

# First-Dose Methylphenidate-Induced Changes in the Anti-Saccade Task Performance and Outcome in Adults with Attention-Deficit/Hyperactivity Disorder

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**Objective:** We examined whether the anti-saccade task (AST) performance after the first methylphenidate (MPH) dose could be associated with subsequent clinical outcome in adults with attention-deficit/hyperactivity disorder (ADHD).

**Methods:** Ninety-seven drug-naïve DSM-5 ADHD adults participated in this study. The AST parameters were measured at baseline, after the first MPH-dose (10 mg orally), and 6 months after chronic MPH treatment. Results were compared with those of 50 healthy control (HC) subjects.

**Results:** At baseline, ADHDs showed longer saccadic reaction times and more direction errors than HCs (both  $p < 0.00001$ ). Acute and chronic MPH administration

resulted in normalization of the AST performances. Multivariate regression analysis after adjusting for age, sex, weight, and severity of symptoms at baseline, revealed that a low percentage of direction errors after the first MPH-dose (i.e.,  $\leq 10\%$ ) could predict remission at month 6 (OR: 5.84; 95% CI: 2.00–17.11;  $p = 0.001$ ).

**Conclusions:** Our findings indicate that: (1) impairments of motor planning and response inhibition in adults with ADHD are improved with MPH, and (2) a low direction error percentage after the first MPH-dose may be an independent predictor of remission.

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Saccadic eye movements have been extensively used as a research tool to investigate the working functions of the brain in different neuropsychiatric diseases (1). Among the numerous saccade paradigms, the anti-saccade task (AST) makes it possible to study the mechanisms of voluntary saccade control. This task requires two processes executed in parallel: an inhibition of a reflexive eye movement towards a visual target (i.e., a pro-saccade), and a volitional saccade directed away from the target to the (unmarked) mirror-symmetrical location (i.e., an anti-saccade) (2). Such a response involves a complex neural circuitry including regions within the occipital, parietal and frontal cortices, superior colliculus, thalamus, striatum/basal ganglia, brainstem reticular formation, and cerebellum (3). Given the dysregulation of prefrontal cortical/striatal and cerebellar circuits in subjects with attention-deficit/hyperactivity disorder (ADHD) (4), the AST may be used to reveal impairments in inhibitory control and executive function in such patients. Even though there are relatively few studies, it has been found in unmedicated adults with ADHD longer saccadic reaction times and more direction errors in the AST compared to healthy volunteers (5–9).

Controlled studies demonstrated that the catecholamine reuptake inhibitor methylphenidate (MPH) is a safe and effective treatment for adults with ADHD (10). However, owing to the heterogeneity of the disorder (i.e., etiological, clinical, neurobehavioral, and neurobiological), almost one-third of adults with ADHD show no or little improvements with MPH treatment (11). It has been shown that, even at low dose, MPH induces procognitive effect via stimulation of dopamine (DA) D1 receptors and

## HIGHLIGHTS

- The antisaccade task (AST) is useful to reveal impairments in inhibitory control in ADHD.
- Never-medicated adult ADHD subjects show delays in reaction times and increased direction errors.
- Methylphenidate (MPH) administration, either acute or chronic, normalizes AST performances.
- Direction error percentages after the first MPH-dose could predict treatment outcome.

$\alpha$ 2-adrenoreceptors in the prefrontal cortex (12). Consistent with this mechanism of action, the AST performances are enhanced following acute and/or chronic MPH administration in children and in adolescents (13, 14). However, in adults, such studies are lacking, although our group recently reported that a single low dose of MPH (10 mg orally) administered in drug-naïve patients normalized the AST reaction times and direction errors (9).

Due to the need for more appropriate intervention strategies in the treatment of ADHD, the primary aim of our study was to examine whether the AST performance after the first MPH-dose in adults newly diagnosed with ADHD could be useful for predicting the long-term response to MPH.

