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Acute Atomoxetine Selectively Modulates Encoding of Reward Value in Ventral Medial Prefrontal Cortex

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Background: A recent neurocognitive model of attention-deficit hyperactivity disorder (ADHD) has proposed a primary deficit in reward function as well as in executive function to account for underlying neural substrates of ADHD symptoms. Atomoxetine has been widely used as a non-stimulant medication for ADHD with little abuse liability. Although animal studies have reported that atomoxetine increases extracellular levels of both noradrenaline and dopamine in the prefrontal cortex, which receives input from a mesocorticolimbic pathway involved in reward function, there have been few studies in humans concerning the effects of atomoxetine in terms of reward function. Therefore, we investigated whether a single dose of atomoxetine (acute atomoxetine) affects reward processing in healthy adults.
Methods: We used functional magnetic resonance imaging and adopted the monetary incentive delay task to separately examine neural responses to monetary reward anticipation in the nucleus accumbens and outcome in the ventral medial prefrontal cortex (vmPFC). The experiment was designed as a randomized, placebo-controlled within-subjects cross-over trial. Fourteen healthy adults completed two series of studies, taking either atomoxetine or placebo.
Results: Atomoxetine significantly decreased vmPFC activation during gain outcome compared to placebo. In gain anticipation, however, atomoxetine did not show a significant increase in the nucleus accumbens activation compared with placebo.
Conclusions: These results suggest that atomoxetine affects reward value encoding through selective modulation of vmPFC activity related to reward outcome. Therefore, such modulatory action may partly contribute to a therapeutic effect of atomoxetine for a group of ADHD patients with increased activity in vmPFC. (J Nippon Med Sch 2019; 86: 98–107)

Key words: atomoxetine, functional MRI, monetary incentive delay task, reward value encoding, ventral medial prefrontal cortex

Introduction

Attention-deficit hyperactivity disorder (ADHD) is characterized by symptoms that include inattention, hyperactivity, and impulsivity[1]. These symptoms have so far been thought to arise from a primary deficit in executive function with higher-level and top-down cognitive processes[2]. A meta-analysis of functional magnetic resonance imaging (fMRI) studies revealed that patients with ADHD show hypoactivity in the frontoparietal network, which supports goal-directed executive processes and guides decision-making[3]. On the other hand, a substantial proportion of patients with ADHD has few impairments in executive function measures[4]. Another neurocognitive model has also proposed the crucial involvement of abnormal reward functions as well as executive dysfunction to account for underlying neural mechanisms of the

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ADHD symptoms[5,6]. For example, it has been reported that patients with ADHD exhibit delay aversion characterized by attempts to escape or avoid delay, and that children with ADHD show a greater preference to select a small but immediate reward than a larger and delayed one compared to normal controls[7], suggesting a possible involvement of reward dysfunction related to impulsivity, a canonical symptom of ADHD.

Reward has several external and internal components that ensure adequate reward functions in association with responsible neural substrates[8]. The key brain substrates for reward functions occur in two midbrain dopamine (DA) pathways[8] - the nigrostriatal pathway projecting from the substantia nigra to the caudate nucleus and putamen, and the mesocorticolimbic pathway consisting of ventral tegmental area (VTA) projections to the nucleus accumbens (NAc) and PFC[9]. It has been reported that aberrant substantia nigra/VTA novelty processing plays an important role in the suboptimal reward-related decision-making in ADHD[10]. Several reports showed that the activity in the ventral striatum was decreased during reward anticipation in ADHD[11,12], although another large-scale study using a similar task reported no substantial change in activation in the ventral striatum[13].

As for the mesocorticolimbic pathway, activities in fronto-striatal circuitry are reportedly increased during anticipation and reward acquisition in ADHD[13], and the impaired signal from VTA to ACC pathway is hypothesized to lead to impaired reinforcement learning processing[14].

