Atomoxetine improves attentional orienting in a predictive context

Amélie Reynaud, Mathilda Froesel, Carole Guedj, Sameh Ben Hadj Hassen, Justine Cléry, Martine Meunier, Suliann Ben Hamed, Fadila Hadj-Bouziane

Neuropharmacology 150 (2019) 59–69

Contents lists available at ScienceDirect

Neuropharmacology

journal homepage: www.elsevier.com/locate/neuropharm

Atomoxetine improves attentional orienting in a predictive context

Amélie J. Reynaud[a,b,*,1], Mathilda Froesel[b,c,1], Carole Guedj[a,b], Sameh Ben Hadj Hassen[b,c], Justine Cléry[b,c], Martine Meunier[a,b], Suliann Ben Hamed[b,c,2], Fadila Hadj-Bouziane[a,b,**,2]

[a] INSERM, U1028, CNRS UMR5292, Lyon Neuroscience Research Center, ImpAct Team, Lyon, F-69000, France
[b] University UCBL, Lyon 1, F-69000, France
[c] CNRS, UMR5229, Institut des Sciences Cognitives Marc Jeannerod, France

HIGHLIGHTS

- Atomoxetine decreases reaction time of the most prevalent trials.
- Atomoxetine modulates the accumulation rate of sensory information.
- Atomoxetine adapts the response strategy to the context.

ARTICLE INFO

Keywords:
Norepinephrine
Monkey
LATER
Visuo-spatial attention
Reaction time

ABSTRACT

The role of norepinephrine (NE) in visuo-spatial attention remains poorly understood. Our goal was to identify the attentional processes influenced by atomoxetine (ATX) injections, a NE-reuptake inhibitor that boosts the level of NE in the brain, and to characterize these influences. We tested the effects of ATX injections, on seven monkeys performing a saccadic cued task in which cues and distractors were used to manipulate spatial attention. We found that when the cue accurately predicted the location of the upcoming cue in 80% of the trials, ATX consistently improved attentional orienting, as measured from reaction times (RTs). These effects were best accounted for by a faster accumulation rate in the valid trials, rather than by a change in the decision threshold. By contrast, the effect of ATX on alerting and distractor interference was more inconsistent. Finally, we also found that, under ATX, RTs to non-cued targets were longer when these were presented separately from cued targets. This suggests that the impact of NE on visuo-spatial attention depends on the context, such that the adaptive changes elicited by the highly informative value of the cues in the most frequent trials were accompanied by a cost in the less frequent trials.

1. Introduction

Visuo-spatial attention is a pervasive function that enables us to selectively process visual information through prioritization of a spatial location while setting aside other locations. It depends on the fronto-parietal network and is under the influence of several neuromodulators including dopamine (DA), acetylcholine (ACh) and norepinephrine (NE) (see Noudoost and Moore, 2011). While a systematic approach to understand the role of DA and ACh in visual-spatial attention has been carried out over the years, the role of NE is currently less understood (see Noudoost and Moore, 2011).

In particular, only a handful of studies have addressed the role of NE transmission in visuo-spatial attention and its sub-components (alerting, orientating and executive control; Posner, 1980, Petersen and Posner, 2012), and the results are inconsistent. Petersen and Posner (2012) suggest a specific role of NE in the maintenance of high sensitivity to incoming stimuli i.e. the alerting sub-component (Petersen and Posner, 2012). At least two studies provide evidence in support of this (Witte and Marrocco, 1997; Coull et al., 2001). Evidence of the contribution of NE to spatial orienting is more inconsistent (Clark et al., 1989; Coull et al., 2001; Witte and Marrocco, 1997). As to attentional executive control, the third attentional sub-component, reaction times to identical external events have been shown to be affected by general task context, and to be much faster in highly predictive contexts than in

* Corresponding author. INSERM, U1028, CNRS UMR5292, Lyon Neuroscience Research Center, ImpAct Team, 16 avenue Doyen, Lépine, 69500, Bron, France.
** Corresponding author. INSERM U1028, CNRS UMR5292, Lyon Neuroscience Research Center, ImpAct Team, 16 avenue Doyen, Lépine, 69500, Bron, France.
E-mail addresses: amelie.reynaud@inserm.fr (A.J. Reynaud), fadila.hadj-bouziane@inserm.fr (F. Hadj-Bouziane).
[1] These authors equally contributed to this work.
[2] These authors equally contributed to this work.

https://doi.org/10.1016/j.neuropharm.2019.03.012
Received 4 December 2018; Received in revised form 11 February 2019; Accepted 7 March 2019
Available online 12 March 2019

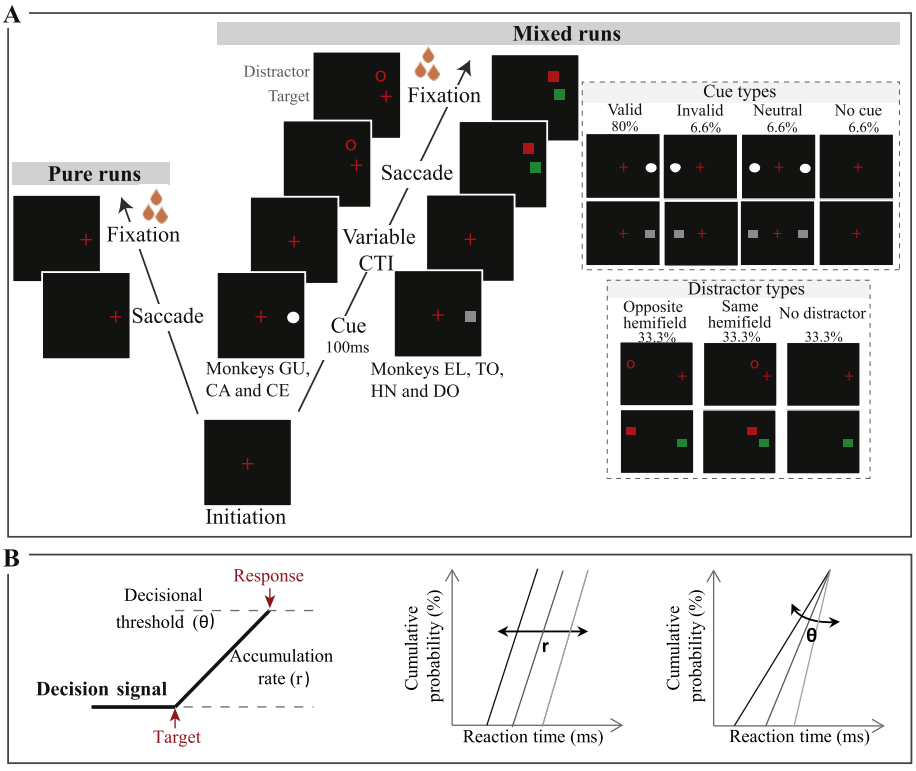

Fig. 1. Behavioral task and LATER model. A: In the mixed runs (spatial attention cued task), monkeys initiated the trial by fixating the red cross. Then, a cue was flashed and the monkey was required to keep his gaze on the red cross. The cue could either be valid, invalid, neutral or absent. After a cue-target interval (CTI), the target appeared on one side of the screen. Simultaneously, a distractor could appear in the same or opposite hemifield of the target location. The monkey had to ignore the distractor and saccade to the new target location to successfully complete the trial and receive a reward. The pure runs did not include any cue nor any distractor and monkey had to saccade to the target location to successfully complete the trial and receive a reward. **B:** According to the LATER model, RT is the culmination of a decisional signal which starts at the apparition of the target, rises in response with a constant linear rate (r) and ends with the initiation of a response at the decision threshold (θ) (left panel). Cumulative RT distributions are plotted as reciprobit plots, so that each distribution corresponds to a line. On this plot, the change of accumulation rate is embodied by a shift of the lines (middle panel) and the change of the decisional threshold by a swivel of the lines (right panel).

less predictive contexts (Los, 1996; Los et al., 2001; Albares et al., 2011; Wardak et al., 2012). While there is, to our knowledge, no direct evidence for an effect of NE onto this attentional sub-component, a recent study shows a selective increase in pupil size, an indirect index of NE activity, in the presence of highly predictive cues (Dragone et al., 2018). In addition, the involvement of the NE system in the ability to shift attentional set was reported in several studies (McGaughy et al., 2008; Newman et al., 2008; Cain et al., 2011; Berridge et al., 2012; Bradshaw et al., 2016). This, thus, suggests a possible interaction between NE and attentional executive control.

Here, we focused onto these three specific attentional components, namely alerting, spatial orienting and executive control and we aimed at 1) clarifying the components that are under the influence of NE availability and 2) characterizing the specific action of NE availability onto them.

We thus tested seven monkeys in a saccadic cued task derived from the attentional network task (Posner, 1980). This task allows manipulating the focus of attention by using cues that precede the appearance of the target. We used a context where the cue accurately predicted the spatial location of the upcoming target in 80% of the trials. A distractor could also appear simultaneously with the target to examine the subjects' ability to filter distractors out when planning their saccadic movement. We tested the monkeys under two pharmacological conditions: after saline administration used as the control condition and after atomoxetine (ATX) administration, a NE reuptake inhibitor.