## METHODS

### Participants and Recruitment

Patients were recruited from the ADHD outpatient unit of the Pôle 8/9, Psychiatric Hospital of Rouffach, France. We screened 120 stimulant medication-naïve patients fulfilling the DSM-5 criteria for adult ADHD (15). Clinical diagnoses were made by consensus of two experienced clinicians (a psychiatrist and a neuropsychologist) on the basis of self-reports, unstructured, and semi-structured clinical interviews, including the French version of the Diagnosis Interview for ADHD in Adults (DIVA 2.0 (16)) containing a retrospective assessment of ADHD in childhood. To be enrolled in the study patients needed to be adult ( $\geq 18$  years of age) and to have a score  $\geq 14$  at the French version of the 6-item Part A of the Adult ADHD Self-Report Scale (ASRS-6) (17), in which the frequency of occurrence of symptoms was scored 0 = never; 1 = rarely; 2 = sometimes; 3 = often; 4 = very often. We excluded subjects with serious comorbid psychiatric disorders (including severe personality disorder or substance abuse or alcohol dependence) or ongoing somatic illnesses (including neurological and cardiovascular diseases), or those currently treated with psychotropic medications, and pregnant or breastfeeding women. At the end of the 6-month treatment period, the final sample consisted of 97 ADHDs (12 patients did not perform the final oculomotor assessment, six took newly prescribed psychotropic treatments, five took MPH treatment irregularly); among them, 81 had a combined presentation, and 16 had inattentive presentation; 76 had, at baseline, moderate functional impairment, and the remaining 21 had marked impairment in social or occupational functioning. One may also mention that 14 patients from the final sample (i.e., 14.4%) participated in our previous study (9). The AST measures in ADHDs were compared with those of 50 healthy adult control subjects (HCs). All HCs were free of concomitant psychiatric and medical illness, and were without current medication use. All participants had a normal (or corrected-to-normal) vision.

The protocol was approved by the local ethical committee (Comité de Protection des Personnes Est IV) and investigations adhered to the principles of the Declaration of Helsinki. All subjects provided written informed consent after receiving a complete description of the study.

### Paradigm

The anti-saccade paradigm we used has been previously described in more detail (9)—it was part of a wider exploration of visual tasks associating three different pro-saccade paradigms (i.e. gap, step, and overlap) (data available on request)—; the pro-saccade block always preceded the anti-saccade block. Eye movements were recorded with the Mobil EyeBrain Tracker (SuriCog). It benefits from cameras that capture the movements of each eye independently by recording the horizontal and vertical position of the eyes. Recording frequency for both eyes was set up to 300 Hz. The precision of this system is 0.25°C. Calibration was performed at the beginning of eye movement recordings, and consists of following 13 red dots (diameter of 0.5°C) presented on a computer screen of 22"—its resolution was 1920  $\times$  1080 (i.e., 1080p) and the refresh rate was 60 Hz. The tasks started immediately after the calibration. During the AST participants look at a central fixation point (FP) on the screen and after a variable fixation period (between 2000 and 3500 ms) the FP disappears. An eccentric target appears for 1000 ms either on the right or left side of the screen, preceded by a 200 ms stimulus-free gap, then subjects generate a voluntary saccade to the mirror position of the target (where no position appeared). The anti-saccade block consisted of 24 trials.

### Procedures

The AST measures were performed in our outpatient unit at 9 a.m. and were repeated three times in ADHDs: at baseline (T1; in never-medicated patients); 2 weeks later, 60 min after the first oral intake of 10 mg MPH (T2); and after 6 months of treatment (T3) with a titrated regimen of oral MPH, the patient having taken his usual morning dose of MPH—under the supervision of a nurse of the ward—1 hour before testing. HCs performed only a baseline session.

After T2, all patients were prescribed MPH as the only psychotropic treatment for ADHD. MPH was administered in open-label fashion for 6 months. All patients started with immediate-release MPH (10 mg/day), taken in the morning. Then, patients underwent a medical assessment every 4 weeks, allowing MPH titration on an individual basis, until each patient's optimal dose was reached without leading to adverse side effects. At the last visit (month 6 of the study), the average daily dose of MPH was  $47.7 \pm 23.0$  mg (SD); 10 patients were treated with immediate-release MPH, 25 with extended-release, and 62 took both at the same time. No patient received cognitive-behavioral therapy during the study period.