Atomoxetine is a selective noradrenaline (NA) reuptake inhibitor[15] and is used as a non-stimulant medication for ADHD. In clinical practice, atomoxetine improves various executive functions in adults and children with ADHD[16,17]. An fMRI study reported that atomoxetine decreased activation in the dorsal ACC and dorsolateral PFC during the counting Stroop task in association with improvement of focused attention in patients with ADHD[18]. On the other hand, atomoxetine normalizes performance by enhancing the activity in the dorsolateral PFC in the working memory task in patients with ADHD[19]. These results suggest that atomoxetine can normalize dysregulated executive function in PFC in patients with ADHD.

While atomoxetine does not increase extracellular levels of either NA or DA in NAc[20], it increases extracellular levels of both NA and DA in PFC[20,21]. Pharmacological manipulation of the NA level with atomoxetine affects exploration of reward-options in humans[22]. Therefore, atomoxetine may modulate some reward functions in PFC through dopaminergic and/or noradrenergic transmission.

In the present study, we investigated whether a single dose of atomoxetine affects reward function in healthy adults. Previous fMRI studies indicate that a single dose of atomoxetine can modulate the performance of executive function and brain activity in healthy adults and medication-naïve ADHD[19,23,24]. As for reward, there has been little study in terms of what reward functions are affected by atomoxetine. In order to better understand the relation between reward function and neurotransmitters in PFC, it is crucial to examine the effect of atomoxetine on neural substrates, responsible for individual reward functions. To reveal individual reward functions separately, we used the monetary incentive delay (MID) task, which is designed to elicit neural responses to monetary incentive anticipation and outcome[25]. In the MID task, NAc activity clearly increases in proportion to the magnitude of the anticipated monetary reward, and the activity in ventral medial PFC (vmPFC) during reward outcome increases when one expects and obtains larger reward[25–27]. Here, we show specific regions involved in reward function that are affected by a single-dose of atomoxetine (acute atomoxetine) using the MID task with fMRI.

Materials and Methods

Participants

Twenty physically and psychiatrically healthy participants (9 females, 11 males; mean age and standard deviation [SD], 31.4 and 5.6 years) were recruited for the study. Before starting the experiment, we excluded subjects whose baseline mood scores or subjective states exceeded the set criteria (see subjective ratings below).

All participants were right-handed according to the Edinburgh Handedness Inventory[28], and none used any drug, had a medical history of psychiatric disorders, or were allergic to atomoxetine. They were instructed to abstain from caffeine and alcohol intake for 48 and 24 hours, respectively, prior to the experiment to avoid their effects on physical and cognitive performance[29].

Over the course of the study, we excluded 6 participants. One was ruled out after deciding to discontinue participation, two for high caffeine concentration in urine (exceeding 2 μg/mL), one for excessive head movement (i.e., more than 2 mm in any direction), one for excessive head movement and excessive button pressing during