To investigate whether alerting and orienting were affected by ATX, we computed attentional network scores from the reaction times (Fan et al., 2002). To identify changes driven by task context and executive control, we compared RTs in same type of trial in two different context. To investigate how these attentional processes were affected by ATX, we used the LATER model (linear approach to threshold with ergodic rate; Carpenter and Williams, 1995) to test whether changes in RT distributions following NE modulation were better accounted for by a change in signal accumulation rate, signing a perceptual process, or a change in decision threshold, signing a top-down process (Noorani and Carpenter, 2016). Following ATX injections, one could expect either 1) a global non-specific effect onto all three attentional components; 2) an effect specific to the alerting non-selective attentional component or 3) an effect specific to the dynamic/flexible components of attention, namely orienting and executive control. Our observations speak in favor of the last prediction.

2. Methods

2.1. Subjects

Seven rhesus monkeys (*Macaca mulatta*) aged 5–14 years participated to this study, three females (monkeys CA, GU and CE) and four males (monkeys EL, TO, HN and DO). Animals had free access to water (CE, CA and GU) or food (EL, TO, HN and DO) and were maintained on a food (CE, CA and GU) or water (EL, TO, HN and DO) regulation schedule, individually optimized to maintain stable motivation and performance. This study was conducted in strict accordance with Directive 2010/63/UE of the European Parliament and the Council of 22 September 2010 on the protection of animals used for scientific purposes and approved by the French Committee on the Ethics of Experiments in Animals (C2EA) CELYNE registered at the national level as C2EA number 42.

2.2. Experimental set-up

Monkeys were seated in a primate chair in a sphinx position, with the head immobilized via a surgically implanted plastic MRI-compatible head post (CE, TO, EL, HN, DO) or a non-invasive head restraint helmet (CA and GU) (Hadj-Bouziane et al., 2013), in front of a computer screen (distance: 57 cm for CE, CA and GU; 78 cm for EL, TO, HN and DO). Gaze location was sampled at 120 Hz using an infrared pupil tracking system (ISCAN Raw Eye Movement Data Acquisition Software) interfaced with a program for stimulus delivery and experimental control (Presentation®).

2.3. Behavioral task

A testing session consisted of alternations of two types of runs: mixed runs and pure runs. In both types of runs, monkeys were required to fixate a central cross to initiate the trial. Then, the target appeared randomly in the left or right side of the screen (10 degrees of eccentricity), and monkeys had to saccade as fast as possible to the target location and hold fixation during 300 ms (EL, TO, HN and DO) or 500 ms (GU, CA and CE) to receive a reward (fruit juice or water). In the mixed runs, derived from the attentional network task (Posner, 1980), several conditions were intermixed, while in the pure runs, only one condition was presented to the animals. For 4 monkeys (EL, TO, HN and DO), the color of the central cross changed across the type of runs (red or yellow cross for mixed and pure runs, respectively).

In the mixed runs (Fig. 1A), for 80% of the trials, a peripheral cue, a white dot or a grey square, was flashed for 100 ms prior to the target onset on one side of the screen, accurately predicting the upcoming target location ('*valid* cue'). In the remaining 20% of the trials, the cue was either absent ('*no* cue'), or presented on the opposite side of target location ('*invalid* cue'), or two cues were simultaneously presented ('*neutral* cue'). In addition, a distractor, a red circle or a red square, could appear simultaneously with the target onset, either in the same or in the opposite hemifield as the target (distance target-distractor: 4.5° for GU, CA and CE and between 2.1° and 3.2° for EL, TO, HN and DO). The '*no distractor*', '*same hemifield*' and '*opposite hemifield*' conditions were intermixed and equally distributed across trials. Monkeys were required to fixate the target and ignore the distractor. In the majority of the animals (except CE), the cue-target interval (CTI) varied across trials to prevent anticipatory responses. CTIs were optimized for each monkey in order to maximize cue validity/invalidity effects, which were key in quantifying the attention orientation effects (200-300-400 ms for GU and CA, 100 ms for CE, 150-200-250 ms for EL and TO, 200-250-300 ms for HN, 140-180-240 ms for DO). The pure runs did not include any cue nor any distractor. These runs served to quantify the effect of NE on task context by comparing RTs on these trials to the same trials performed in the mixed runs (i.e. taking place in a context in which cued trials were most frequent). The mixed runs included ~90 trials for monkeys CE, CA, GU, ~150 trials for monkeys EL, TO, ~300 trials for monkey HN and ~400 trials for monkey DO. Pure runs included ~20 trials for monkeys CA, GU, ~50 trials for monkeys EL, TO, ~100 trials for monkey HN and ~150 trials for monkey DO. Note that only mixed runs were presented to monkey CE.

The overall structure of the task was similar for all animals. Only the physical characteristics of the stimuli (cues, target and distractors) and the timings varied across animals depending on their previous experience with the task and their overt behavior (Fig. 1A).

2.4. Drug administration

Once the animals reached stable performance and were accustomed to intramuscular injections, atomoxetine (ATX, Tocris Bioscience, Ellisville, MO) and saline (control) administration sessions began. As shown in previous studies (Bymaster et al., 2002; Koda et al., 2010), ATX is a potent NE reuptake inhibitor. In prefrontal cortex of mice, injection of 1 mg/kg of ATX induced a significant increase of the extracellular levels of NE and DA. Yet, the concentration of NE was 4 times larger than that of DA. Based on previous studies conducted in monkeys (in particular Gamo et al. 2010,) we chose the smallest efficient doses that corresponded to the recommended doses by the U.S. Food and Drug Administration in children with attention deficits (0.5–1.2 mg/kg). Each experiment started with one or two weeks of saline administration, followed by 3–4 weeks of testing with different doses of ATX: 0,1 mg/kg, 0,5 mg/kg, 1 mg/kg and 1,5 mg/kg. For a given week, the same dose of ATX was administered every day to the animals. Note that the dose of 1,5 mg/kg was tested only in the two younger monkeys (GU and CA). ATX or saline was administered intramuscularly 30 min prior to testing (Gamo et al., 2010). In total, for each animal, we collected 4 to 6 sessions with each dose of ATX and 1 to 5 sessions of saline condition.

2.5. Data analysis

The data were analyzed separately for each monkey. Eye movements were visually inspected with a customized toolbox implemented in MATLAB.

2.5.1. Pupil diameter

We computed the averaged normalized pupil diameter, in the trial initiation period (500 ms before the cue onset), for each animal and each pharmacological condition. In each trial, the mean pupil diameter across this 500 ms window was divided by the root mean square separately for each animal. These measures were compared across runs and pharmacological conditions.

2.5.2. Number of trials

We examined the number of initiated trials (i.e. Fig. 1A: completion of the first step: initiation) and the number of correct trials. A trial was considered correct after the animal reached and fixated the correct target location within the imparted time (270 ms for DO, 300 ms for EL and HN, 350 ms for TO or 500 ms for CA, GU and CE). Incorrect trials corresponded to either incomplete trials, anticipations (RT $<$ 80 ms), saccades with artifacts related to blink or trials where saccades were made to the wrong target location or to the distractor location.

2.5.3. Reaction times (RTs)

2.5.3.1. Attentional scores in mixed runs. To assess the effect of cues and distractors on RTs in mixed runs, we computed four scores derived from the attentional network scores (Fan et al., 2002) and integrating the effect of distractors (Walker and Benson, 2013): alerting score, orienting score, remote distractor score and proximal distractor score. Given that these different conditions were randomly presented within runs, these scores were calculated for each run. Runs where the number of trials per cue type was under-represented (i.e. less than 3 trials) were excluded.

$$Orienting\ score\ = \frac{RT_{valid} - median\ RT_{invalid}}{|median\ RT_{invalid}|} \times 100$$

$$Alerting\ score\ = \frac{RT_{neutral} - median\ RT_{nocue}}{|median\ RT_{nocue}|} \times 100$$

$$Remote\ distractor\ score\ = \frac{RT\ different\ hemifield - median\ RT_{no\ distractor}}{|median\ RT\ no\ distractor|} \times 100$$

$$Proximal\ distractor\ score\ = \frac{RT_{same\ hemifield} - median\ RT_{no\ distractor}}{|median\ RT_{no\ distractor}|} \times 100$$

2.5.3.2. RT distributions in mixed runs. We used the LATER model (linear Approach to Threshold with Ergodic Rate) to examine changes in RT distribution for each attentional process (Noorani and Carpenter, 2016). This model proposes that RT is the culmination of a decisional process which starts at the onset of the target, rises in response with a constant linear rate (r) and ends with the initiation of a response at the decision threshold (θ) (Fig. 1B left panel). According to this model, a change in RT distribution can be explained by a change in the accumulation rate or in the decision threshold. Cumulative RT distributions are plotted as reciprobit plots, so that each distribution corresponds to a line. On this plot, the change of accumulation rate is embodied by a shift of the lines and the change of the decision threshold by a swivel between them (Fig. 1B right panel). To characterize how RT distribution was affected by trial type (i.e. to characterize a given attentional process or NE effect), we calculated the log likelihood ratio that the difference between one RT distribution and

the other is accounted for by a shift or by a swivel. A negative log likelihood ratio represents a change in accumulation rate between the two distributions (i.e. a shift) and a positive log likelihood ratio represents a change in decisional threshold (i.e. a swivel).

