Atomoxetine Increases Fronto-Parietal Functional MRI Activation in Attention-Deficit/Hyperactivity Disorder: A Pilot Study

George Bush[a,b,c,d], **Jennifer Holmes**[b], **Lisa M. Shin**[b,e], **Craig Surman**[a,d], **Nikos Makris**[d,f], **Eric Mick**[a,d], **Larry J. Seidman**[a,d,g], and **Joseph Biederman**[*,a,d]

[a]Harvard Medical School, Department of Psychiatry, Boston, MA 02114, USA

[b]Psychiatric Neuroscience Division, Massachusetts General Hospital Department of Psychiatry, Boston, MA 02114, USA

[c]MGH/MIT/HMS Athinoula A. Martinos Center for Functional and Structural Biomedical Imaging (Massachusetts Institute of Technology, Harvard Medical School and Massachusetts General Hospital), Charlestown, MA 02129, USA

[d]Massachusetts General Hospital, Clinical and Research Program in Pediatric Psychopharmacology, Boston, MA 02114, USA

[e]Department of Psychology, Tufts University, Medford, MA, USA

[f]Harvard Medical School Departments of Neurology and Radiology Services, Center for Morphometric Analysis, Massachusetts General Hospital, Boston, MA 02129, USA

[g]Harvard Medical School, Department of Psychiatry, Massachusetts Mental Health Center Public Psychiatry Division, Beth Israel Deaconess Medical Center, Boston, MA 02115, USA

Abstract

We hypothesized that atomoxetine (ATMX) would produce similar brain effects in attention-deficit/hyperactivity disorder (ADHD) as those of methylphenidate (MPH). Eleven ADHD adults performed the Multi-Source Interference Task (MSIT) during fMRI at baseline and after 6 weeks of ATMX treatment. ATMX was associated with increased fMRI activation of dorsolateral prefrontal cortex, parietal cortex and cerebellum; but not dorsal anterior midcingulate cortex (daMCC). These results suggest that ATMX and MPH have similar but non-identical brain effects.

Keywords

Neuroimaging; Psychopharmacology; Neurobiology

1. Introduction

Attention Deficit Hyperactivity Disorder (ADHD) is among the most common neurobehavioral disorders in children and adolescents, and frequently persists into adulthood. Atomoxetine (ATMX), a non-stimulant norepinephrine transporter (NET) specific reuptake inhibitor, is a safe and effective treatment for ADHD (Adler et al., 2005). While a few studies have provided insights (Arnsten, 2006; Seneca et al., 2006; Logan et al., 2007; Pliszka, 2007; Chamberlain et al., 2009; Takano et al., 2009), the neural mechanisms by which ATMX exerts therapeutic effects remain unresolved.

Convergent data implicate dysfunction of many brain regions in ADHD pathophysiology, including the dorsal anterior midcingulate (daMCC), dorsolateral prefrontal (DLPFC), and parietal cortices (together, the cingulo-frontal-parietal [CFP] cognitive-attention network), along with striatum and cerebellum (Paloyelis et al., 2007; Bush, 2009; Bush, 2011). Thus, it was expected that ATMX treatment would affect the CFP network. We used the Multi-Source Interference Task (MSIT), a cognitive fMRI paradigm with demonstrated ability to activate daMCC and the CFP network (Bush and Shin, 2006). Since clinical response may not maximally differentiate from placebo until 6 weeks with ATMX (Montoya et al., 2009) or MPH (Spencer et al., 2005; Biederman et al., 2006), we scanned subjects at baseline and after 6 weeks treatment.

Specifically, we hypothesized ATMX would increase fMRI activation in CFP regions that subserve attention and cognition. We also predicted that compared to our previously published sample of 21 adults with ADHD-childhood onset (ADHD-CO) (Bush et al., 2008) ATMX fMRI responses would be similar to those produced by MPH and differentiable from placebo. To facilitate cross-study comparability and explore the degree of neurobiological overlap of ADHD-NOS with ADHD-CO, we compared baseline MSIT fMRI data of the 11 adults with ADHD-NOS to that from the previously published sample.