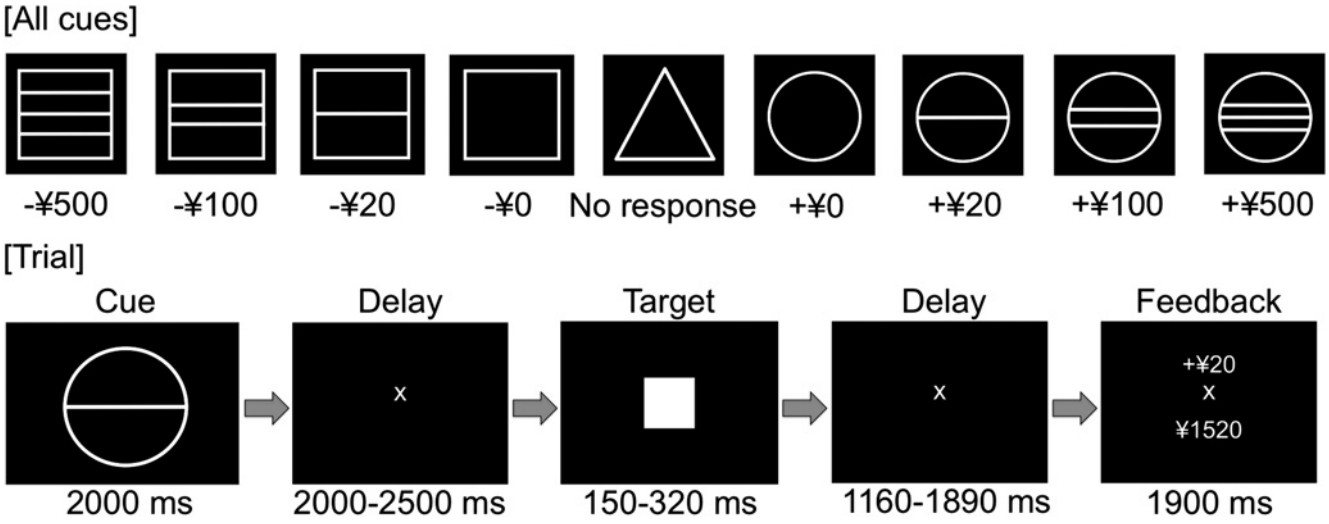

Fig. 1 Structure of the monetary incentive delay task

Gain (+¥20, +¥100, and +¥500), loss (–¥20, –¥100, and –¥500), neutral (+¥0 and –¥0), and no response (triangle) cues were presented pseudo-randomly within each run. In each trial, each one of nine cues, delay (anticipation period), target, delay, and feedback (outcome period) was sequentially presented.

the MID task, and one for excessive head movement and unknown caffeine concentration in urine due to sample collection failure. The excessive count of button presses during the MID task was based on the ratio of the number of button presses with short reaction time below 150 ms to the number of all targets requiring the button press (n = 144)[30]. The average excessive counts were 12.21 ± 12.68% (mean ± SD) and 8.99 ± 9.01% (mean ± SD) under placebo and atomoxetine, respectively. Participants with excessive counts over 3 SD from the average[31] were excluded from the subsequent analyses.

Finally, data obtained from 14 subjects (6 females, 8 males; mean age and SD, 32.4 and 5.1 years) were used for the analysis. All participants gave written informed consent, and the study was approved by the ethics committee of Nippon Medical School (approval number 224016).

Subjective Ratings

To assess baseline mood and subjective states of the participants, they underwent 2 psychological tests: Beck Depression Inventory (BDI)[32,33] and State-Trait Anxiety Inventory (STAI)[34]. Transient subjective mood states were also evaluated by 16 items (e.g., alert, calm, strong, clear-headed, well-coordinated, etc.) with visual analogue scales before and 1 hour after drug administration[35]. Subjects with scores of BDI>11, STAI-state>45, or STAI-trait> 46 were excluded from the study, as high depression and anxiety scores may affect brain activity in reward processing and reward-related behaviors[36,37].

Experimental Design

The experiment was designed as a randomized, placebo-controlled within-subjects cross-over trial. To carefully monitor adverse drug reactions in participants, we conducted the current study in a single-blind manner. The participants took a single dose of atomoxetine (40 mg in a Strattera capsule formula, Eli Lilly, Japan) or placebo capsule (same shape, the latter containing lactose) in the first series. The participants given atomoxetine for the first series were given the placebo, and those given the placebo in the first series were given atomoxetine during the second series of the study. The washout period was at least a one week between the first and second series.

They were asked not to eat or drink anything except water from 2 h prior to, and throughout the experiment. The fMRI study started 1.5 h after drug administration, at which time the peak level of atomoxetine in plasma would be expected[38,39].

Monetary Incentive Delay Task

We used the MID task to examine neural responses to monetary anticipation and outcome[40-42]. Participants were informed that they would receive a gift voucher according to the amount of money they had earned during the task. The task consisted of 2 sessions totaling 180 trials (**Fig. 1**). During scanning, participants saw one of nine cue shapes for 2,000 ms, which indicated that they could either gain or avoid losing different amounts of money (￥0, ￥20, ￥100, or ￥500) if they pressed the response button during the target presentation. Cues signified po-