2.5.3.3. Non-cued trials in pure versus mixed runs. We compared RTs of correct trials in non-cued trials presented in the pure and in the mixed runs. We also used the LATER model to examine the changes in RT distribution between the types of runs.

2.6. Statistical analysis

First, we used one-sample *t*-test to determine whether the changes in the attentional scores differed significantly from 0 in the saline condition, i.e. to determine the influence of the different cues and distractors condition in the saline condition. Then, we used linear mixed models (using the 'lme4' package for R, Bates et al., 2014) to examine the effect of ATX on the different variables computed above, for each monkey. As a first step, we defined a model containing the most appropriate random effects (i.e. factors of non-interest). Random effects were thus introduced sequentially, and their effect on model fit was assessed through Likelihood Ratio Tests (LRT): residuals of each model were compared, and the one with significantly lower deviance as assessed by a chi-squared test was chosen (Table 1). We then tested the effect of pharmacological condition as fixed factor to evaluate the effect of ATX on pupil diameter, number of initiated and correct trials and the different attentional scores. To evaluate the effect of ATX on RTs in the different cue conditions, we tested the effect of pharmacological condition and cue condition as fixed factors. Finally, post-hoc comparisons were carried out using pairwise comparisons through the 'lsmeans' package for R (p-adjusted with false discovery rate method, Lenth, 2016) to assess the effect of the different doses of ATX (and the different cue conditions when assessing their effects on RTs).

In order to assess the relationship between the effect of ATX on pupil diameter (mean normalized pupil diameter) and on the different attentional scores, we computed the difference in pupil diameter and in attentional scores between saline and ATX conditions (for highest dose of ATX, i.e. 1.0 mg/kg for monkeys CE, EL, TO, HN, DO and 1.5 mg/kg for monkeys GU and CA). We then tested the relationship between these two variables using a Spearman's correlation test.

To determine whether a particular strategy was used between the different conditions (different cue conditions, distractor conditions or types of runs), LATER model log likelihood ratio tests were performed for each subject. To evaluate the effect of ATX on the strategy, we performed a wilcoxon non-parametric paired test on the group of subjects.

3. Results

In the results section below, the ATX dose-response curves are provided for pupil diameter (Fig. 2) and attentional orienting effect (Fig. 3). Other results are detailed for the highest, and most effective, dose of ATX (1.0 mg/kg for monkeys CE, EL, TO, HN, DO and 1.5 mg/kg for monkeys GU and CA).

3.1. Effect of ATX in the mixed runs

3.1.1. ATX effect on pupil size (Fig. 2)

We found a significant main effect of pharmacological condition on pupil diameter in all monkeys ($\chi^2_{(4)} = 12675$, $p < 0.001$ for GU; $\chi^2_{(4)} = 10196$, $p < 0.001$ for CA; $\chi^2_{(3)} = 9231.8$, $p < 0.001$ for CE; $\chi^2_{(3)} = 14905$, $p < 0.001$ for EL; $\chi^2_{(3)} = 2838$, $p < 0.001$ for TO; $\chi^2_{(3)} = 47527$, $p < 0.001$ for HN; $\chi^2_{(3)} = 18776$, $p < 0.001$ for DO). For all monkeys except DO, the highest dose of ATX increased the pupil diameter compared to the saline condition ($|z| = -94.3$, $p < 0.001$ for GU, $|z| = -71.6$, $p < 0.001$ for CA, $|z| = -60.7$, $p < 0.001$ for CE,

Table 1
Linear mixed models in statistical analysis. For each variable, we defined a model containing the most appropriate random effects (i.e. factors of non-interest) and we tested the effect of fixed factor (i.e. factor of interest). Random effects were sequentially introduced, and their effect on model fit was assessed through Likelihood Ratio Tests (see methods).

	Variables	Family of linear mixed model	Random factors	Fixed factors
Mixed run	Pupil diameter	Gaussian	Runs nested in sessions	Pharmacological condition
	Number of initiated trials	Binomial	Runs nested in sessions	Pharmacological condition
	Number of correct trials	Binomial	CTI; Target position; Cue condition; Distractor condition; Runs nested in sessions	Pharmacological condition
	RTs	Gaussian	Target position; Cue condition; Distractor condition; Runs nested in sessions	Pharmacological condition; Cue condition
	Alerting score	Gaussian	CTI; Target position; Distractor condition; Runs nested in sessions	Pharmacological condition
	Orienting score	Gaussian	CTI; Target position; Distractor condition; Runs nested in sessions	Pharmacological condition
	Remote distractor score	Gaussian	CTI; Target position; Cue condition; Runs nested in sessions	Pharmacological condition
	Proximal distractor score	Gaussian	CTI; Target position; Cue condition; Runs nested in sessions	Pharmacological condition
Pure run	Number of initiated trials	Binomial	Runs nested in sessions	Pharmacological condition
	Number of correct trials	Binomial	Target position; Runs nested in sessions	Pharmacological condition
	RTs	Gaussian	Target position; Runs nested in sessions	Pharmacological condition

Table 2

Attentional scores in mixed runs for the highest dose of ATX (1.0 mg/kg for CE, EL, TO, HN, DO and 1.5 mg/kg for GU and CA). *p-values reflects pairwise comparisons between the saline and the highest dose of ATX with corrections for multiple comparisons. *: significant effect in the saline condition (p < 0.05). ↗ or ↘: significant increase or decrease, respectively, after ATX administration. -: no difference between saline and ATX conditions.* Overall, ATX modulates all attentional scores but the most consistent effect was found for the orienting score.

Monkeys	Alerting score				Orienting score				Remote distractor score				Proximal distractor score			
	Saline	ATX	p value	ATX effect	saline	ATX	p value	ATX effect	saline	ATX	p value	ATX effect	saline	ATX	p value	ATX effect
GU	−4.2	−2.7	–	–	−6.2*	6.6	< 0.001	↗	−12.7*	−11.4	0.17	–	3.18*	1.8	–	–
CA	−3.4	−4.5	–	–	−4.5*	3	< 0.001	↗	−7.5*	−5.5	0.04	↘	1	−0.4	–	–
CE	6.4*	14	0.05	–	3.3*	8.9	< 0.001	↗	−3.1*	−8.4	< 0.001	↗	15.8*	12.6	< 0.001	↘
EL	19.1*	24.7	0.003	↗	31.7*	34.8	< 0.001	↗	−16.5*	−22.9	< 0.001	↗	−4.7*	−14.1	< 0.001	↗
TO	5.5*	2.9	0.007	↘	4.3*	6.7	0.015	↗	−2.3*	−1.4	–	–	2.4*	3.4	–	–
HN	24.7*	28.5	0.21	–	38.2*	40.3	< 0.001	↗	−14.7*	−14.3	–	–	−10.3*	−13.2	0.005	↗
DO	27.5*	23.2	0.02	↘	9.9*	−0.3	< 0.001	↘	−4.5*	−3.4	0.56	–	−2.9*	−3	0.79	–

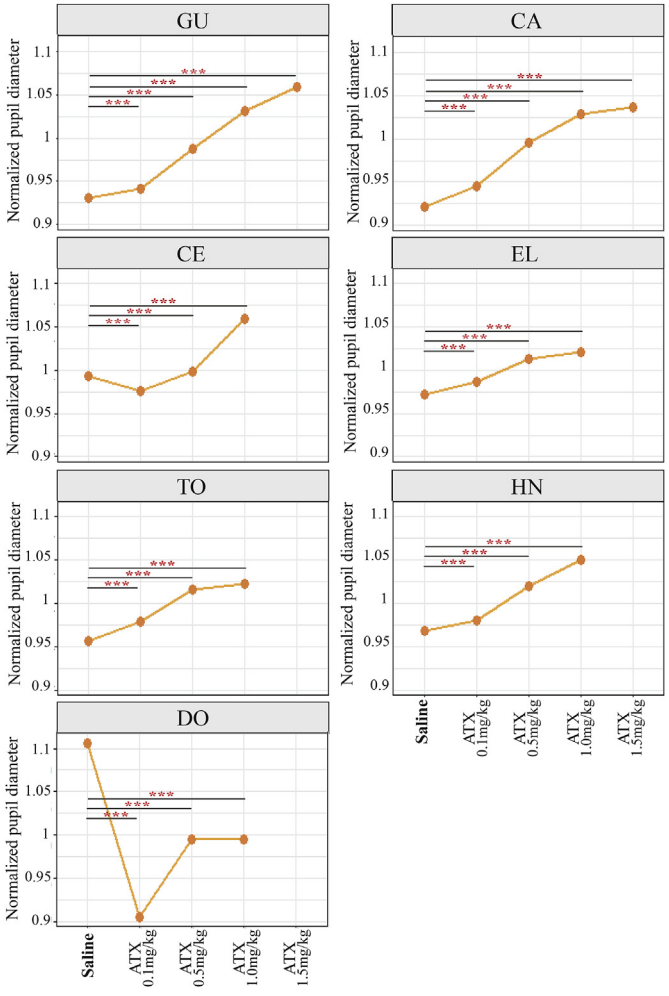

Fig. 2. ATX effect on pupil size. For each animal and each pharmacological condition, we computed normalized averaged pupil diameter (mean ± s.e) during the initiation period (fixation cross). ATX significantly increased pupil diameter as a function of the dose, in most of the monkeys, during the initiation period. ***:*p-value < 0.001.*