## Outcomes

The primary outcome measure was the total score on the ASRS-6 scale. ASRS ratings were obtained at baseline (mean score  $\pm$  SD =  $17.2 \pm 2.9$ ) and after 6 months (mean score =  $7.6 \pm 5.3$ ). We also used the investigator-rated Clinical Global Impression-scale (CGI) (18). At baseline the CGI-severity scale mean score was  $4.6 \pm 0.9$ ; after 6 months of MPH treatment the CGI-improvement scale mean score was  $2.3 \pm 1.1$ . Throughout the course of the study, psychiatrists and patients were blind to the AST data.

## Data Analyses

Analysis of the eye movement data was performed using the MeyeAnalysis© software provided with the eye tracker (9). Correct saccadic reaction times (SRTs) were defined as having regular latencies higher than 130 ms (i.e., time from stimulus appearance and beginning of the saccade). Direction errors were defined as saccades made towards the stimulus (i.e., erroneous pro-saccades). Anticipatory saccades (latency below 80 ms) and express saccades (latency between 80 and 130 ms) were discarded from analyses of regular latencies and direction errors. The mean number of valid trials for each group was as follows: ADHD group, T1:  $22.6 \pm 1.8$ ; T2:  $23.0 \pm 2.0$ ; T3:  $23.1 \pm 2.0$ ; HC group,  $23.0 \pm 1.1$ .

Statistical analyses were performed using software from the R Project for Statistical Computing (19). We employed nonparametric statistical tests since some data were not normally distributed (according to the Kolmogorov-Smirnov test). Comparisons between HCs and ADHDs were tested with the Mann-Whitney two-tailed test (*U*-test). Within patients' differences were evaluated with the Wilcoxon two-tailed signed-rank test (*T*-test) for paired data. In order to avoid type I errors, since we used multiple testing, Bonferroni's adjustments were made for four pairwise comparisons among HCs and ADHDs (at T1, T2, T3), and for three pairwise comparisons among ADHDs (T1, T2, T3). Relationships between quantitative data were estimated with the Spearman's rho statistic. Optimal cut-off values were determined using receiver operating characteristics (ROC) curve analysis (20); qualitative data were analyzed using the Fisher's Exact Test (two-tailed). Logistic regression was used to estimate the probability of remission at month 6 based on direction error percentages after the first dose of MPH (T2). Results were considered significant when  $p \leq 0.05$ .

## RESULTS

As shown in Table 1, HCs and ADHDs were comparable for age, weight and gender.

### AST Results

Medication-naïve ADHDs (T1) showed slower SRTs and more direction errors than HCs (Figure 1). After the first

**TABLE 1. Demographic and anti-saccade task data on healthy control subjects and never-medicated ADHD patients**

Measure	Control subjects (N = 50)		ADHD patients (N = 97)		<i>p</i> Fisher's exact test	
	N	%	N	%		
Female	25	50.0	49	50.5	1	
		Mean	SD	Mean	SD	<i>U</i> -test
Age (years)		32.6	8.7	35.1	9.5	0.15
Weight (kg)		73.4	11.5	74.6	16.3	0.68
<b>AST measures</b>					<b><i>U</i>-test with Bonferroni's adjustment</b>	
SRT (ms)	256.1	49.8	298.0	68.5	0.0003	
Direction errors (%)	8.5	9.1	17.8	15.6	0.0001	
Anticipatory saccades (%)	0.5	1.3	1.6	4.6	1	
Express saccades (%)	5.3	8.3	6.5	11.4	1	