tential reward (n=72, denoted by circles), potential punishment (n=72; denoted by squares), or no response requirement (n=36; denoted by triangles). Reward cues (circle) signaled the possibility of gaining ¥0 (n=18; no lines), ¥20 (n=18; one horizontal line), ¥100 (n=18; two horizontal lines), or ¥500 (n=18; three horizontal lines). Similarly, punishment cues (square) consisted of four signals with the possibility of losing ¥0 (n=18; no lines), ¥20 (n=18; one horizontal line), ¥100 (n=18; two horizontal lines), or ¥500 (n=18; three horizontal lines). Participants were instructed that they should not respond during "No response" trials (n=36; triangle) and instead wait until the appearance of the cue signaling the next trial. Trial types were presented in pseudo-random order within each session. Between cue and target, an x-shaped fixation cross was shown for a variable anticipation delay period (2,000-2,500 ms). Then a solid white target square was presented for a variable length of time (150-320 ms; target), and participants were asked to push a button as quickly as possible. Feedback (1,900 ms) following disappearance of the second delay (1,160-1,890 ms) indicated how much money participants had gained or lost in that trial and the total amount of money they had earned up to that time point during the session. By controlling the duration of the target cue presentation, the task difficulty was standardized to a hit rate of approximately 66% for all participants.

MRI Data Acquisition

All imaging data were collected on an Intera Achieva 1.5 T Nova scanner (Phillips Electronics, The Netherlands). The high-resolution T1-weighted anatomical images were acquired using the following parameters: repetition time (TR) = 9.3 ms, echo time (TE) = 4.6 ms, flip angle = 8°, field of view (FOV) = 250 mm, matrix = 256×256, slice thickness = 1.2 mm, number of slices = 160. Functional images were collected with the following parameters: TR = 2,000 ms, TE = 40 ms, flip angle = 90°, FOV = 256 mm, matrix = 64×64. A total of 740 functional images were acquired from each participant with a T2*-weighted gradient-echo echo-planar imaging sequence sensitive to blood-oxygenation-level dependent contrast. Whole-brain coverage was obtained with 5-mm slice thickness and 28 axial slices.

fMRI Data Analysis

The obtained fMRI data were preprocessed using SPM8 (Wellcome Department of Imaging Neuroscience, UK) running with MATLAB (Mathworks, USA). The anatomical T1 image and the functional images were manually reoriented to the anterior commissure-posterior commissure line. To correct for between-scan movements, the functional images were realigned to the first image of each session and again realigned to the mean image created after the first realignment. The individual anatomical T1 image was then co-registered to the mean functional image. The transformed anatomical image was then segmented to create spatial normalization parameters that were applied to functional images in the next normalization step. The functional images were spatially normalized to the standard space defined by the Montreal Neurological Institute (MNI) template. After normalization, all scans had a resolution of 2×2×2 mm.

The functional images were spatially smoothed with an isotropic Gaussian kernel (full width at half maximum of 8 mm) to increase the signal-to-noise ratio. For subject-level statistical analyses, the functional images were analyzed using the general linear model.

Hemodynamic responses to each stimulus were modeled with a δ function convolved with a synthetic hemodynamic response function time-locked to the onset time of delay following the cue and feedback. Low frequency noise was removed by applying a high-pass filter (cutoff period 128 s) to the fMRI time-series data of each voxel.

The statistical parametric map for each contrast, (1) gain outcome ("hit" versus "miss" outcomes on potential gain trials) and (2) gain anticipation (anticipation of monetary gain versus neutral trial, i.e. +¥0) of the *t* statistic, was calculated on a voxel × voxel basis. We set vmPFC for gain outcome and NAc for gain anticipation as a priori region of interest (ROI) based on previous fMRI studies using the MID task[40,43]. The vmPFC ROI was defined based on the anatomically and functionally defined areas[26,27]. The vmPFC ROI was extracted using the Wake Forest University PickAtlas. One single NAc ROI was anatomically defined by bilateral NAc templates using the Wake Forest University PickAtlas. For group-level analyses, the one-sample *t* test was performed to determine group-level activation for each contrast. Then, for group comparisons, paired *t* test was performed to assess the difference between the placebo and atomoxetine administrations. The contrast images obtained from subject-level statistical analyses were entered into paired *t* test analyses. The ROIs were analyzed at a family-wise error (FWE)-corrected $p<0.05$ using small volume correction.

The percent signal change within vmPFC ROI was calculated for the contrast of "hit" versus "miss" during the gain outcome period using MarsBaR. The values of percent signal change with gain outcome under placebo and atomoxetine conditions were analyzed using the paired *t*

test, because they followed normal distribution.