2. Methods

Methods were identical to those used in the previously published sample (Bush et al., 2008), except as indicated here, and are included in the Supplemental Material. Written informed consent was obtained per Massachusetts General Hospital Subcommittee on Human Subjects guidelines. Eleven unmedicated adults (6M/5F) with ADHD, Not Otherwise Specified (ADHD-NOS) completed the study. The previously published MPH ($N = 11$) and placebo ($N = 10$) samples (Bush et al., 2008) were diagnosed with ADHD-childhood onset (ADHD-CO). Inclusion and exclusion criteria for all subjects ($N = 32$) were otherwise identical. MSIT procedures (Bush and Shin, 2006; Bush et al., 2008) are summarized in Supplemental Figure 1. The ATMX group displayed the expected performance effects and did not differ in severity or demographically from the prior published sample (see Supplemental, Table 1).

Functional MRI analyses were as follows. The primary contrast examined which brain regions displayed an effect of 6 weeks of ATMX. A multi-step random effects repeated measures ANOVA GLM analysis was used. First, a mask representing all voxels $MSIT_{Interference} > MSIT_{Control}$ ($P < .05$ uncorrected) for all 32 subjects (11 ATMX, 11 MPH, 10 placebo) during Scan 2 was applied to restrict analysis to brain areas specifically involved in cognition. Within masked voxels for the ATMX group, a random effects repeated measures ANOVA GLM identified regions with $MSIT_{Interference}$ fMRI activation higher at 6 weeks of ATMX treatment than at baseline. A stringent cluster constraint requiring 7 contiguous $P < .05$ voxels (Forman et al., 1995) produced a regional false

positive probability of $P < 1 \times 10^{-4}$ corrected for multiple comparisons and matched prior conservative α thresholds.

Secondary analyses compared ATMX fMRI responses to published MPH and placebo data (Bush et al., 2008). For ATMX versus placebo and MPH analyses, a mask representing all $MSIT_{Interference} > MSIT_{Control}$ voxels ($P < .05$ uncorrected) for all 32 subjects during Scans 1 and 2 restricted analyses to brain areas specifically involved in cognitive task performance. Within masked voxels, random effects repeated measures ANOVA GLMs identified brain regions with higher Scan 2 $MSIT_{Interference}$ activation in the ATMX group than the MPH and Placebo groups. An additional step tested for interactions (i.e., regions had to show *both* a treatment group (ATMX versus placebo or MPH, respectively) × scan (Scan 1 baseline versus Scan 2 six weeks) interaction, *and* a confirmatory two-tailed *t*-test had to indicate significantly different Scan 2 activation in ATMX than placebo or MPH, respectively.

Exploratory analysis compared baseline fMRI responses of the ADHD-CO ($N = 21$) and ADHD-NOS ($N = 11$) groups during the MSIT. A GLM compared the $MSIT_{Interference}$ activation levels at baseline.

3. Results

Primary within subject analysis showed six weeks of ATMX treatment increased activation of many elements of the CFP cognitive-attention network and other brain regions that MPH was shown to activate previously (Bush et al., 2008). Specifically, Figure 1 and Supplemental Table 2 show ATMX increased activation of right DLPFC, inferior parietal lobule, supplementary motor area, insular cortex, caudate, bilateral cerebellum and fusiform gyrus. Notably, ATMX did not produce the predicted increase of daMCC activation.

Although the ATMX versus Placebo contrast did not show differences at 6 weeks in *a priori* predicted areas of the CFP attention network, seven *post hoc* clusters showed ATMX>Placebo at six weeks (Supplemental Table 2). Similarly, ATMX versus MPH analysis produced no differences in *a priori* areas, but two *post hoc* clusters in MCC showed ATMX>MPH at 6 weeks. No region showed MPH > ATMX group at six weeks.