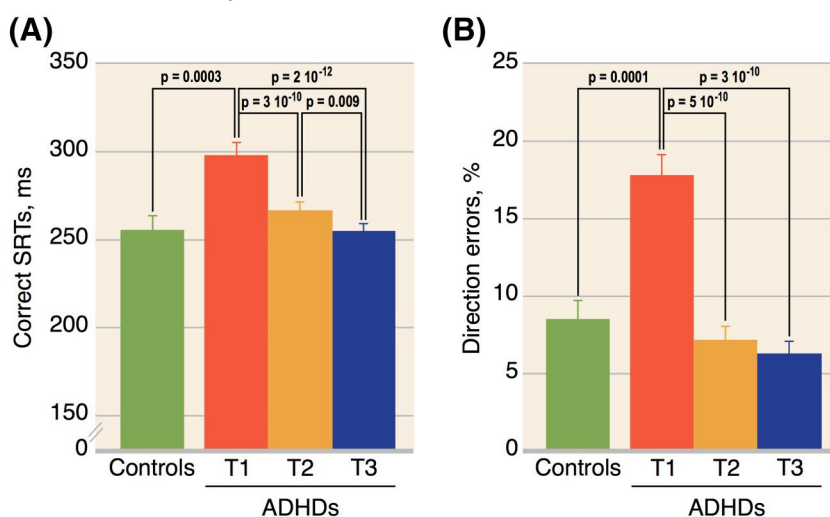
Abbreviations: ADHD, attention-deficit/hyperactivity disorder; AST, anti-saccade task; SRT, correct saccadic reaction times.

administration of MPH (T2), SRTs and direction errors were no longer different from those of HCs. After 6 months' treatment with MPH (T3), direction errors remained normalized, and SRTs were even slightly improved compared to T2. On the other hand, the frequency of anticipatory and express saccades did not change after acute or chronic MPH administration compared to baseline and remained at the same level as HCs. While the percentages of direction errors and SRTs were interrelated, they were decorrelated after the first MPH-dose (Table 2). Enhancements in the AST performance were not related to the daily dose of MPH and were not influenced by age, gender, weight or symptom scores at baseline. However, at endpoint (T3), the AST performances were related to intensity of clinical symptoms (SRTs: ASRS-6 scores,  $\rho = 0.24$ ;  $n = 97$ ;  $p = 0.018$ ; CGI scores,  $\rho = 0.22$ ;  $n = 97$ ;  $p = 0.029$ , direction errors: ASRS-6 scores,  $\rho = 0.26$ ;  $n = 97$ ;  $p = 0.009$ ; CGI scores,  $\rho = 0.33$ ;  $n = 97$ ;  $p = 0.0007$ )—these relationships were not observed at baseline.

### Clinical Outcome

Subjective and objective evaluations were intimately related. ASRS-6 and CGI scores were highly correlated at both baseline (T1) and endpoint (T3) (both  $\rho > 0.86$ ;  $n = 97$ ;  $p < 10^{-30}$ ). Initial ASRS-6 and CGI scores decreased significantly after 6 months of MPH treatment (both  $p < 10^{-15}$ ). At endpoint, 64 patients (66%) were classified as remitters (i.e., final ASRS-6 score  $\leq 9$ ), and 33 (34%) as non-remitters. Scores 0–9 correspond to the stratum 1 of the ASRS-6 (17). No baseline demographic and clinical features appeared to be significantly associated with subsequent MPH response (age, sex, weight, symptom severity or DSM-5 specifiers).

**FIGURE 1** Ocular performances during the anti-saccade task in 50 healthy control subjects, and in 97 adults with attention-deficit/hyperactivity disorder (ADHD) at baseline (T1), after the first methylphenidate-dose (10 mg orally [T2]), and after 6 months' administration of MPH (T3). A. Correct saccade reaction times (SRTs). B. Percentage of trials with regular latency direction errors. Histograms represent the group mean ( $\pm$ SD). Comparisons between control and ADHD subjects by *U*-test, within ADHD subjects by *T*-test; all *p* are corrected with Bonferroni's adjustment



**TABLE 2.** Relationships between correct saccadic reaction times and direction errors during the anti-saccade task over time in 97 ADHD adults