To investigate the correlation between brain activation (percent signal changes) and MID performance, we performed linear correlation analysis. Pearson's correlation was used for the analysis because of the normal distribution of the data.

Whole-brain analysis was performed at an uncorrected $p<0.001$ at voxel level with FWE-corrected $p<0.05$ at cluster level. Activation foci in vmPFC were used to construct ROI with a sphere of 4-mm radius, centered at the maximum peak coordinates (x = −8, y = 58, z = −4) of the region showing prominent activation during the gain outcome period under placebo in the whole-brain analysis.

Results

Effect of Atomoxetine on Subjective Mood States

We examined changes in subjective mood before and after drug administration, as atomoxetine or noradrenergic agents may modulate mood[44–46].

Changes in subjective mood rating were calculated by subtracting the values before drug administration from those at 1 h after drug administration. There was no significant difference in subjective mood states between placebo and atomoxetine. These results suggest that a single dose of atomoxetine does not modify mood states.

Effects of Atomoxetine on Task Performance

During the MID task (**Fig. 1**), we examined the effects of atomoxetine on reaction time, hit rate, and total sum earned by participants (**Table 1**). No significant difference was observed in mean reaction time and total amount of money earned between placebo and atomoxetine conditions. The mean hit rate, however, showed a significant decrease under atomoxetine as compared to placebo.

Effect of Atomoxetine on Brain Activation During Gain Outcome and Gain Anticipation

We focused on vmPFC for gain outcome and NAc for gain anticipation as a priori ROI based on previous fMRI studies using the MID task[40,43] and examined the effect of atomoxetine on brain activation. Under both placebo and atomoxetine conditions, a significant activation in the left vmPFC was observed during gain outcome ($p<0.05$ FWE-corrected for vmPFC ROI), consistent with a previous study[26,43] (**Table 2**).

Group-level analysis revealed that atomoxetine showed a significant decrease in the left vmPFC activation during gain outcome as compared with placebo ($p<0.05$ FWE-corrected for vmPFC ROI) (**Table 2** and **Figure 2, 3**).

Table 1 Drug effects on MID task performance

	Placebo Mean (SE)	Atomoxetine Mean (SE)
Reaction time (ms)	206.7 (7.74)	203.0 (7.25)
Hit rate (%) **	64.2 (0.32)	62.7 (0.39)
Total amount of money earned (¥)	3,134.3 (123.2)	2,722.9 (175.9)

**$p<0.01$ between placebo and atomoxetine treatments
SE, standard error of mean

Table 2 Activated brain regions during gain outcome and gain anticipation under placebo and atomoxetine conditions

	Region	BA	MNI			*t* value
			x	y	z	
Gain outcome						
Placebo	L vmPFC	10	–8	58	–4	5.12
Atomoxetine	L vmPFC	10	–6	56	–2	2.54
Placebo > Atomoxetine	L vmPFC	10	–6	58	–2	2.85
Atomoxetine > Placebo	None					
Gain anticipation						
Placebo	L nucleus accumbens		–14	6	–10	3.45
Atomoxetine	R nucleus accumbens		16	10	–10	4.85
	L nucleus accumbens		–14	10	–10	4.62
Placebo > Atomoxetine	None					
Atomoxetine > Placebo	None					

$p<0.05$ FWE-corrected for ROIs in ventral medial prefrontal cortex and nucleus accumbens.
BA, Brodmann area
MNI, Montreal Neurological Institute
L, left; *R*, right
vmPFC, ventral medial prefrontal cortex

