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Dissociable effects of ADHD and Methylphenidate treatment on the capture and the inhibition of impulsive actions

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Abstract (135 words)

The deficit in “interference control” commonly reported in children with Attention Deficit Hyperactivity Disorder (ADHD) could be due to at least two distinct processes, which are not disentangled in most studies: a larger susceptibility to activating prepotent response impulses and a deficit in suppressing them. In this study, we investigated the effect of 1/ADHD and 2/ MPH, on these two components of interference control.

We compared interference control between children with ADHD without medication, children with ADHD under methylphenidate (MPH), and typically developing children performing a Simon conflict task.

The main findings were that 1/ children with ADHD were more susceptible to reacting impulsively but less efficient at suppressing impulsive actions than typically developing children, and 2/ MPH improved the selective inhibition of impulsive actions but did not modify the strength of response impulse activation.

Key-words: ADHD; interference control; methylphenidate; activation-suppression model, Simon task

Attention Deficit Hyperactivity Disorder (ADHD) is considered one of the most common developmental disorders diagnosed in childhood. It is characterized by symptoms of inattention, hyperactivity, and impulsivity (American Psychiatric Association, 2000) that lead to severe impairments across cognitive, behavioral, and interpersonal domains, resulting in great difficulties in school learning and social and familial relationships.

Several authors described ADHD as a disorder of executive functioning (Barkley, 1997; Sergeant, Geurts, & Oosterlaan, 2002). Response inhibition is a key component of executive functioning and is required when suppressing prepotent but inappropriate responses. Difficulties in inhibiting prepotent actions have been investigated in children with ADHD with motor inhibition tasks (such as go-no go tasks, or stop tasks), but also with conflict tasks (such as Eriksen tasks, Simon tasks, or Stroop tasks), in which an automatic response (also called response impulse) triggered by irrelevant parameters of the stimuli needs to be suppressed to the benefit of the response required by the rule of the task. Most of the studies (for an overview, see Mullane, Corkum, Klein, & McLaughlin, 2009) but not all (Van Mourik et al., 2009) have found that children with ADHD manifest poor performance in conflict tasks. Lower accuracy rates, longer and more variable reaction times (RTs) (Cao et al., 2013; Homack & Riccio, 2004; Tsal, Shalev, & Mevorach, 2005), and larger interference effects (Jonkman et al., 1999) were usually reported.

Several studies have highlighted the role of frontal-basal ganglia circuitry in selecting and inhibiting impulsive actions (Fortsmann et al., 2008; Fortmann, van den Wildenberg, & Ridderinkhof, 2008; Hazeltine, Poldrack, & Gabrieli, 2000; Ridderinkhof, Ullsperger, Crone, & Nieuwenhuis, 2004; Ridderinkhof, van den Wildenberg, Segalowitz, & Carter, 2004). Imaging studies of ADHD that report a dysfunction of the prefrontal cortex and its connections, especially with the basal ganglia (Bush et al., 1999; Dickstein, Bannon,

Castellanos, & Milham, 2006; Durston, Van Belle, & De Zeeuw, 2011; Konrad & Eickhoff, 2010; Rubia et al., 2010; Vaidya et al., 2005) support the plausibility that resolving response conflict might be impaired in individuals with ADHD.

Furthermore, the symptoms of ADHD (inattention, hyperactivity and impulsivity) are usually improved under Methylphenidate (MPH) (for review, see Wilens, 2003), which is one of the most frequently prescribed treatments for ADHD. It is hypothesized that MPH would block the dopamine transporter molecules (DAT) and DA reuptake (Solanto, 1998; Volkow et al., 2001, 2002b, 2002c, 2005). It would mainly act by increasing the inhibitory influences of frontal cortical activity on subcortical structures (Zametkin & Rapoport, 1987). Studies by positron emission tomography (PET) have revealed that the highest concentrations of MPH were found in basal ganglia, and more specifically in striatum rich in DAT molecules (Madras, Miller & Fischman, 2005; Swanson & Volkow, 2002; Volkow et al., 2002b, 2002c). Therefore, it is plausible that MPH reduces ADHD symptoms (Cantwell, 1996; Volkow et al., 2002a) by increasing the level of extracellular dopamine (DA) in the basal ganglia and frontal cortex (Madras, Miller & Fischman, 2005; Rubia et al., 2011; Volkow et al., 1995; 2001).