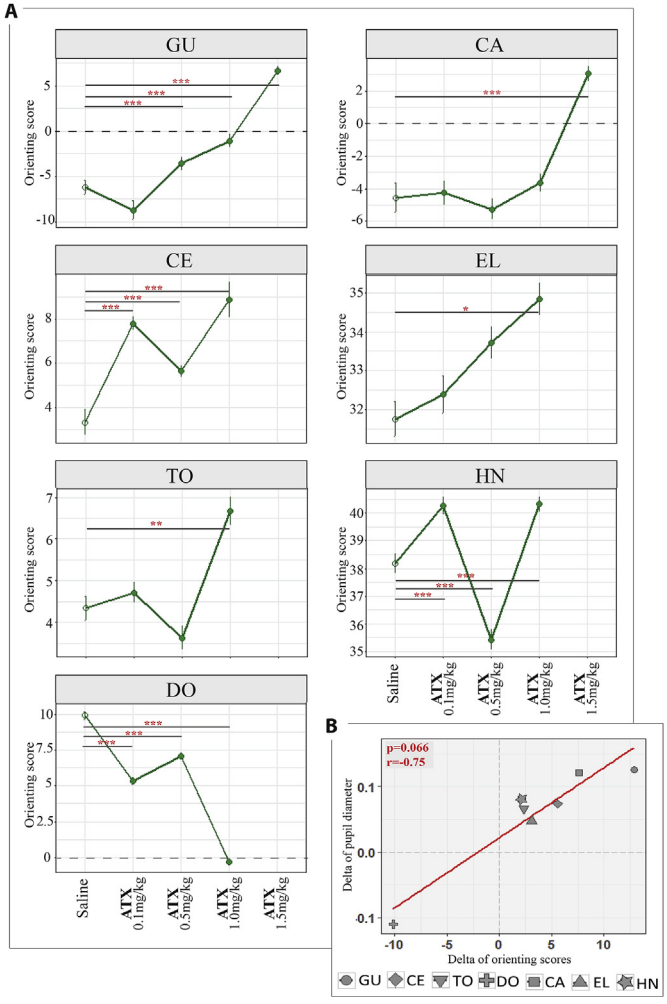

Fig. 3. ATX effect on attentional orienting. A: For each animal and each pharmacological condition, we computed the normalized averaged orienting scores across runs in the different pharmacological conditions (mean ± s.e). Our results show that ATX enhanced the orienting score in most monkeys. *:*p-value < 0.05; **:p-value < 0.01; ***:p-value < 0.001.* **B**: For each animal, we computed the effect of ATX on pupil diameter and on the orienting score as the difference between saline and ATX conditions (highest dose of ATX, i.e. 1.0 mg/kg for monkeys CE, EL, TO, HN, DO and 1.5 mg/kg for monkeys GU and CA). Our results show that ATX-mediated changes in pupil diameter tended to be correlated with changes in attentional orienting scores.

|z| = -107, p < 0.001 for EL, |z| = -146.4, p = 0.015 for TO, |z| = -182.5, p < 0.001 for HN). For DO, the highest dose of ATX (1.0 mg/kg) significantly decreased the pupil diameter compared to the saline condition (|z| = 76.8, p < 0.001).

3.1.2. ATX effect on attentional scores (Table 2)

As predicted (Posner, 1980), in the saline condition, 5 out of 7 monkeys exhibited a significant alerting effect, i.e. shorter RTs in neutral trials compared to non-cued trials, and a significant orienting effect, i.e. shorter RTs in valid trials compared to invalid trials (*alerting effect*: $t_{(808)} = 5.6$, p = 0.002 for CE, $t_{(155)} = 12.3$, p < 0.001 for EL,

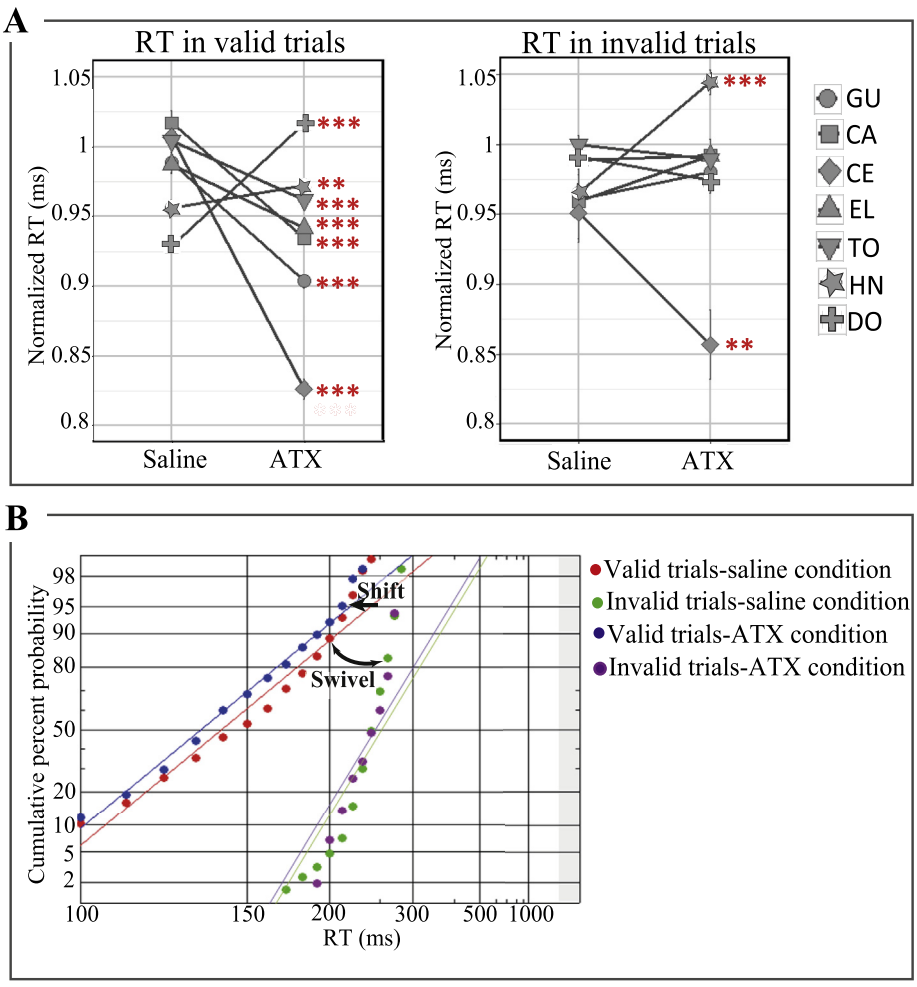

Fig. 4. ATX effect on RTs in valid and invalid trials for the highest dose of ATX (1.0 mg/kg for CE, EL, TO, HN, DO and 1.5 mg/kg for GU and CA)**. A:** For each animal and each pharmacological condition, we computed the normalized RTs in valid (left panel) and invalid (right panel) trials across runs (mean ± s.e) by dividing RTs by the root mean square separately for each type of trial (valid and invalid) and each monkey. **B:** Example of reciprobit plot in valid and invalid trials in the saline and ATX conditions for monkey EL. ***:p-value < 0.01; ***:p-value < 0.001*.

$t^{(179)} = 8.5$, $p < 0.001$ for TO, $t_{(173)} = 20.7$, $p < 0.001$ for HN, $t_{(380)} = 33.5$, $p < 0.001$ for DO - *orienting effect*: $t_{(808)} = 5.6$, $p < 0.001$ for CE, $t_{(1363)} = 71.8$, $p < 0.001$ for EL, $t_{(1693)} = 15.2$, $p < 0.001$ for TO, $t_{(1999)} = 103.9$, $p < 0.001$ for HN, $t_{(4850)} = 36.8$, $p < 0.001$ for DO). For all monkeys, the remote distractor led to longer RTs ($t_{(290)} = -10.9$, $p < 0.001$ for GU, $t_{(205)} = -5.9$, $p < 0.001$ for CA, $t_{(331)} = -4.3$, $p < 0.001$ for CE, $t_{(432)} = -13$, $p < 0.001$ for EL, $t_{(557)} = -4.8$, $p < 0.001$ for TO, $t_{(596)} = -11.2$, $p < 0.001$ for HN, $t_{(1426)} = -7.8$, $p < 0.001$ for DO) whereas the proximal distractor had different effects depending on monkeys. The proximal distractor either reduced RTs ($t_{(291)} = 3.8$, $p < 0.001$ for GU, $t_{(342)} = 24.2$, $p < 0.001$ for CE, $t_{(558)} = 5.1$, $p < 0.001$ for TO) or increased RTs ($t_{(523)} = -4.7$, $p < 0.001$ for EL, $t_{(652)} = -8.1$, $p < 0.001$ for HN, $t_{(1502)} = -5.3$, $p < 0.001$ for DO).