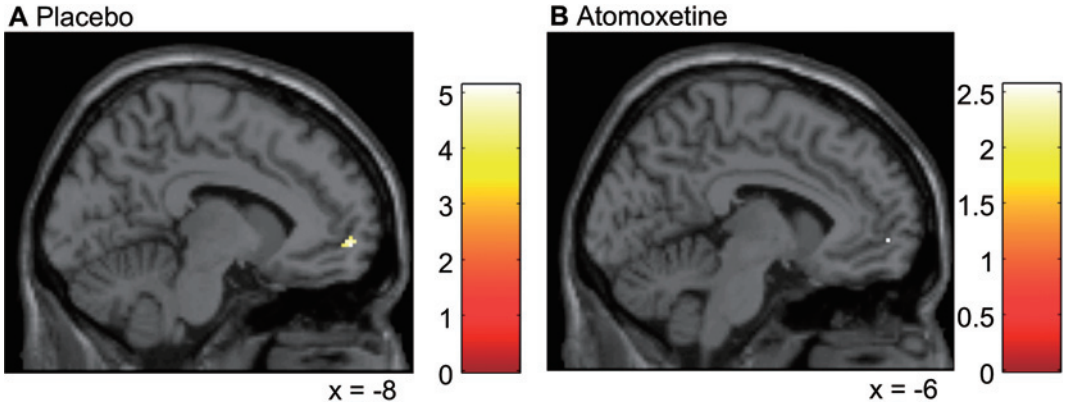

Fig. 2 Neural responses to gain outcome in the ventral medial prefrontal cortex
(A) Brain activation in the ventral medial prefrontal cortex during gain outcome ("hit" versus "miss" outcomes in potential gain trials) under placebo and (B) atomoxetine conditions. Familywise error-corrected $p<0.05$ for the ROI in the ventral medial prefrontal cortex. Color bars indicate t statistics.

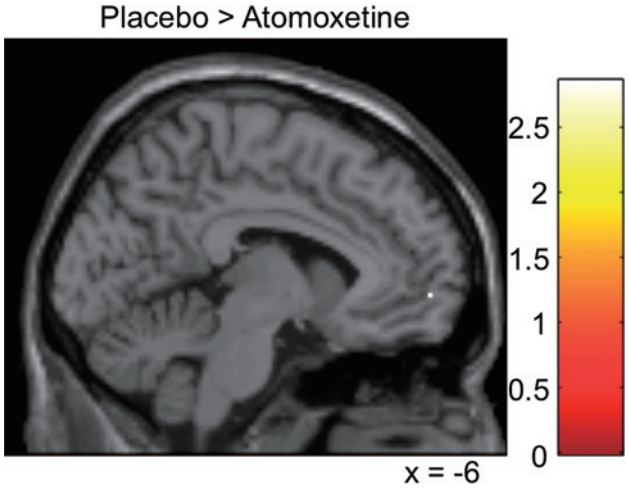

Fig. 3 Effects of atomoxetine on neural responses to gain outcome
Atomoxetine reduced activation in the ventral medial prefrontal cortex during gain outcome compared to placebo. Familywise error-corrected $p<0.05$ for the ROI in the ventral medial prefrontal cortex. Color bar indicates t statistics.

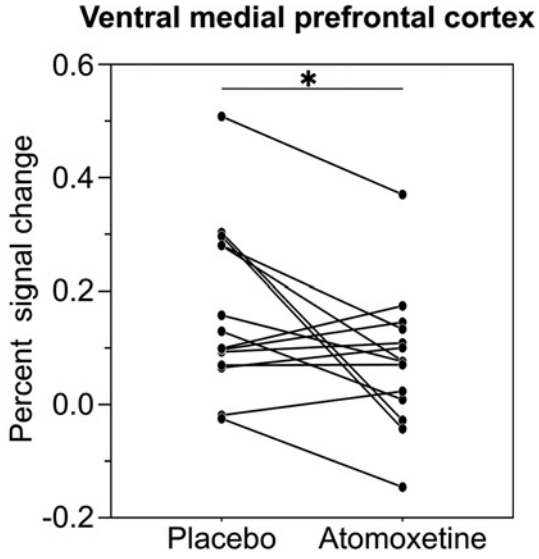

Fig. 4 Percent signal changes in ventral medial prefrontal cortex (vmPFC) during gain outcome
Percent signal changes from vmPFC ROI were calculated for the contrast of "hit" versus "miss" during gain outcome. *$p<0.05$.