Baseline GLM comparisons of $MSIT_{Interference}$ activation between the ADHD-CO ($N = 21$) and ADHD-NOS ($N = 11$) samples showed no significant differences between the two groups.

4. Discussion

Six weeks of ATMX treatment was associated with increased activation of the CFP cognitive-attention network and other brain regions that were previously documented to activate by MPH treatment (Bush et al., 2008). Notably ATMX did not increase daMCC activation from baseline. Secondarily, while ATMX did not differentiate versus MPH or Placebo in *a priori* predicted areas, *post hoc* analyses identified ATMX>Placebo at 6 weeks in multiple MCC clusters and caudate; and ATMX>MPH in two MCC clusters. Neither of these comparisons showed a significant treatment group × scan interaction. Also, no differences were found in baseline fMRI activation between ADHD-CO and ADHD-NOS groups. Together, the data indicate ATMX and MPH have similar but non-identical brain effects.

To our knowledge this is the first fMRI study of ATMX in ADHD. In fact, there have been few imaging studies of ATMX, and all have used a single dose in healthy humans or were done in patients with schizophrenia (Friedman et al., 2008; Chamberlain et al., 2009; Graf et

al., 2011; Marquand et al., 2011; Hester et al., 2012; Marquand et al., 2012). Our findings complement and extend such work by showing ATMX effects in adults with ADHD over a longer, clinically relevant trial period, and using a different task.

The data show that ATMX was associated with increased activation of DLPFC, parietal cortex, caudate, and cerebellum—brain regions implicated in attention, motor control and the pathophysiology of ADHD (Bush, 2010). Further, the brain responses to ATMX and MPH were generally similar, but notable differences existed. ATMX did not activate daMCC as MPH has been shown to do (Bush et al., 2008). Also, ATMX did not produce significant activation of other regions activated by MPH, such as premotor cortex and thalamus. Together, the data indicate that while drug effects may overlap, differences exist in neurobiological actions.

Together with reported findings of ATMX NET binding changes (Logan et al., 2007), our data suggest ATMX may exert primary effects by NET receptor binding in the locus coeruleus, thalamus, midbrain, cingulate cortex and supplementary motor area, along with possible secondary downstream modulatory effects of DLPFC, parietal cortex and cerebellum. ATMX may initiate effects by blocking NET and increasing synaptic availability of norepinephrine, which may boost "downstream" signal-to-noise in fronto-parietal and cerebellar regions. This could improve attention, filtering of distracting information, and possibly regulate motor inhibition (thereby reducing hyperactivity and impulsivity). Differential actions of ATMX and MPH are broadly in line with the conceptualization of Arnsten (Arnsten, 2009) who concluded ATMX works mainly through postsynaptic alpha(2A)-receptors on the dendritic spines of PFC pyramidal cells and partially through D1-dopamine receptor actions. Some of the overlap of ATMX and MPH effects could be explained by findings that both inhibit NET (Hannestad et al., 2010), though complex differences between the drugs remain to be characterized.

Limitations include results being only valid for ADHD adults and that, aside from predicted fronto-parietal and cerebellar activations, other identified regions are *post hoc* and must be replicated. Moreover, the sample was small and there was no direct comparison group. Future work seeking to compare ATMX, MPH and/or placebo should consider a randomized or crossover design. Specifically, a crossover design would serve to eliminate anatomical variability between different subject groups in case the ATMX effect is subtle. Also, while identifying regions by post-medication activation is justifiable and valid for this pilot study, it does introduce the potential for circularity. Future work building on this pilot study should consider employing a matched healthy control group whose data will allow independent definition of regions of interest, avoiding circularity (Kriegeskorte et al., 2010). Finally, ADHD-NOS and ADHD-CO comparisons in this pilot study are preliminary pending replication.