ATX differentially modulated these attentional scores. Table 2 summarizes the effect of the highest dose of ATX (1.0 mg/kg for monkeys CE, EL, TO, HN, DO and 1.5 mg/kg for monkeys GU and CA). Specifically, ATX more consistently affected the orienting process as compared to the alerting and distractor filtering processes (see also Fig. 3A). Indeed, ATX injection significantly modified the orienting scores in all monkeys ($\chi^2_{(4)} = 383.5$, $p < 0.001$ for GU, $\chi^2_{(4)} = 166.9$, $p < 0.001$ for CA, $\chi^2_{(3)} = 49$, $p < 0.001$ for CE, $\chi^2_{(3)} = 39.7$, $p < 0.001$ for EL, $\chi^2_{(3)} = 61.7$, $p < 0.001$ for TO, $\chi^2_{(3)} = 305.5$, $p < 0.001$ for HN, $\chi^2_{(3)} = 1771.1$, $p < 0.001$ for DO) regardless of the pattern observed in the saline condition. Post-hoc tests revealed that ATX enhanced the orienting effect in 6 out of 7 monkeys ($|z| = -14$, $p < 0.001$ for GU, $|z| = -8.1$, $p < 0.001$ for CA, $|z| = -3.8$, $p < 0.001$ for CE, $|z| = -3.4$, $p < 0.001$ for EL, $|z| = -2.5$, $p = 0.015$ for TO, $|z| = -2.1$, $p < 0.001$ for HN). The enhancement of the orienting effect increased as a function of the ATX dose in 5 out of 7 monkeys (Fig. 3A). One monkey (monkey DO) had a reversed modulation, the orienting effect decreasing as a function of the ATX dose ($|z| = 10.7$, $p < 0.001$). By comparison, our results showed that ATX either decreased or increased the alerting scores and the remote or proximal distractor scores depending on the animal. Moreover, as illustrated in Fig. 3B, the effect of ATX on pupil diameter tended to be correlated with the effect of ATX on attentional orienting ($p = 0.066$, $r = 0.75$) but not with the other attentional scores (alerting scores: $p = 0.66$, $r = 0.21$; remote distractor scores: $p = 0.26$, $r = 0.5$; proximal distractor scores: $p = 0.96$, $r = -0.3$).

3.1.3. ATX effect on attentional orienting

The most consistent effect of ATX on the attentional scores across animals was an improvement of the orienting effect, i.e. shorter RTs on valid than on invalid trials. To identify whether this was driven by a change in sensory accumulation or a change in decision threshold, we compared the response strategy, as assessed from RT distributions, in the saline and ATX conditions, using the LATER model. In the saline condition, in 3 out of the 5 animals exhibiting an orienting effect, this effect resulted from a lower decisional threshold in the valid compared

to the invalid trials (Log likelihood (LL): 2365.5, Log likelihood ratio (LLR): 65.950, $p < 0.001$ for EL, LL: 3294.1, LLR: 23.693, $p < 0.001$ for HN and LL: 6725.6, LLR: 15.692, $p < 0.001$, for DO). The two other monkeys did not exhibit any specific strategy. Under ATX, in all animals except monkey DO, the improvement of the orienting effect corresponded to a reinforcement of this decision threshold-based strategy in valid compared to invalid trials ($|z| = 2.201$, $p = 0.028$). For the one animal whose orienting score was significantly deteriorated under ATX (monkey DO), ATX induced the opposite effect, i.e. a switch in the strategy, from a change in the decisional threshold in the saline condition (LL: 6725.6, LLR: 15.692, $p < 0.001$) toward a change of the accumulation rate in the ATX condition (LL: 9508, LLR: −11.55, $p < 0.001$).

The enhancement of the orienting effect under ATX could result from faster RTs in both valid and invalid trials. Alternatively, it could be that ATX affects in only one type of trials. We thus examined the effect of ATX on the RTs in valid and invalid trials. All animals, with the exception of EL, exhibited a significant two-way interaction between pharmacological conditions (Saline and 3 or 4 doses of ATX) and cue type (Valid, Invalid, Neutral and No cue) ($\chi^2_{(8)} = 41.6$, $p < 0.001$ for GU, $\chi^2_{(8)} = 28.3$, $p < 0.001$ for CA, $\chi^2_{(9)} = 70.9$, $p < 0.001$ for CE, $\chi^2_{(6)} = 29.8$, $p < 0.001$ for TO, $\chi^2_{(6)} = 87.2$, $p < 0.001$ for HN, $\chi^2_{()} = 106.3$, $p < 0.001$ for DO, and $\chi^2_{(6)} = 7.9$, $p = 0.25$ for EL). As shown in Fig. 4A, for the majority of monkeys, this effect was driven by shorter RTs in the valid trials ($|z| = 11.2$, $p < 0.001$ for GU, $|z| = 9.6$, $p < 0.001$ for CA, $|z| = 21.8$, $p < 0.001$ for CE, $|z| = 8.3$, $p < 0.001$ for TO, $|z| = 6.5$, $p < 0.001$ for EL). RTs in the invalid trials were only marginally affected by ATX. The analysis of the RT distributions with the LATER model further demonstrated a faster accumulation rate for the valid trials in the ATX condition compared to the saline condition for 4 monkeys (LL: 4150.2, LLR: −3.246, p 0.039, for EL, LL: 15148, LLR: −3.763, $p < 0.023$ for DO, LL: 4777, LLR: −6.116, $p < 0.002$ for GU and LL: 5053, LLR: −5.299, $p < 0.005$ for CA, data not shown). For the invalid trials, ATX had no systematic impact on the RT distributions. This effect is exemplified in Fig. 4B for monkey EL. Overall, this indicates that the improvement of orienting induced by ATX injection is driven by faster accumulation rates following the presentation of a valid cue as compared to the saline condition.

3.2. Pure versus mixed runs: ATX enhances task context effects

3.2.1. ATX effect on number of trials

Table 3 summarizes the effect of the highest dose of ATX (1.0 mg/kg for monkeys CE, EL, TO, HN, DO and 1.5 mg/kg for monkeys GU and CA) on animals' performance in pure and mixed runs. For 3 out of 7 monkeys, ATX increased the number of initiated trials in both types of runs (mixed runs: $|z| = -15.4$, $p < 0.001$ for GU, $|z| = -17.6$, $p < 0.001$ for CA, $|z| = -2.7$, $p = 0.04$ for EL; pure runs: $|z| = -8.9$, $p < 0.001$ for GU, $|z| = -2.6$, $p = 0.02$ for CA, $|z| = -2.8$, $p = 0.01$ for EL). By contrast, it increased the number of correct trials in only one animal ($|z| = -4.3$, $p = 0.001$ for TO) in the pure runs compared to 5 in the mixed runs ($|z| = -3.5$, $p = 0.001$ for CA, $|z| = 0.4$, $p = 0.004$ for EL, $|z| = -7.8$, $p < 0.001$ for TO, $|z| = -5.6$, $p < 0.001$ for HN, $|z| = -10.5$, $p < 0.001$for DO). In other words, ATX equally increased the number of initiated trials in half of the animals in both mixed and pure runs while its effect on accuracy, measured as the number of correct trials, was more pronounced in the mixed runs as compared to the pure runs.

3.2.2. ATX effect on RTs

We then focused on RTs on the non-cued trials in the pure versus the mixed runs (Table 3, Fig. 5A). We found that ATX increased RTs in pure runs in the majority of monkeys ($|z| = -4.5$, $p < 0.001$ for EL, $|z| = -4.9$, $p < 0.001$ for TO, $|z| = -13.1$, $p < 0.001$ for HN, $|z| = -21.6$, $p < 0.001$for DO), whereas its effect was subtler in mixed runs where it increased RTs in only two animals ($|z| = -3.1$, $p = 0.01$ for EL, $|z| = -8.1$, $p < 0.001$ for DO). The analysis of the RT distributions with the LATER model further demonstrated a slower accumulation rate in the pure ATX runs compared to the pure saline runs for 3 monkeys (LL: 4561.2, LLR: −88.993, $p < 0.001$ for EL, LL: 15730.7, LLR: −9.599, $p < 0.001$ DO and LL: 10253, LLR: −3.412, $p < 0.033$ HN) as well as compared to the mixed ATX runs for 3 monkeys (LL: 4561.2, LLR: −88.993, $p < 0.001$ for EL, LL: 7404.9, LLR: −168.680, $p < 0.001$ for HN and LL: 11252.8, LLR: −12.273, $p < 0.001$ for DO). This effect is exemplified in Fig. 5B for monkey EL.

4. Discussion

We tested the impact of ATX, a NE reuptake inhibitor that increases NE availability in the brain, on visuo-spatial attention, in seven monkeys performing a predictive saccadic cued task. We report two new findings. First, we found that ATX differentially impacted the three attentional scores measured in the mixed runs, namely alerting, orienting and the distractor interference effects, most consistently improving the orienting process across the animals. Second, we found that the animals were slower to detect non-cued targets, specifically in pure runs, in the ATX compared to the saline condition. Our results suggest that the NE influences specific processes of visuo-spatial attention, and that this influence depends on the context.