We then examined the percent signal change in blood-oxygenation-level dependent signal in vmPFC during gain outcome (**Fig. 4**). In gain outcome, atomoxetine showed a lower activation than placebo ($p=0.027$). Next, we investigated the activity of gain anticipation in NAc. In gain anticipation, the left NAc activation under placebo and bilateral NAc activation under atomoxetine were increased (**Table 2**). Group-level analyses revealed that atomoxetine did not show any significant increase in NAc activation during gain anticipation compared with placebo ($p<0.05$ FWE-corrected for NAc ROI).

Consistent with previous studies[27,43], whole-brain analysis during gain outcome under placebo condition showed a significant increase in activation in the caudate, putamen, and amygdala as well as in vmPFC ($p<0.001$ uncorrected) (**Table 3**).

To investigate whether the vmPFC and NAc activities are associated with MID performance, correlations between vmPFC or NAc activation and the hit rate were calculated under both conditions. The activation in vmPFC did not show significant correlations with performance under either condition (placebo hit rate, $r=0.089$, $p=0.763$; atomoxetine hit rate, $r=0.292$, $p=0.311$). Similarly, there were no significant correlations between

Table 3 Whole-brain analysis during gain outcome under placebo and atomoxetine conditions

Treatment	Region	BA	MNI coordinates			*t* value
			x	y	z	
Placebo	L amygdala		–26	0	–16	9.59
	R amygdala		22	–2	–20	9.13
	R caudate		8	24	2	7.99
	L caudate		–18	–10	28	7.85
	R claustrum		24	–8	30	5.95
	L vmPFC	10	–8	58	–4	5.12
	L superior frontal gyrus	10	–4	64	2	5.09
	L putamen		–22	10	14	5.08
	L claustrum		–28	2	18	4.82
	L parahippocampal gyrus	34	–16	0	–18	4.54
	R parahippocampal gyrus	35	28	–14	–28	4.45
	R putamen		28	0	–10	4.06
Atomoxetine	L putamen		–16	18	–10	12.26
	L middle occipital gyrus	18	–28	–82	–4	9.84
	L thalamus		–16	–36	6	6.96
	L posterior cingulate	30	–10	–54	14	6.24
	R middle occipital gyrus	19	34	–78	0	5.59
	L superior frontal gyrus	9	–14	44	38	5.39
	L globus pallidus		–18	–2	–10	4.93
	R putamen		24	10	–8	4.48
	L lingual gyrus	17	–22	–90	–8	4.29
	R inferior occipital gyrus	19	40	–78	–6	3.99

$p<0.001$ uncorrected
BA, Brodmann area
MNI, Montreal Neurological Institute
L, left; *R*, right
vmPFC, ventral medial prefrontal cortex

NAc activity and MID task performance under either condition (placebo hit rate, $r=-0.182$, $p=0.533$; atomoxetine hit rate, $r=0.286$, $p=0.321$).

Discussion

We showed that atomoxetine significantly decreased brain activation in vmPFC during reward outcome compared with placebo, while it did not affect NAc activity during reward anticipation.

A meta-analysis of functional neuroimaging studies with MID task revealed that ventral striatum, vmPFC including medial orbitofrontal cortex, posterior cingulate cortex, and amygdala showed preferential activation during successful reward outcome as compared with unsuccessful reward outcome or neutral outcome[27]. Consistently, vmPFC and amygdala were activated during reward outcome in the present study. As for MID task, vmPFC activity increased when participants expected and obtained larger reward, whereas it decreased when they expected, but did not obtain the reward[25,26]. The present result also showed that vmPFC activation during reward outcome was larger under both placebo and atomoxetine when the participants obtained larger reward as compared with when they missed the reward. In addition, because the activation in vmPFC, as well as in NAc, did not show any significant correlations with performance under both conditions, it is unlikely that the behavioral differences could be the cause of the different brain activity. Therefore, these results suggest that the activation in vmPFC during reward outcome encodes the reward value.

Imaging studies of ADHD have so far focused on dysfunction in the ventral striatum during reward anticipation[11,12]. A large-scale study using the MID task has shown enhanced neural responses in fronto-striatal circuitry to anticipation and acquisition of reward in ADHD[13]. In addition, patients with ADHD have a tendency to prefer immediate reward and avoid delayed reward[7,47]. This tendency may cause impulsive behavior, as they are unable to wait for the outcome, or their atten-

tion is distracted due to the reward delay[6]. Given that medial PFC activity is related to encoding of the expected reward value[48,49], PFC hyperactivity in ADHD might represent overestimation of the immediate reward or preparation for the next reward opportunity.