Through neuromodulation of fronto-striato-cerebellar circuits, DA could play a critical role in prefrontal-dependent executive functions often reported to be suboptimal in individuals with ADHD (Del campo, Chamberlain, Sahakian, & Robbins, 2011) but improved by MPH (Cantwell, 1996; Ridderinkhof, Scheres, Oosterlaan, & Sergeant, 2005). Control of interference involved in conflict tasks, which seems particularly weak in children with ADHD (Cao et al., 2013; Crone, Jennings, & Van der molen, 2003; Homack & Riccio, 2004; Jonkman et al., 1999; Mullane, Corkum, Klein, & McLaughlin, 2009; Tsal, Shalev, & Mevorach, 2005), could be due to a deficit associated with striato-frontal dopaminergic

projections, which seem to play a critical role in executive control (Ridderinkhof, Ullsperger, Crone, & Nieuwenhuis, 2004).

The difficulties of these children in conflict tasks may be due not only to a deficit in suppressing response impulse, but also to a larger susceptibility to activate automatic responses. These two processes are not disentangled in most of studies, in which performance is analyzed in terms of mean RT, accuracy rate, and interference effect only.

The well-known Simon task (Simon, 1969) interpreted in the theoretical framework of the Activation-Suppression model (Ridderinkhof, 2002) provides a very powerful experimental and conceptual context for investigating the expression and suppression of action impulses and therefore for investigating the control of interference. In the color Simon RT task, participants are required to choose between a right or a left response, depending on the color of a stimulus presented to either the right or the left of a central fixation point. Although the stimulus position is irrelevant to the task, performance—expressed in terms of mean RT and error rate—is better when the required response spatially corresponds to the stimulus location (congruent trials, CGs) than when it does not correspond (incongruent trials, IGs). A widely accepted interpretation of the interference effect is that the stimulus location (which is irrelevant for the task) automatically triggers a response impulse in the ipsilateral hand via a fast route, while the stimulus color (which is the relevant information) must be translated into the required response according to task instructions via a slower controlled processing route (de Jong, Liang and Lauber, 1994; Kornblum, 1994; Kornblum, Hasbroucq, & Osman, 1990; Proctor, Lu, Wang, & Duta, 1995). Therefore, in incongruent trials, the impulse triggered by the irrelevant location activates the non-required response in the ipsilateral hand, which then competes with the required one (contralateral to the stimulus). This competition is thought to be at the origin of the performance impairment.

Ridderinkhof (2002) extended the dual-route hypothesis by proposing the Activation-Suppression model which allows for dissociating two temporally distinct cognitive processes that are masked in analyses of mean interference effects: The expression of impulse capture and the inhibitory control. This model assumes that the impulse capture triggered by the irrelevant location of the stimulus would occur very quickly after the onset of the stimulus and it further adds an active suppression of the inappropriate impulse response that would need time to get in place and reduce the interference generated by the stimulus location (Ridderinkhof, 2002). Therefore, the model enables two predictions. First, if the suppression of the automatic response is progressive and then takes time to be efficient, it can be assumed that it has no time to build up for the shortest RTs, and hence, more errors can be expected, namely fast errors. Consequently, the strength of impulse capture should then be reflected in the proportion of fast errors, which can be evaluated by plotting accuracy rates against RT (known as conditional accuracy functions, CAF; Suarez et al., 2015; Van den Wildenberg et al., 2010; van Wouve et al., 2015; Wylie et al., 2010, 2012, 2013). On the other hand, inhibitory control should be more evident during slower responses when the inhibition of the automatic response becomes more fully engaged, and the difference between the congruent and incongruent trials, that is the interference effect, should decrease. The pattern of reduced interference can be observed by plotting the difference between incongruent RTs and congruent RTs, which reflects the magnitude of interference effects as a function of response speed (so-called delta plots). The interference effect decrease in the longest RTs can be considered a reliable measure of the efficiency of the inhibition (Suarez et al., 2015; Suarez, Vidal, Burle, & Casini, 2015; Ridderinkhof, 2002; Ridderinkhof et al., 2004; Van den Wildenberg et al., 2010; Van Wouve et al., 2016; Wylie et al., 2010, 2013). Consequently, according to the activation-suppression model, the slope of the Simon effect at the longest