4.1. Boosting NE transmission most consistently modulates attentional orienting in a predictive context

We assessed the impact of ATX on attentional processes in mixed runs. In these runs, the cue accurately predicted the upcoming target location in 80% of the trials rendering the context highly predictive. We found that ATX affected, though not equally, all attentional processes tested in the present work, namely alerting, orienting and the distractor interference effect. Specifically, ATX changed, in a dose-dependent manner, the orienting process in all animals; deterioration did occur (1/7 monkeys), but the typical effect was an improvement (6/7 monkeys). Difference in behavioral responses to ATX between individuals has been previously reported. Such difference could reflect genetic determinants differences, in particular in a NE transporter gene (Kim et al., 2006; Greene et al., 2009; Hart et al., 2012; Whelan et al., 2012), or could be due to variability in neuronal and synaptic properties in response to neuromodulators (Hamood and Marder, 2014). The ATX-dependent improvement of the orienting process resulted from faster RTs in the trials where the cue accurately predicted the location of the target (valid trials), i.e. the most prevalent trials in our task. This result is in line with two previous studies that reported that clonidine, which decreases NE transmission, attenuated the orienting process in humans (Coull et al., 2001; Clark et al., 1989) in a predictive context. In another study, Witte and Marrocco, (1997) failed to reveal such an effect using a task in which valid trials constituted 57% of the total trials, i.e. in a task, in which the spatial cues were much less predictive than in the present study or the Coull et al. (2001) and Clark et al. (1989) studies. As a result, in the absence of a highly predictive context, monkeys probably had to rely more heavily on stimulus-driven processes as opposed to both stimulus-driven and goal-directed processes elicited by informative peripheral cues (Chica et al., 2014). This suggests that the impact of NE modulating agents might depend on the predictability of the cue and in more general terms on the context. In line with this idea, a recent study reported larger diameter of the pupil, often considered as a proxy of the LC-NE activity, in highly predictive contexts (in which the cue accurately predicted the location of the upcoming target in 80% of the trials) as compared to none predictive contexts (50%, chance level, Dragone et al., 2018). Our results also show that ATX modulated pupil diameter in a dose-dependent manner as found by Larsen and Waters (2018). Interestingly, the effect of ATX on pupil diameter tended to be correlated with the improvement (or deterioration for monkey DO) in attentional orienting and not with the other attentional scores,

Table 3

Number of trials and RTs to non-cued targets in mixed and pure runs for the highest dose of ATX (1.0 mg/kg for CE, EL, TO, HN, DO and 1.5 mg/kg for GU and CA). *↗ or ↘: significant increase or decrease, respectively, after ATX administration. -: no difference between saline and ATX conditions. NA: not applicable, note that CE did not perform the pure run condition.* Overall, ATX tended to increase the number of initiated trials in both types of runs while it tended to improve accuracy only in mixed runs. In addition, ATX increased RTs in pure runs in the majority of monkeys whereas its effect on RTs was subtler in mixed runs.

Monkeys	**Number of initiated trials**							
	pure runs			**mixed runs**			**ATX Effect**	
	saline	**ATX**	**P values**	**saline**	**ATX**	**P values**	**pure runs**	**mixed runs**
GU	167	283	< 0.001	1067	1663	< 0.001	↗	↗
CA	122	381	0.01	813	1846	< 0.001	↗	↗
CE	*NA*	*NA*	*NA*	1113	*2240*	< 0.001	*NA*	↘
EL	1048	1528	0.01	3323	4225	0.04	↗	↗
TO	1095	1208	–	3531	4742	0.99	–	–
HN	1504	3058	< 0.001	3757	6435	–	↗	–
DO	3459	3898	–	8820	11678	< 0.001	–	–
Monkeys	**Number of correct trials**							
	pure runs			**mixed runs**			**ATX Effect**	
	saline	**ATX**	**P values**	**saline**	**ATX**	**P values**	**pure runs**	**mixed runs**
GU	166	278	0.45	1002	1514	0.31	–	–
CA	116	359	–	755	1781	0.001	–	↗
CE	*NA*	*NA*	*NA*	1070	1618	< 0.001	NA	↘
EL	710	697	< 0.001	1980	2283	0.004	↘	↗
TO	760	966	< 0.001	2271	3352	< 0.001	↗	↗
HN	1176	2054	< 0.001	2601	4697	< 0.001	↘	↗
DO	2917	3232	0.09	6418	8938	< 0.001	–	↗
Monkeys	**RT (ms) in no cued trials** (mean RT ± S.E.)							
	pure runs			**mixed runs**			**ATX Effect**	
	saline	**ATX**	**P values**	**saline**	**ATX**	**P values**	**pure runs**	**mixed runs**
GU	156 ± 1.4	158 ± 1.2	0.32	165.5 ± 2.9	163.1 ± 2	0.54	–	–
CA	201 ± 3.7	198 ± 1.7	0.36	203.7 ± 5.7	208.5 ± 3.1	–	–	–
CE	*NA*	*NA*	NA	231.2 ± 4.5	212.8 ± 5.5	0.06	*NA*	–
EL	226.2 ± 1.2	245.8 ± 1.1	< 0.001	231.5 ± 2.3	240.7 ± 1.3	0.01	↗	↗
TO	243.2 ± 1.2	244.4 ± 1	< 0.001	261.1 ± 2.4	259.9 ± 2	–	↗	–
HN	225.1 ± 1.3	244.2 ± 1	< 0.001	245.9 ± 1.9	246 ± 1.5	–	↗	–
DO	217.9 ± 0.4	231.6 ± 0.4	< 0.001	227.6 ± 1	236.6 ± 0.7	< 0.001	↗	↗

which suggest a link between pupil size and attentional orienting. This result nicely fits with previous reports revealing a link between pupil diameter and cognitive load or attentional performance (Murphy et al., 2014; Brink et al., 2016; Irons et al., 2017). All these results suggest that the impact of a boost in NE availability on visuo-spatial attention can be predicted from the pupil size and might depend on the level of prediction provided by the context. This effect might be more pronounced when attentional orienting involves highly informative and reliable cues.

In addition, our results show a different effect of ATX in pure *versus* mixed runs, the former being devoid of spatial cues and distractors as opposed to the latter one. First, ATX more consistently affected the rate of success (i.e. number of correct trials) across animals in the mixed runs compared to the pure runs. Second, when focusing on the non-cued trials in both types of runs, it appears that ATX more consistently increased RTs for these trials in pure runs while it only marginally affected RTs for these particular trials in mixed runs. In our experimental design, the monkeys performed about 3 times more mixed runs trials compared to pure runs trials. It is thus possible that the impact of ATX on performance was biased toward the most prevalent type of runs (i.e. mixed runs) and more specifically toward the most prevalent type of trials (i.e. valid trials that represented 80% of the trials, with a spatial cue accurately predicting the location of the target). At the time of testing, all the animals had extensive experience with the task and the alternations between the pure and mixed runs. We thus suggest that the difference of ATX effect on pure *versus* mixed runs might be interpreted in terms of a trade-off in performance that depended on the context. This finding is in line with the idea that the LC-NE system facilitates the mobilization of sensory and attentional resources to process information of the environment (Varazzani et al., 2015) and to provide behavioral flexibility, notably in the ability to shift attentional set (Lapiz and Morilak, 2006; McGaughy et al., 2008; Newman et al., 2008; Seu et al., 2009; Cain et al., 2011; Bradshaw et al., 2016). NE-dependent improvement in performance has been reported in other tasks involving working memory (Gamo et al., 2010), cognitive control (Faraone et al., 2005), sustained attention (Berridge et al., 2012) or sensory discrimination (Gelbard-sagiv et al., 2018). Our results further suggest that, beyond a global adjustment of the behavior to the context, ATX