In the present study, we observed that atomoxetine significantly decreased brain activation in vmPFC during reward outcome compared with placebo. Previous studies using fMRI have reported that atomoxetine normalizes both abnormal activation and deactivation in executive function in ADHD[18,19]. Therefore, although the results observed in healthy adults should be carefully interpreted, the present study suggests that atomoxetine acts on vmPFC and might be beneficial for a group of patients with hyperactivity in vmPFC.

Atomoxetine did not significantly increase activation in NAc during reward anticipation. Psychostimulants, such as methylphenidate, have been used for a long time as first-line therapeutics for ADHD because of their higher effectiveness in clinical practice. Methylphenidate inhibits DA and NA transporters and increases the extracellular DA level in the striatum and NAc, as well as in PFC[50]. On the other hand, it has been reported that atomoxetine increases extracellular levels of DA in PFC, but not in the striatum and NAc[20]. Activation of DA transmission in reward function, particularly the VTA-NAc pathway, is critical for the development of addiction[51]. The difference in effect on DA in the striatum and NAc may explain the difference in abuse potential between methylphenidate and atomoxetine[52–54].

As for task performance, atomoxetine significantly reduced the hit rate during the task in the present study. It has been reported that low to moderate levels of NA and DA have a beneficial effect on working memory in PFC, whereas high concentrations of NA and DA in PFC impair such executive function[55]. Consistently, 80 mg of atomoxetine reportedly increases failure of response inhibition during Go/NoGo task[24], while 60 mg of atomoxetine improves inhibition control during stop-signal task[56]. It has been reported that DA receptor agonists improved cognition in subjects with lower baseline cognitive ability in pre-treatment state, but that it worsens in those with higher baseline capacity[57], showing that the relationship between cognitive performance and DA levels follows an "inverted-U-shaped" function. Moreover, a similar "inverted-U-shaped" effect has been reported with NA[55]. Atomoxetine increases extracellular levels of both NA and DA in PFC[20,21]. Therefore, reduced performance might be due to the increase in NA and DA levels in PFC beyond individual optimal ranges by acute administration of atomoxetine in healthy volunteers.

This study has several experimental limitations. First, we examined the effects of single-dose atomoxetine on reward function. However, to treat patients with ADHD, atomoxetine needs to be chronically administered. Although previous reports observed significant effects of a single dose of atomoxetine on executive function in healthy adults and patients with ADHD[19,23,24], we need to further clarify whether chronic atomoxetine administration has similar effects on reward function in these patients. Other methodological limitations consist of the single-blind study and the limited volunteer number, which may also affect the behavioral and fMRI analyses. The present study was conducted in a single-blind manner in order to carefully observe whether the participants suffered from unexpected adverse drug effects. While no subjective judgment intervened in the fMRI experiments, the process of data analysis might affect interpretation of the results. Finally, because the sample size was small in the present study, this may affect the outcome of the behavioural and fMRI analyses. In this regard, some statistical analyses may also be insufficient. Future studies (e.g. further investigations to confirm that atomoxetine does not affect brain activity in NAc during reward anticipation) will be required using larger numbers of participants with sufficient statistical power.

The present study revealed that acute atomoxetine decreased brain activity in vmPFC during reward outcome, but not in NAc during reward anticipation. These results suggest that atomoxetine has the potential to selectively modulate reward value encoding in reward function in vmPFC. Therefore, such modulatory action may partly contribute to a therapeutic effect of atomoxetine for a group of patients with ADHD.

Conflict of Interest: Nippon Medical School Hospital has conducted a clinical trial supported by Eli Lilly. Amane Tateno has received honoraria as a participant in a research performed by Eli Lilly. These researches are unrelated to the submitted work. Yoshiro Okubo has received speaker's honoraria from Eli Lilly. For the remaining authors, none are declared.

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