal cortex seem to be mediated by its effects on α-2 adrenoreceptors and D1 receptors (14).

Pharmacological work in rodents has shown that, although ATM selectively inhibits NET in prefrontal cortex, there is a resultant threefold increase in both NA and DA levels, without any concomitant change in serotonin (13). However, within the striatum NET is sparse, and ATM has only a limited ability to modulate catecholamine levels. Although ATM and MPH have similar effects on both DA and NA in prefrontal cortex, a key difference is conferred by the ability of MPH to selectively increase DA within the striatum (13).

Current models of behavioral inhibition emphasize the interaction of prefrontal and basal ganglia circuits (15,16). Specifically, prefrontal circuits might provide a top-down, stimulus-driven input to the basal ganglia, signaling the need for enhanced behavioral control. Both MPH and ATM are well-placed to exert a neuromodulatory influence over the prefrontal cortex, and indeed functional magnetic resonance imaging studies of response inhibition demonstrate effects of both drugs on prefrontal activity (9,17). Dopamine, however, might play an important neuromodulatory role within the basal ganglia, acting to transform the top-down inputs into a focused, context-dependent signal that is able to suppress or facilitate behavior via the appropriate balance of activity within the indirect or direct pathways, respectively (18). Future studies should attempt to modulate SSRT with selective D1/D2 agonists or antagonists as well as with a broader range of cognitive tasks to accurately reflect the complexity and breadth of the construct of inhibition.

Recent evidence from ADHD suggests that response time variability and inhibition load onto distinct, familial cognitive factors (19), with the former potentially linked to diminished arousal and drifting attention (6) and the latter linked to executive processes. Interestingly, although both stop-signal reaction time and response time variability were robustly improved by MPH in the current study, these measures were largely uncorrelated in each of the

drug conditions, providing further evidence that they are potentially dissociable.

Chamberlain *et al.* (9) reported that an acute dose of ATM 40 mg reduced SSRT compared with PLAC. A comparison of the effect size associated with the ATM versus PLAC difference in Chamberlain *et al.* and the current study revealed Cohen's *d* effect sizes of .37 and .32, respectively. Because these effect sizes are modest, non-replications are likely. It is also notable that the PLAC condition of the current study yielded comparable results (Chamberlain: SSRT: 278 msec; Nandam *et al.*: SSRT: 275 msec), suggesting that baseline differences between the studies are unlikely to account for this non-replication. Participant factors such as DNA variation in the NET genes (20) might also account for the weaker effect of ATM in the present study.

Although we found strong evidence that MPH specifically improved response inhibition and response time variability, we found no significant change compared with PLAC for ATM. Our results provide foundational data that might help to explain why acute doses of MPH have therapeutic value in disorders such as ADHD.

*This work was supported by grants from the Australian Research Council (DP0770337) to MAB and from the Australian National Health and Medical Research Council to MAB, RLH, PJN, and JBM. We would like to thank Dr. Chris Chambers for comments on the manuscript. We would also like to thank the Wesley Hospital Pharmacy for dispensing the drugs associated with this project.*

*Both LSN and MAB have received reimbursement from Lilly Pharmaceuticals for conference travel expenses and for speaking at conferences. The authors MAB and B-NK have received speaker's fees from Jannsen Cilag. The author LSN has received speaker's fees from Bristol-Myers Squibb, Boehringer, and Janssesn Cilag. The authors RH, JW, TDRC, KG, AJD, PJN, and JBM report no biomedical financial interests or potential conflicts of interest.*