RTs provides a measure of inhibitory control, whereas the first point of the distribution analysis of the accuracy rate in incongruent trials, corresponding to the proportion of fast errors, provides a measure of the strength of impulse capture (Figure 1). Several studies using both non-clinical and clinical populations provide empirical support for this assertion (Burle et al., 2002; Ridderinkhof, Scheres, Oosterlaan, & Sergeant, 2005; Suarez et al., 2015; Suarez, Vidal, Burle, & Casini, 2015; Van Wouve et al., 2016; Wijnen & Ridderinkhof, 2007; Wylie, Ridderinkhof, Eckerle, & Manning, 2007; Wylie et al., 2009, 2010, 2012, 2013; for review, see Ridderinkhof, Wylie, & van den Wildenberg, 2011; Van den Wildenberg et al., 2010).

Figure 1. Example of a distributional analysis of performance with five quantiles. (a) Conditional accuracy functions (CAF) for congruent (white circles) and incongruent (black circles) trials. (b) Delta plot representing the interference effect as a function of the response speed.

The aims of the study were to determine how the expression and suppression of impulse actions are affected by 1/ ADHD and 2/ methylphenidate treatment to better understand both the physiopathology of ADHD and the neural mechanisms and processes involved in interference control. We compared the performance of three groups of children when they were engaged in a Simon RT task: children diagnosed with ADHD who had never received medication, children diagnosed with ADHD while under MPH, and control children (typically developing peers). Our hypothesis was that the control of interference should be impaired in children with ADHD but improved by MPH because of the putative effects of this molecule on the DA system. Moreover, based on the data of the only study that used distributional analyses to study interference control in children with ADHD performing an

Eriksen task, we expected that MPH improved response inhibition but not automatic response activation (Ridderinkhof, Scheres, Oosterlaan, & Sergeant, 2005).

1. Material and methods

1.1. Participants

Sixty-five children participated in this study: 25 untreated children with ADHD (aged 12–15; mean = 13.6; 11 males), 20 children with ADHD treated with MPH (aged 10–16; mean = 13.9; 14 males), and 20 control children (aged 11–15; mean = 13.7; 9 males). Demographic data are presented in Table 1.

Table 1: Demographic variables for the three groups (mean and standard error of the mean, SEM). IQ = Intellectual quotient; Attention symptoms and Impulsivity/Hyperactivity symptoms were assessed by using the Conner's Parent Rating scales.

	Untreated ADHD children (n = 25) Mean (sem)	ADHD children with MPH (n = 20) Mean (sem)	Control group (n = 20) Mean (sem)	Untreated ADHD children <i>versus</i> Control $t_{43} =$	MPH- ADHD children <i>versus</i> Control $t_{38} =$
Age (years)	13.6 (0.5)	13.9 (0.4)	13.7 (0.4)	.64, $p=.52$	.71, $p=.48$
IQ	98.25 (4)	102 (5.8)	101.1 (2.4)	.38, $p=.7$	.34, $p=.73$
Attention (T-score)	85.4 (4.8)	79.9 (2.8)	46 (1.8)	7.7, $p<.001$	6.6, $p<.001$
Impulsivity/Hyperactivity (T-score)	79.8 (6.2)	74.8 (4)	45.6 (1.9)	6.16, $p<.001$	6.03, $p<.001$

1.1.1. Selection procedure for the ADHD group

Children with ADHD were recruited from a sample of patients who had been referred to the Department of Child and Adolescent Psychiatry (Salvator Hospital, Marseille, France) by a pediatrician or a child psychiatrist.

They all met the DSM IV diagnostic criteria for ADHD (American Psychiatric Association, 2000). The assessment was made on the basis of a semi-structured clinical diagnostic interview (Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version; K-SADS-PL) conducted with parents and children separately by child psychiatrists. The K-SADS-PL has been used extensively to make diagnostic decisions based on DSM criteria and has previously been validated in children from 6 to 17 years old (Kaufman, Birmaher, Brent, Rao, & Ryan, 1997).