In this pilot study, six weeks of treatment with ATMX was associated with increased activation of brain regions implicated in the pathophysiology of ADHD including DLPFC, parietal cortex, caudate and cerebellum. Many of these regions had been activated by MPH in our prior fMRI study, and here the observed differences between ATMX and MPH activation patterns were minimal. Notably, ATMX did not significantly activate daMCC. The data indicate that differences in cortical effects of ATMX and MPH may underlie their differential clinical effects.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

References

Adler LA, Spencer TJ, et al. Long-term, open-label study of the safety and efficacy of atomoxetine in adults with attention-deficit/hyperactivity disorder: an interim analysis. J Clin Psychiatry. 2005; 66(3):294–299. [PubMed: 15766294]

Arnsten AF. Stimulants: Therapeutic Actions in ADHD. Neuropsychopharmacology. 2006; 31(11): 2376–2383. [PubMed: 16855530]

Arnsten AF. Toward a new understanding of attention-deficit hyperactivity disorder pathophysiology: an important role for prefrontal cortex dysfunction. CNS Drugs. 2009; 23(Suppl 1):33–41. [PubMed: 19621976]

Biederman J, Mick E, et al. A randomized, placebo-controlled trial of OROS-methylphenidate in adults with attention-deficit/hyperactivity disorder. Biol Psychiatry. 2006; 59(9):829–835. [PubMed: 16373066]

Bush, G. Cingulate Neurobiology and Disease. B.A. Vogt: Oxford University Press; 2009. Dorsal anterior midcingulate cortex: Roles in normal cognition and disruption in attention-deficit/ hyperactivity disorder.

Bush G. Attention-deficit/hyperactivity disorder and attention networks. Neuropsychopharmacology. 2010; 35(1):278–300. [PubMed: 19759528]

Bush G. Cingulate, frontal, and parietal cortical dysfunction in attention-deficit/hyperactivity disorder. Biol Psychiatry. 2011; 69(12):1160–1167. [PubMed: 21489409]

Bush G, Shin LM. The Multi-Source Interference Task: an fMRI task that reliably activates the cingulo-frontal-parietal cognitive/attention network. Nat Protoc. 2006; 1(1):308–313. [PubMed: 17406250]

Bush G, Spencer TJ, et al. Functional magnetic resonance imaging of methylphenidate and placebo in attention-deficit/hyperactivity disorder during the multi-source interference task. Arch Gen Psychiatry. 2008; 65(1):102–114. [PubMed: 18180434]

Chamberlain SR, Hampshire A, et al. Atomoxetine modulates right inferior frontal activation during inhibitory control: a pharmacological functional magnetic resonance imaging study. Biol Psychiatry. 2009; 65(7):550–555. [PubMed: 19026407]

Forman SD, Cohen JD, et al. Improved assessment of significant activation in functional magnetic resonance imaging (fMRI): use of a cluster-size threshold. Magn Reson Med. 1995; 33(5):636–647. [PubMed: 7596267]

Friedman JI, Carpenter D, et al. A pilot study of adjunctive atomoxetine treatment to second-generation antipsychotics for cognitive impairment in schizophrenia. J Clin Psychopharmacol. 2008; 28(1):59–63. [PubMed: 18204342]

Graf H, Abler B, et al. Neural correlates of error monitoring modulated by atomoxetine in healthy volunteers. Biol Psychiatry. 2011; 69(9):890–897. [PubMed: 21168122]

Hannestad J, Gallezot JD, et al. Clinically relevant doses of methylphenidate significantly occupy norepinephrine transporters in humans in vivo. Biol Psychiatry. 2010; 68(9):854–860. [PubMed: 20691429]

Hester R, Nandam LS, et al. Neurochemical Enhancement of Conscious Error Awareness. J Neurosci. 2012; 32(8):2619–2627. [PubMed: 22357846]

Kriegeskorte N, Lindquist MA, et al. Everything you never wanted to know about circular analysis, but were afraid to ask. J Cereb Blood Flow Metab. 2010; 30(9):1551–1557. [PubMed: 20571517]

Logan J, Wang GJ, et al. Imaging the norepinephrine transporter in humans with (S,S)-[11C]O-methyl reboxetine and PET: problems and progress. Nucl Med Biol. 2007; 34(6):667–679. [PubMed: 17707807]