*Supplementary material cited in this article is available online.*

1. Bellgrove MA, Chambers CD, Vance A, Hall N, Karamitsios M, Bradshaw JL (2006): Lateralized deficit of response inhibition in early-onset schizophrenia. *Psychol Med* 36:495–505.
2. Menzies L, Achard S, Chamberlain SR, Fineberg N, Chen CH, del Campo N, *et al.* (2007): Neurocognitive endophenotypes of obsessive-compulsive disorder. *Brain* 130:3223–3236.
3. Lijffijt M, Kenemans JL, Verbaten MN, van Engeland H (2005): A meta-analytic review of stopping performance in attention-deficit/hyperactivity disorder: Deficient inhibitory motor control? *J Abnorm Psychol* 114:216–222.
4. Logan GD, Schachar RJ, Tannock R (1997): Impulsivity and inhibitory control. *Psychol Sci* 8:60–64.
5. Bellgrove MA, Hester R, Garavan H (2004): The functional neuroanatomical correlates of response variability: Evidence from a response inhibition task. *Neuropsychologia* 42:1910–1916.
6. Johnson KA, Kelly SP, Bellgrove MA, Barry E, Cox M, Gill M, Robertson IH (2007): Response variability in attention deficit hyperactivity disorder: Evidence for neuropsychological heterogeneity. *Neuropsychologia* 45: 630–638.
7. Chamberlain SR, Muller U, Blackwell AD, Clark L, Robbins TW, Sahakian BJ (2006): Neurochemical modulation of response inhibition and probabilistic learning in humans. *Science* 311:861–863.
8. Bari A, Eagle DM, Mar AC, Robinson ES, Robbins TW (2009): Dissociable effects of noradrenaline, dopamine, and serotonin uptake blockade on stop task performance in rats. *Psychopharmacology (Berl)* 205:273–283.
9. Chamberlain SR, Hampshire A, Muller U, Rubia K, Campo ND, Craig K, *et al.* (2008): Atomoxetine modulates right inferior frontal activation during inhibitory control: A pharmacological functional magnetic resonance imaging study. *Biol Psychiatry* 65:550–555.
10. Eagle DM, Bari A, Robbins TW (2008): The neuropsychopharmacology of action inhibition: Cross-species translation of the stop-signal and go/no-go tasks. *Psychopharmacology (Berl)* 199:439–456.
11. Volkow ND, Wang G, Fowler JS, Logan J, Gerasimov M, Maynard L, *et al.* (2001): Therapeutic doses of oral methylphenidate significantly increase extracellular dopamine in the human brain. *J Neurosci* 21:RC121.
12. Berridge CW, Devilbiss DM, Andrzejewski ME, Arnsten AF, Kelley AE, Schmeichel B, *et al.* (2006): Methylphenidate preferentially increases catecholamine neurotransmission within the prefrontal cortex at low doses that enhance cognitive function. *Biol Psychiatry* 60:1111–1120.
13. Bymaster FP, Katner JS, Nelson DL, Hemrick-Luecke SK, Threlkeld PG, Heiligenstein JH, *et al.* (2002): Atomoxetine increases extracellular levels of norepinephrine and dopamine in prefrontal cortex of rat: A potential mechanism for efficacy in attention deficit/hyperactivity disorder. *Neuropsychopharmacology* 27:699–711.
14. Arnsten AF, Dudley AG (2005): Methylphenidate improves prefrontal cortical cognitive function through alpha2 adrenoceptor and dopamine D1 receptor actions: Relevance to therapeutic effects in attention deficit hyperactivity disorder. *Behav Brain Funct* 1:2.
15. Aron AR, Poldrack RA (2006): Cortical and subcortical contributions to stop signal response inhibition: Role of the subthalamic nucleus. *J Neurosci* 26:2424–2433.
16. Chambers CD, Garavan H, Bellgrove MA (2009): Insights into the neural basis of response inhibition from cognitive and clinical neuroscience. *Neurosci Biobehav Rev* 33:631–646.
17. Vaidya CJ, Bunge SA, Dudukovic NM, Zalecki CA, Elliott GR, Gabrieli JD (2005): Altered neural substrates of cognitive control in childhood ADHD: Evidence from functional magnetic resonance imaging. *Am J Psychiatry* 162:1605–1613.
18. Mink JW (1996): The basal ganglia: Focused selection and inhibition of competing motor programs. *Prog Neurobiol* 50:381–425.
19. Kuntsi J, Wood AC, Rijsdijk F, Johnson KA, Andreou P, Albrecht B, *et al.* (2010): Separation of cognitive impairments in attention-deficit/hyperactivity disorder into 2 familial factors. *Arch Gen Psychiatry* 67:1159–1166.
20. Ramoz N, Boni C, Downing AM, Close SL, Peters SL, Prokop AM, *et al.* (2009): A haplotype of the norepinephrine transporter (Net) gene Slc6a2 is associated with clinical response to atomoxetine in attention-deficit hyperactivity disorder (ADHD). *Neuropsychopharmacology* 34: 2135–2142.