The Conner's Parent and Teacher Rating Scales (Conners, 1969) were also included as additional measures of ADHD. These were completed either by the clinical referral or the parents of the participants. Diagnosis was performed by trained child psychiatrists specialized in ADHD. The full history of the child's development and academic performance, an interview with parents and child, and behavioral observations served to confirm the diagnosis.

For this study, in order for the ADHD groups to be as homogeneous as possible but also not reduced to only one symptom (impulsivity or attention), all children met the criteria for the combined subtype. Moreover, exclusion criteria were the following: 1/ IQ inferior to 80; 2/ evidence of a neurological disorder such as epilepsy; 3/ associated medical disorders; 4/ history or evidence of psychosis; and 5/ absence of parental consent. The IQ was evaluated with the short form of the French Wechsler Intelligence Scale for Children (WISC-V) (Wechsler, 2005), including four subtests: similarities and vocabulary tests to estimate verbal

IQ and matrices and concept identification to estimate performance IQ. The working memory index was also assessed by using three items of the WISC-V (Arithmetic, Digit Span, and Letter–Number sequencing).

It has to be noted that children of the untreated group had never received medication. The children of the treated group were all on medication during the experiment and they all took a daily treatment, included on the day of the experiment.

1.1.2. Criteria for the control group

The control group comprised 20 typically developing children. They were recruited via local schools in Marseille. They all attended normal classes corresponding to their age. Inclusion criteria were the following: 1/ absence of present or past diagnosis of ADHD determined by the completion of the Conner's Parent Rating Scale (T-score below the 80th percentile); 2/ absence of emotional disturbance or learning disabilities; and 3/ no concurrent treatment with psychotropic medication. They all had an IQ superior or equal to 80. A partial IQ was evaluated on the basis of the same four subtests as those taken by ADHD children. The children were chosen to globally match with the mean age of both groups of children with ADHD (see Table 1).

1.2. Procedure of the Simon RT task

1.2.1. Stimuli and apparatus

Participants were comfortably seated facing a black computer screen, located 80 cm away, on which stimuli appeared. Responses were given by pressing one of two response buttons with either the right or the left finger. All stimuli and responses were controlled by a computer

running t-scope (Stevens, Lammertyn, Verbruggen, & Vandierendonk, 2006). RTs were recorded at the nearest millisecond.

1.2.2. Task and procedure

The children's task was to respond as fast and accurately as possible on the basis of the color of the stimulus. After the experimenter had verified that all instructions were understood, subjects first performed 24 randomized trials, corresponding to 12 CGs (response side ipsilateral to stimulus side) and 12 IGs (response side contralateral to the stimulus side), to familiarize themselves with the task and stabilize their performance. Next, four experimental blocks of 48 trials were presented. Each trial started with the appearance of a central fixation point that participants had to fixate during the entire trial. After a delay of 400 ms, a red or a green circle appeared on either the right or the left of the fixation point. Children had to briefly press the left or the right button according to the color, red or green, of the circle. The color-response mapping was balanced across participants.

In each block, there were 24 green and 24 red stimuli. For each color, there were 12 congruent CGs and 12 IGs. The blocks were separated by a pause of 2 minutes. The entire experiment lasted about 25 minutes.

1.3. Dynamic analysis of performance

1.3.1. Dynamic analysis of interference effect

The dynamic analysis of the interference effect relies on distribution analyses of RTs. The cumulative density functions (CDF) of correct trials were estimated for each participant and averaged through the so-called "vincentizing" procedure (Ratcliff, 1979; Vincent, 1912): RTs were rank ordered separately for each type of trial (CGs and IGs) and binned into five

quantiles of equal frequencies (same number of trials). The mean of each bin was computed and equivalent bins were averaged across participants. Delta plots were constructed by plotting the difference between incongruent and congruent bins as a function of the mean of incongruent and congruent bin values (for more information, see Burle, Possamaï, Vidal, Bonnet, & Hasbroucq, 2002; Ridderinkhof, 2002; Suarez, Vidal, Burle & Casini, 2015). The slope of the last segment of the delta plot was used as an index of the efficiency of the inhibition of automatic responses, as exposed in the Introduction section.