Marquand AF, De Simoni S, et al. Pattern classification of working memory networks reveals differential effects of methylphenidate, atomoxetine, and placebo in healthy volunteers. Neuropsychopharmacology. 2011; 36(6):1237–1247. [PubMed: 21346736]

Marquand AF, O'Daly OG, et al. Dissociable effects of methylphenidate, atomoxetine and placebo on regional cerebral blood flow in healthy volunteers at rest: A multi-class pattern recognition approach. Neuroimage. 2012; 60(2):1015–1024. [PubMed: 22266414]

Montoya A, Hervas A, et al. Evaluation of atomoxetine for first-line treatment of newly diagnosed, treatment-naive children and adolescents with attention deficit/hyperactivity disorder. Curr Med Res Opin. 2009; 25(11):2745–2754. [PubMed: 19785510]

Paloyelis Y, Mehta MA, et al. Functional MRI in ADHD: a systematic literature review. Expert Rev Neurother. 2007; 7(10):1337–1356. [PubMed: 17939771]

Pliszka SR. Pharmacologic treatment of attention-deficit/hyperactivity disorder: efficacy, safety and mechanisms of action. Neuropsychol Rev. 2007; 17(1):61–72. [PubMed: 17242993]

Seneca N, Gulyas B, et al. Atomoxetine occupies the norepinephrine transporter in a dose-dependent fashion: a PET study in nonhuman primate brain using (S,S)-[18F]FMeNER-D2. Psychopharmacology (Berl). 2006; 188(1):119–127. [PubMed: 16896954]

Spencer T, Biederman J, et al. A large, double-blind, randomized clinical trial of methylphenidate in the treatment of adults with attention-deficit/hyperactivity disorder. Biological Psychiatry. 2005; 57(5):456–463. [PubMed: 15737659]

Takano A, Gulyas B, et al. Saturated norepinephrine transporter occupancy by atomoxetine relevant to clinical doses: a rhesus monkey study with (S,S)-[(18)F]FMeNER-D (2). Eur J Nucl Med Mol Imaging. 2009; 36(8):1308–1314. [PubMed: 19300997]
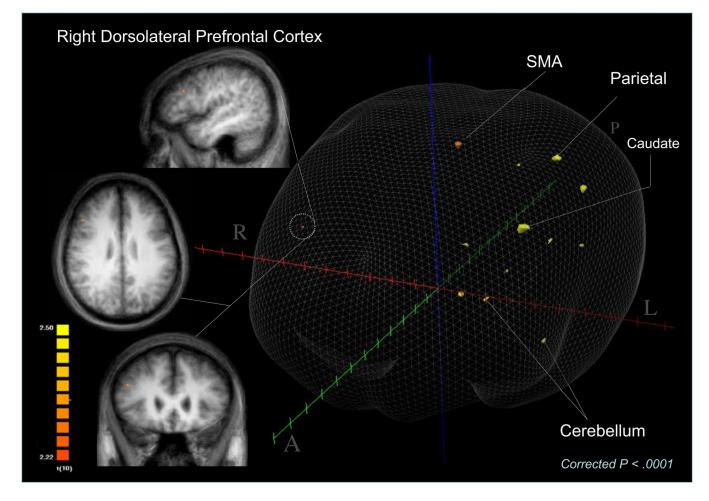
Figure 1.
Atomoxetine Produces Higher fMRI Activation at 6 Weeks

Table 1

MSIT Performance Data

Group	Scan 1 (Baseline, t = 0) Interference	Scan 1 (Baseline, t = 0) Control	Scan 2 (t = 6 weeks) Interference	Scan 2 (t = 6 weeks) Control
REACTION TIMES (ms)				
ATMX (All)	1026 ± 77	702 ± 104	922 ± 145	634 ± 121
ACCURACY (%)				
ATMX (All)	95.6 ± 3.1	95.4 ± 5.8	92.1 ± 9.0	90.0 ± 8.4