	Baseline (T1)	First-MPH dose (T2)	6 months MPH treatment (T3)
SRTs (T1)		0.62 ( $p < 10^{-11}$ )	0.55 ( $p < 10^{-8}$ )
SRTs (T2)			0.71 ( $p < 10^{-15}$ )
DEs (T1)		0.45 ( $p < 10^{-5}$ )	0.25 ( $p < 0.02$ )
DEs (T2)			0.26 ( $p < 0.01$ )
SRTs vs. DEs	0.25 ( $p < 0.02$ )	0.08 ( $p = 0.40$ )	0.22 ( $p < 0.03$ )

Note: T1 indicates, baseline (in never medicated patients); T2, after the first administration of methylphenidate (MPH); T3, after 6 months of MPH treatment. Spearman's rank correlation coefficient (significance).

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; DEs, direction errors; SRTs, correct saccadic reaction times; SRTs vs. DEs, correlation between saccadic reaction times and direction errors.

**AST Performance after the First MPH-Dose and 6-Month Clinical Outcome**

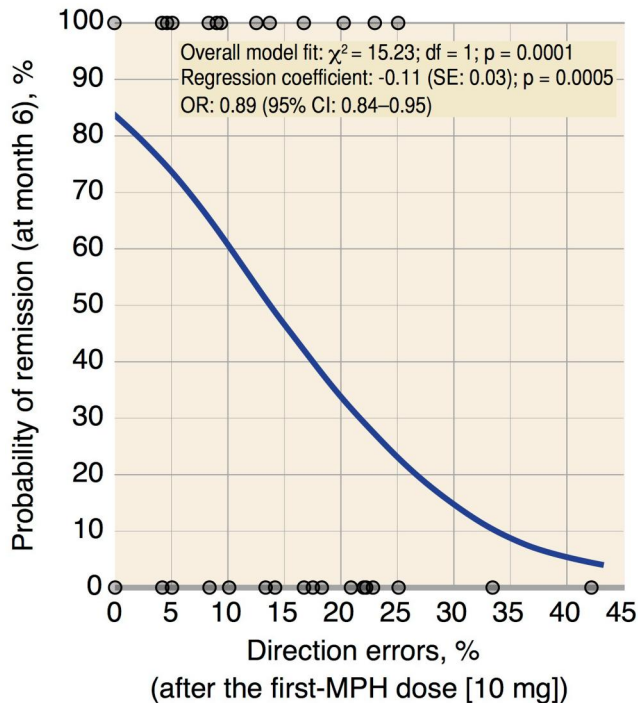
Although changes in AST performance from T1 to T2 were not significantly associated with clinical outcome at 6 months, there was a relationship between the direction error percentages after the first MPH-dose and the reduction in ASRS-6 scores from baseline to endpoint ( $\rho = 0.35$ ;  $n = 97$ ;  $p = 0.0005$ ); this relationship did not exist for SRTs ( $\rho = 0.15$ ).

ROC analysis was used to determine optimal normality thresholds for SRTs (i.e.,  $\leq 290$  ms) and percentages of direction errors (i.e.,  $\leq 10\%$ ). Medication-naïve ADHDs ( $n = 52$ ) showed more frequently SRTs above 290 ms than HCs ( $n = 10$ ) ( $p < 0.0001$  by Fisher exact test). After the first administration of MPH this difference was no longer observed ( $p = 0.83$  by Fisher exact test). Nevertheless, SRT status after the first MPH-dose was not associated with long-term outcome: 50 out of 75 patients with SRTs  $\leq 290$  ms were remitters at month 6, while 8 out of 22 patients with

SRTs  $> 290$  ms were non-remitters ( $p = 0.80$  Fisher exact test).