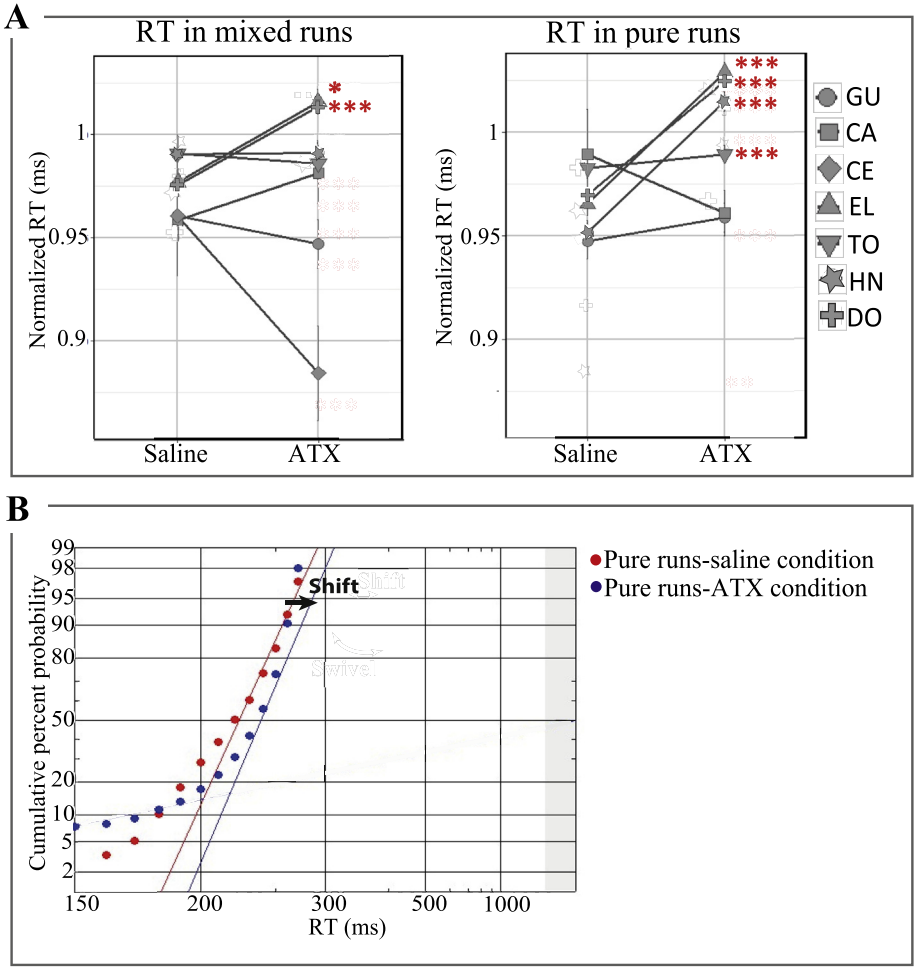

Fig. 5. ATX effect on RTs in non-cued trials in mixed and pure runs for the highest dose of ATX (1.0 mg/kg for CE, EL, TO, HN, DO and 1.5 mg/kg for GU and CA). **A:** For each animal and each pharmacological condition, we computed the normalized RTs in non-cued trials in mixed (left panel) and pure (right panel) runs across runs (mean ± s.e) by dividing RTs by the root mean square separately for each type of runs (pure and mixed) and each monkey. B: Example of reciprobit plot in non-cued trials in mixed and pure runs in the saline and ATX conditions for monkey EL. **:p-value < 0.05; ***:p-value < 0.001.*

fine-tunes the behavior at the level of the trial to maximize reward rate, leading to a trade-off in the infrequent trials (Aston-Jones and Cohen, 2005; Bouret and Sara, 2005; Corbetta et al., 2008; Fazlali et al., 2016).

Thus, to answer our first question as to which components of visuo-spatial attention are under the influence of NE availability, our results points towards a specific effect onto the dynamic and flexible components of attention, namely spatial orienting and executive control when the context is highly predictive. Note that the effect of ATX, at the highest dose used in the present study, might have also influenced the dopamine transmission in the brain and in particular in the prefrontal cortex (Bymaster et al., 2002; Upadhyaya et al., 2013). At this stage, one cannot rule out this possibility and future studies should tackle this difficult challenge to tease apart the specificity of each of these two major neuromodulators onto attentional processes.

4.2. ATX-boosting effect on spatial orienting reflects changes on both sensory accumulation rate and decision threshold

The detection of a target involves both a perceptual process that can be modelled by an accumulation of information, and a decision-making step more related to top-down processes, that can be modelled by the application of a decision threshold (Noorani and Carpenter, 2016). Thus, in addition to measuring the impact of ATX on attentional scores using median reaction times, we also sought to identify ATX-driven variations in accumulation rate and decision threshold by comparing RT distributions using LATER model statistics. First, the LATER model revealed that the adaptation to the context observed under ATX condition, highlighted by a specific improvement of attentional orienting, is explained by a lower decisional threshold in ATX condition compared to saline condition. Second, we found a faster accumulation rate specifically for the trials in which the target was preceded by a predictive spatial cue (validly cued trials) under ATX with respect to saline. In other words, under high NE availability, monkeys both accumulated the available sensory evidence faster and needed less sensory information to take their decision to saccade toward the target, specifically in the prevalent valid trials. On the contrary, we observed a slower accumulation rate in the ATX condition compared to the saline condition in the pure runs. This finding is in line with an increasing number of studies showing that NE influences bottom-up processes, even at very early-stages of sensory signal processing improving the signal-noise ratio in sensory cortex in response to incoming stimuli, to shape the behavior according to the environment (see Navarra and Waterhouse, 2018; Waterhouse and Navarra, 2018). For example, it has been shown that following a systemic injection of ATX, neuronal responses to light stimuli was enhanced in dorsal lateral geniculate nucleus (i.e. the primary sensory relay for visual information from the retina to the visual cortex) in anesthetized rats (Navarra et al., 2013). A recent study showed that manipulating the NE level in humans modulates the perceptual sensitivity to detect a visual target and this effect reflected changes in evoked potentials and fMRI signals in visual cortex (Gelbard-sagiv

et al., 2018). At rest, ATX was also found to reduce the functional correlation strength within sensory networks and to modify the functional connectivity between the LC and the fronto-parietal attention network (Guedj et al., 2016, 2017), involved in visuo-spatial orienting (Corbetta et al., 2008).

Thus, to get to our second aim that was to characterize the action of NE availability onto the visuo-spatial components, our results points toward two complementary actions of NE, on both bottom-up and top-down processes. Our results bring new evidence to the role of NE on attentional processes. We highlight, in particular, the impact of the context on its effect on attentional processes. We also pinpoint its complex mechanism of action on spatial attention, exerted at different levels, likely reflecting changes within sensory cortex leading to faster accumulation rate to incoming stimuli as well as the adjustment of the decisional threshold via an action of NE within prefrontal regions (Robbins and Arnsten, 2009; Arnsten, 2011; Arnsten and Pliszka, 2011).

Conflict of Interest

The authors declare no competing financial interests.

Acknowledgements

We thank Gislène Gardechaux, Frédéric Volland, Roméo Salemme, Eric Koun, Jean-Luc Charieau, Fidji Francioly and Serge Pinède for technical and engineering assistance and Elvio Blini for his help with the linear mixed models. This work was funded by the French National Research Agency (ANR) ANR-14-CE13-0005-1 grant. It was also supported by the NEURODIS Foundation and the James S. McDonnell Scholar award. It was performed within the framework of the LABEX CORTEX (ANR-11-LABX-0042) of Lyon University within the program “Investissements d’Avenir” (ANR-11-IDEX-0007) operated by the ANR.

References

Albares, M., Criaud, M., Wardak, C., Nguyen, S.C.T., Ben Hamed, S., Boulinguez, P., 2011. Attention to baseline: does orienting visuospatial attention really facilitate target detection? J. Neurophysiol. 106.

Arnsten, A.F.T., 2011. Catecholamine influences on dorsolateral prefrontal cortical networks. Biol. Psychiatry 69, e89–e99.

Arnsten, A.F.T., Pliszka, S.R., 2011. Catecholamine influences on prefrontal cortical function: relevance to treatment of attention deficit/hyperactivity disorder and related disorders. Pharmacol. Biochem. Behav. 99, 211–216.

Aston-Jones, G., Cohen, J.D., 2005. An integrative theory of locus coeruleus-norepinephrine function: adaptive gain and optimal performance. Annu. Rev. Neurosci. 28, 403–450.

Bates, D., Mächler, M., Bolker, B., Walker, S., 2014. Fitting Linear Mixed-Effects Models using lme4.ArXiv14065823 Stat.

Berridge, C.W., Shumsky, J.S., Andrzejewski, M.E., McGaughy, J.A., Spencer, R.C., Devilbiss, D.M., Waterhouse, B.D., 2012. Differential sensitivity to psychostimulants across prefrontal cognitive tasks: differential involvement of noradrenergic α_1 - and α_2-receptors. Biol. Psychiatry 71, 467–473.

Bouret, S., Sara, S.J., 2005. Network reset: a simplified overarching theory of locus coeruleus noradrenaline function. Trends Neurosci. 28, 574–582.

Bradshaw, S.E., Agster, K.L., Waterhouse, B.D., Mcgaughy, J.A., 2016. Age-related changes in prefrontal norepinephrine transporter density: the basis for improved cognitive flexibility after low doses of atomoxetine in adolescent rats. Brain Res. 1641, 245–257.

Brink, RL Van Den, Murphy, P.R., Nieuwenhuis, S., 2016. Pupil Diameter Tracks Lapses of Attention 1–16.

Bymaster, F.P., Katner, J.S., Nelson, D.L., Hemrick-Luecke, S.K., Threlkeld, P.G., Heiligenstein, J.H., Morin, S.M., Gehlert, D.R., Perry, K.W., 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.

Cain, R.E., Wasserman, M.C., Waterhouse, B.D., McGaughy, J.A., 2011. Atomoxetine facilitates attentional set shifting in adolescent rats. Dev Cogn Neurosci 1, 552–559.

Carpenter, R.H., Williams, M.L., 1995. Neural computation of log likelihood in control of saccadic eye movements. Nature 377, 59–62.

Chica, A.B., Martín-Arévalo, E., Botta, F., Lupiáñez, J., 2014. The Spatial Orienting paradigm: how to design and interpret spatial attention experiments. Neurosci. Biobehav. Rev. 40, 35–51.

Clark, C.R., Geffen, G.M., Geffen, L.B., 1989. Catecholamines and the covert orientation of attention in humans. Neuropsychologia 27, 131–139.