Means and standard deviations are presented for RT (ms) and accuracy (% correct). RT and accuracy data were lost/corrupted for two subjects, both of whom were ATMX treatment responders. Thus the term 'all' refers to full remaining group data (N = 9 of 11), divided between ATMX Responders ($N = 5$ of 7 responders) and ATMX Failures ($N = 4$). Repeated measures ANOVAs showed that the ATMX group displayed the expected interference effects ($RT_{interference} > RT_{control}$ with significant main effects of condition [$F_{1,8} = 130.2$, $P < .001$]) and scan ($F_{1,8} = 9.5$, $P < .05$), but no scan × condition interaction ($P = .12$, N.S.) for RT. For accuracy, the ATMX group did not show a significant main effect of condition [$F_{1,8} = 1.1$, $P = .32$, N.S.]) or scan ($F_{1,8} = 2.9$, $P = 1.3$, N.S.), and did not display a significant scan × condition interaction ($P = .53$, N.S.). Separate 3 (Group: ATMX vs. MPH vs. Placebo) by 2 (Condition: $MSIT_{interference}$ vs. $MSIT_{control}$) by 2 (Scan [Scan 1 (baseline, t = 0) vs. Scan 2 (t = 6 weeks)] repeated measures ANOVAs were performed for RT and accuracy. For RT, there were main effects of group ($F_{2,27} = 11.2$, P < .001), scan ($F_{2,27} = 68.3$, $P < .001$) and condition ($F_{2,27} = 503.5$, $P < .0001$), but no scan × group ($P = .98$), condition × group (P = .53), nor scan × condition × group (P = .72) interactions for RT. For accuracy, there were main effects of group ($F_{2,27} = 8.3$, $P < .01$) and condition ($F_{2,27} = 4.7$, $P < .05$), but not of scan ($F_{2,27} = 1.0$, $P = .33$). There were scan × group ($F_{2,27} = 3.7$, $P < .05$) and condition × group ($F_{2,27} = 5.6$, $P < .01$) interactions, but not a scan × condition × group ($F_{2,27} = 0.1$, $P = .92$, N.S.) interaction.

Table 2

Brain Regions Showing Higher MSIT Activation After a 6-Weeks Trial of Atomoxetine than at Baseline (time = 0) in ADHD Adults

Brain Region	x	y	z	Region Size (Voxels)
R. DLPFC - Middle Frontal Gyrus (9)	45	22	28	7
L. Supplementary Motor Area (6)	−8	−4	58	23
L. Insula	−30	2	13	7
L. Substantia nigra	−3	−14	−8	25
L. Postcentral Gyrus (1)	−51	−23	40	29
L. Inferior Parietal Lobule (40)	−36	−33	46	35
L. Caudate Tail	−22	−34	15	56
L. Posterior Cingulate Cortex (31)	−12	−55	34	9
L. Cerebellum	−21	−60	−47	17
R. Cerebellum	4	−54	−29	16
L. Fusiform Gyrus (19)	−24	−58	1	13
L. Fusiform Gyrus (19)	−36	−64	−2	15

Group-averaged activation locations and extents are shown for brain regions that showed higher fMRI activation in ADHD adults ($N = 11$) during MSIT Interference trials after 6 weeks of ATMX. The activation locations shown are the result of a random effects GLM analysis, with a voxel-wise threshold of $P < .05$ and to which an additional rigorous 7 contiguous voxel cluster constraint was applied to correct for multiple comparisons (cluster corrected $P < .0001$). Stereotactic coordinates are presented for local maxima according to the convention of Talairach and Tournoux (1988). Coordinates are expressed in millimeter units. The origin (0,0,0) is the anterior commissure at the midsagittal plane, with $x > 0$ corresponding to right of midsagittal, $y > 0$ corresponding to anterior, and $z > 0$ corresponding to superior. Cytoarchitectural areas are indicated in parentheses after the named structure.