Sixty-one drug-naïve ADHDs had a percentage of direction errors above 10%. This distribution differed significantly from HCs ( $n = 9$ ) ( $p < 0.0000003$  by Fisher exact test), while after the first MPH-dose this difference disappeared ( $p = 0.66$  by Fisher exact test). Almost 75% of patients (56/75) who had direction errors  $\leq 10\%$  after the first MPH-dose were remitters; conversely, 64% (14/22) who still had direction errors  $> 10\%$  were non-remitters ( $p < 0.002$  by Fisher exact test). Univariate binary logistic regression analysis confirmed that ADHDs with direction errors  $\leq 10\%$  after the first MPH-dose were more likely remitters relative to ADHDs with direction errors  $> 10\%$  (OR: 5.16; 95% CI: 1.87–14.20;  $p = 0.001$ ). Multivariate logistic regression analysis after adjusting for age, sex, weight, and severity of symptoms at baseline, revealed that low direction errors after the first MPH-dose ( $\leq 10\%$ ) was an independent predictor of remission (OR: 5.84; 95% CI: 2.00–17.11;  $p = 0.001$ ). Figure 2 displays a model provided

**FIGURE 2** Predicted probability of remission at month 6 based on regular latency direction error percentages after the first methylphenidate-dose (10 mg orally) using logistic regression prediction curve. Logistic regression produces the regression coefficient (and standard error [SE] of estimate, and significance level) and odds ratio (OR, with 95% confidence interval [CI]) associated with error value



by simple logistic regression analysis, predicting the likelihood of remission for any value of direction error percentage after the first MPH-dose.

## DISCUSSION

The main findings of our pilot study are as follows: (1) never-medicated adults with ADHD make more direction errors and have longer SRTs in the AST than HCs; (2) MPH administration, either acute or chronic, normalizes the AST performances; and (3) a low percentage of direction errors after the first MPH-dose ( $\leq 10\%$ ) is associated with subsequent remission.

Our results of increased direction error rates, at baseline, are consistent with all previous AST published studies in unmedicated ADHD adults (5–9). Moreover, delayed SRTs and normal rates of express saccades have also been previously described (5, 7–9), although it has been sometimes reported normal SRTs (6) or increased anticipatory saccades (7, 9). These few discrepancies may come from methodological differences, and more particularly from the heterogeneity of the populations studied. In previous studies, patients were also very often treated chronically with stimulating drugs despite a short period of

withdrawal before the oculomotor tests (5–8). Thus, one cannot rule out a remanent effect of stimulant treatment on the AST performances—or, conversely, a “rebound effect” given upregulation of DA transporter availability during long-term treatment (21).

It is commonly agreed that SRTs reflect the programming stage duration in the saccadic system and that directions errors triggered at regular latencies are produced when the automated signals override the voluntary signals (2). From a pathophysiological viewpoint, slower SRTs and increased direction errors in ADHD could be attributable to impairments of motor planning and response inhibition (22), although it is likely that multiple factors and pathways contribute to the suppression process. Hence, in line with the hypothesis of frontostriatal hypoactivation in ADHD (23, 24), difficulty in suppressing the automatic pro-saccade may be accounted for the impaired function of the frontal lobes (especially the dorsolateral prefrontal cortex) mediating top-down inhibition of saccade neurons (3). The generation of volitional saccades, on the other hand, requires activation of the neural saccade network, including the superior colliculus, the frontal eye fields (whose activity has been correlated with the anti-saccade reaction time), the supplementary eye fields (which play an essential role in the execution of voluntary saccades), and the anterior cingulate cortex (activated in preparing saccades) (3). Hakvoot Schwerdtfeger et al. (8) hypothesized that extended SRTs and increased direction error rates in ADHD reflect mainly a poor preparation for inhibiting automatic pro-saccades, rather than a deficit in the saccade execution. Given the heterogeneity of ADHD, it is conceivable that deficits in the AST performance could also be related to hyper-responsivity of the superior colliculus (25)—although in our ADHDs the proportion of anticipatory/express saccades was rather low—, and/or reduced vigilance/arousal levels (26) given adults with ADHD show frequently poor sleep quality and excessive daytime sleepiness ((27), for review).