Corbetta, M., Patel, G., Shulman, G.L., 2008. The reorienting system of the human brain: from environment to theory of mind. Neuron 58, 306–324.

Coull, J.T., Nobre, A.C., Frith, C.D., 2001. The noradrenergic 2 agonist clonidine modulates behavioural and neuroanatomical correlates of human attentional orienting and alerting. Cerebr. Cortex 11, 73–84.

Dragone, A., Lasaponara, S., Pinto, M., Rotondaro, F., Luca, M De, Doricchi, F., 2018. Expectancy modulates pupil size during endogenous orienting of spatial attention. Cortex 102, 57–66.

Fan, J., McCandliss, B.D., Sommer, T., Raz, A., Posner, M.I., 2002. Testing the efficiency and independence of attentional networks. J. Cogn. Neurosci. 14, 340–347.

Faraone, S.V., Biederman, J., Spencer, T., Michelson, D., Adler, L., Reimherr, F., Seidman, L., 2005. Atomoxetine and stroop task performance in adult attention-deficit/hyperactivity disorder. J. Child Adolesc. Psychopharmacol. 15, 664–670.

Fazlali, Z., Ranjbar-Slamloo, Y., Adibi, M., Arabzadeh, E., 2016. Correlation between cortical state and locus coeruleus activity: implications for sensory coding in rat barrel cortex. Front. Neural Circuits 10, 14.

Gamo, N.J., Wang, M., Arnsten, A.F.T., 2010. Methylphenidate and atomoxetine enhance prefrontal function through α2-adrenergic and dopamine D1 receptors. J. Am. Acad. Child Adolesc. Psychiatry 49, 1011–1023.

Gelbard-sagiv, H., Magidov, E., Gelbard-sagiv, H., Magidov, E., Sharon, H., Hendler, T., Nir, Y., 2018. Noradrenaline modulates visual perception and late article noradrenaline modulates visual perception and late visually evoked activity. Curr. Biol. 28, 2239–2249 e5.

Greene, C.M., Bellgrove, M.A., Gill, M., Robertson, I.H., 2009. Noradrenergic genotype predicts lapses in sustained attention. Neuropsychologia 47, 591–594.

Guedj, C., Meunier, D., Meunier, M., Hadj-Bouziane, F., 2017. Could LC-NE-dependent adjustment of neural gain drive functional brain network reorganization? Neural Plast. 2017, 4328015.

Guedj, C., Monfardini, E., Reynaud, A.J., Farnè, A., Meunier, M., Hadj-Bouziane, F., 2017. Boosting norepinephrine transmission triggers flexible reconfiguration of brain networks at rest. Cerebr. Cortex 27 (10), 4691–4700.

Hadj-Bouziane, F., Monfardini, E., Guedj, C., Gardechaux, G., Hynaux, C., Farnè, A., Meunier, M., 2014. The helmet head restraint system: a viable solution for resting state fMRI in awake monkeys. Neuroimage 86, 536–543.

Hamood, A.W., Marder, E., 2014. Animal-to-Animal variability in neuromodulation and circuit function. Cold Spring Harbor Symp. Quant. Biol. 79, 21–28.

Hart, A.B., de Wit, H., Palmer, A.A., 2012. Genetic factors modulating the response to stimulant drugs in humans. Curr Top Behav Neurosci 12, 537–577.

Irons, J.L., Jeon, M., Leber, A.B., 2017. Pre-stimulus pupil dilation and the preparatory control of attention. PLoS One 12, 1–21.

Kim, C.-H., Hahn, M.K., Joung, Y., Anderson, S.L., Steele, A.H., Mazei-Robinson, M.S., Gizer, I., Teicher, M.H., Cohen, B.M., Robertson, D., Waldman, I.D., Blakely, R.D., Kim, K.-S., 2006. A polymorphism in the norepinephrine transporter gene alters promoter activity and is associated with attention-deficit hyperactivity disorder. Proc. Natl. Acad. Sci. U. S. A. 103, 19164–19169.

Koda, K., Ago, Y., Cong, Y., Kita, Y., Takuma, K., Matsuda, T., 2010. Effects of acute and chronic administration of atomoxetine and methylphenidate on extracellular levels of noradrenaline, dopamine and serotonin in the prefrontal cortex and striatum of mice. J. Neurochem. 114 (no-no).

Lapiz, M.D.S., Morilak, D.A., 2006. Noradrenergic modulation of cognitive function in rat medial prefrontal cortex as measured by attentional set shifting capability. Neuroscience 137, 1039–1049.

Larsen, R.S., Waters, J., 2018. Neuromodulatory correlates of pupil dilation. Front. Neural Circuits 12, 21.

Los, S.A., 1996. On the origin of mixing costs: exploring information processing in pure and mixed blocks of trials. Acta Psychol. 94, 145–188.

Los, S.A., Knol, D.L., Boers, R.M., 2001. The foreperiod effect revisited: conditioning as a basis for nonspecific preparation. Acta Psychol. 106, 121–145.

McGaughy, J., Ross, R.S., Eichenbaum, H., 2008. Noradrenergic, but not cholinergic, deafferentation of prefrontal cortex impairs attentional set-shifting. Neuroscience 153, 63–71.

Murphy, P.R., Vandekerckhove, J., Nieuwenhuis, S., 2014. Pupil-Linked Arousal Determines Variability in Perceptual Decision Making. pp. 10.

Navarra, R.L., Clark, B.D., Zitnik, G.A., Waterhouse, B.D., 2013. Methylphenidate and atomoxetine enhance sensory-evoked neuronal activity in the visual thalamus of male rats. Exp. Clin. Psychopharmacol 21, 363–374.

Navarra, R.L., Waterhouse, B.D., 2018. Considering noradrenergically mediated facilitation of sensory signal processing as a component of psychostimulant-induced performance enhancement. Brain Res. https://doi.org/10.1016/j.brainres.2018.06.027.

Newman, L.A., Darling, J., McGaughy, J., 2008. Atomoxetine reverses attentional deficits produced by noradrenergic deafferentation of medial prefrontal cortex. Psychopharmacology (Berlin) 200, 39–50.

Noorani, I., Carpenter, R.H.S., 2016. The LATER model of reaction time and decision. Neurosci. Biobehav. Rev. 64, 229–251.

Noudoost, B., Moore, T., 2011. The role of neuromodulators in selective attention. Trends Cognit. Sci. 15, 585–591.

Posner, M.I., 1980. Orienting of attention. Q. J. Exp. Psychol. 32, 3–25.

Robbins, T.W., Arnsten, A.F.T., 2009. The Neuropsychopharmacology of Fronto-Executive Function: Monoaminergic Modulation Executive Function: the Set of Processes that Help to Optimize Performance in Complex Conditions Requiring Several Components of Cognitive Function.

Seu, E., Lang, A., Rivera, R.J., Jentsch, J.D., 2009. Inhibition of the norepinephrine transporter improves behavioral flexibility in rats and monkeys. Psychopharmacology (Berlin) 202, 505–519.

Upadhyaya, H.P., Desaiah, D., Schuh, K.J., Bymaster, F.P., Kallman, M.J., Clarke, D.O., Durell, T.M., Trzepacz, P.T., Calligaro, D.O., Nisenbaum, E.S., Emmerson, P.J., Schuh, L.M., Bickel, W.K., Allen, A.J., 2013. A review of the abuse potential assessment of

atomoxetine: a nonstimulant medication for attention-deficit/hyperactivity disorder. Psychopharmacology (Berlin) 226, 189–200.
Varazzani, C., San-Galli, A., Gilardeau, S., Bouret, S., 2015. Noradrenaline and dopamine neurons in the reward/effort trade-off: a direct electrophysiological comparison in behaving monkeys. J. Neurosci. 35, 7866–7877.
Walker, R., Benson, V., 2013. Remote distractor effects and saccadic inhibition: spatial and temporal modulation. J. Vis. 13, 1–21.
Wardak, C., Ramanoël, S., Guipponi, O., Boulinguez, P., Ben Hamed, S., 2012. Proactive inhibitory control varies with task context. Eur. J. Neurosci. 36, 3568–3579.
Waterhouse, B.D., Navarra, R.L., 2018. The locus coeruleus-norepinephrine system and sensory signal processing : a historical review and current perspectives. Brain Res. 1–15.
Whelan, R., Conrod, P.J., Poline, J.B., Lourdusamy, A., Banaschewski, T., Barker, G.J., Bellgrove, M.A., Büchel, C., Byrne, M., Cummins, T.D.R., Fauth-Bühler, M., Flor, H., Gallinat, J., Heinz, A., Ittermann, B., Mann, K., Martinot, J.L., Lalor, E.C., Lathrop, M., Loth, E., Nees, F., Paus, T., Rietschel, M., Smolka, M.N., Spanagel, R., Stephens, D.N., Struve, M., Thyreau, B., Vollstaedt-Klein, S., Robbins, T.W., Schumann, G., Garavan, H., 2012. Adolescent impulsivity phenotypes characterized by distinct brain networks. Nat. Neurosci. 15, 920–925.
Witte, E.A., Marrocco, R.T., 1997. Alteration of brain noradrenergic activity in rhesus monkeys affect the alterting component of convert orienting. Psychopharmacology (Berlin) 132, 315–323.