Confirming our previous findings (9), the first dose of the psychostimulant MPH administered at a low dose (10 mg) in drug-naïve ADHDs normalizes SRTs and direction errors. It has been suggested that acute MPH induced-DA and noradrenaline changes in corticostriatal-cerebellar systems (associated with top-down executive control improvements) (28), and ventral striatal-limbic systems (associated with bottom-up motivation and reward improvements) (29), mediate enhancements in the AST performance. Consequently, by increasing catecholaminergic activity, especially in the prefrontal cortex even at a low dose (12, 30), MPH may restore voluntary inhibitory control on saccades. Moreover, by elevating the arousal level (31), MPH may also increase the inhibitory power of the prefrontal cortex-basal ganglia circuitry (5).

In accordance with the existing literature (11), about two-thirds of our ADHDs experienced clinical remission after 6 months of MPH treatment. Interestingly, the AST

measures at endpoint are quite comparable with those obtained with acute MPH administration, despite a modest but significant reduction in SRTs possibly reflecting slight improvements on the neural saccade network secondary to chronic MPH administration. It is noteworthy that the initial AST performances (at baseline) are not associated with subsequent treatment outcomes, while after the first MPH-dose low direction error percentages (i.e.,  $\leq 10\%$ ), but not SRTs, are associated with clinical remission, even adjusting for age, sex, weight, and severity of symptoms at baseline. As revealed using multivariate logistic regression analysis, ADHDs with direction errors  $\leq 10\%$  after the first MPH-dose are 85% more likely to become remitters than those with direction errors  $> 10\%$ . The biological bases for the inter-variability of clinical responses to MPH in adults are not clearly elucidated, but they probably involve differences in the catecholaminergic tone (32, 33). Thus, it can be presumed that stimulant therapy would be efficient by correcting the baseline hypocatecholaminergic condition (34). This is in line with evidence that enhanced catecholamine transmission in response to MPH administration mediates frontal activation (12, 30, 35) and regularizes the arousal level (31). In this frame, the percentage of direction errors after the first MPH-dose, by indirectly assessing the catecholaminergic system responsivity, may provide a reliable clue for predicting subsequent response to MPH treatment. This is further supported by the fact that there is a relationship between the direction error rates after the first MPH-dose and the evolution of ADHD symptoms following 6 months of MPH treatment.

The strengths of this present study are that we evaluated never-MPH medicated adults with ADHD (avoiding therefore previous treatment bias), and that we repeated the AST three times in the same subjects (at baseline, after acute administration of a standard dose of MPH, and 6 months after chronic administration of MPH, titrated to a dose producing maximal benefits without adverse side effects). To the best of our knowledge, this is the first study to examine long-term effects of MPH on the AST performances in adults with ADHD. Our findings are also buttressed by the large sample that was treated with MPH ( $n = 97$ ). However, some limitations should be mentioned. The first one might be the lack of placebo use as a comparative treatment. However, the aim of our study was not to demonstrate the effectiveness of MPH in ADHD but to evaluate the oculomotor correlates of clinical response. As previously discussed (9), it seems unlikely that improvement in the AST performances with MPH may be attributed to a placebo effect or a learning effect. Second, we did not evaluate the effects of MPH on the AST performances in HCs. To date, only one study (36) performed in healthy subjects reported that anti-saccades latency and errors are unaffected following acute administration of 20 mg of MPH. Third, as in the vast majority of studies, we did not measure plasma concentration of MPH, and consequently

no link can be drawn between plasma MPH concentration and improvement in the AST performances. Finally, although our findings appear to be statistically robust, they must be considered preliminary until replicated in a larger population.

In conclusion, this pilot study provides evidence that MPH administration, either acute or chronic, can reverse the AST abnormalities in adults with ADHD. Interestingly, a low rate of direction errors triggered at regular latencies after the first MPH-dose is independently associated with favorable clinical outcome; this could potentially provide early therapeutic decision help in a clinical setting. Further controlled studies in a wider population are needed to confirm the value of this prognostic oculomotor marker.

## AUTHOR AND ARTICLE INFORMATION

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