1.3.2. Dynamic analysis of error rates

The dynamic analysis of error rates is based on the distributional accuracy analysis. We computed the so-called “conditional accuracy function” (CAF): Correct and erroneous trials were mixed together and the resulting distributions were vincentized as a function of the RT distribution. Five bins (quintiles) were used. For each bin, the proportion of “correct” trials was computed, along with the mean RT of the bin. These data pairs were averaged per bin through participants. This provided the mean accuracy as a function of increasing RTs. The first point of the distribution corresponding to IG trials was used as an index of the strength of vulnerability to activating automatic responses, as exposed in the Introduction section.

2. Results

Extreme RT values, either too fast (< 150 ms, also called anticipatory errors) or too slow (> 3 standard deviations) were removed from the analysis. This accounted for fewer than 1% of trials across participants.

The results section includes two parts. In the first part, we present data classically reported in the literature, that is, overall mean RTs and error rates. One two-way ANOVA

with the between-subject factor Group (ADHD, MPH-ADHD, and Control) and the within-subject factors Congruency (CG *versus* IG) was performed on both mean RTs and accuracy rates. More precisely, since percentages cannot be submitted to ANOVA directly—as the means and variances of percentages tend to be closely related—accuracy rates were arc-sine transformed before being analyzed (Winer, 1970).

In the second part, we present the two indices computed from distributional analyses. The first one is the accuracy rates for the fastest RT bin of the CAFs which have been demonstrated to be the most sensitive measure of response capture, with stronger capture reflected by a higher percentage of fast errors. The second one was inferred from the delta plots (which plot the interference effect as a function of RT). It corresponds to the slope between the delta values of the 2 slowest RT bins. It is considered as the most sensitive measure of the response impulse inhibition. More efficient inhibition is reflected by steeper reduction of interference (that is a larger negative-going final delta slope). A one-way ANOVA was performed on the accuracy rate values for the fastest RT bin of the IG CAFs and then t-tests were carried out for pairwise comparisons. For the interference effect, all values derived from the delta plots were first submitted to separate repeated-measures ANOVAs to examine group differences on the entire functions, and more specifically the second order interaction Group x Congruency x Quantiles. Then t-tests were performed on the slope of the last segment of the delta plot to evaluate the efficiency of the inhibition.

Homogeneity of variance was tested for each dependent variable using the nonparametric version of Levene's test of equality of error variances. The error variances between groups were not statistically different.

2.1. Mean RTs and accuracy rates

2.1.1. Mean RTs

Figure 2a illustrates mean RTs for the three groups of children. We can observe that response speeds were significantly different depending on the groups ($F_{2,62} = 11.43$; $p < 0.0001$). Mean RTs were faster for the control group (434.1 ms; $SD = 58$) than for the untreated children with ADHD (584.6 ms; $SD = 129$) ($t_{43} = 5.03$; $p < 0.0001$; effect size: Cohen's $d = 1.50$). The children with ADHD taking medication were faster (498.9 ms; $SD = 111$) than the children not taking medication ($t_{43} = 2.62$; $p < 0.01$; effect size: Cohen's $d = 0.71$) but were significantly slower than the control children ($t_{38} = 2.58$; $p < 0.01$; effect size: Cohen's $d = 0.73$).

Moreover, as classically observed, RTs were faster in the CG trials (492.2 ms; $SD = 120$) than in the IG trials (532.5 ms; $SD = 126$) ($F_{1, 62} = 95.8$; $p < 0.0001$) for all groups, but the difference of RT between the CG and the IG trials, corresponding to the interference effect, varied between groups, as confirmed by Group x Congruency interaction ($F_{2, 62} = 5.84$; $p < 0.01$). The interference effect was larger in the untreated children with ADHD (57 ms; $SD = 36$) compared with control children (26.3 ms; $SD = 28$) ($t_{43} = 3.37$; $p < 0.001$; effect size: Cohen's $d = 0.95$) and children with ADHD taking MPH (32.9 ms; $SD = 29$) ($t_{43} = 2.66$; $p < 0.01$; effect size: Cohen's $d = 0.72$). There was no significant difference between the interference effect obtained by the control children and that obtained by the children with ADHD taking medication ($t_{38} = 1.23$; $p = 0.22$; effect size: Cohen's $d = 0.24$).

Figure 2. Simon task performance. Overall mean RT (a) and accuracy rate (b) for congruent (white bars) and incongruent (black bars) trials for control children, untreated children with ADHD, and children with ADHD under MPH. Error bars are mean standard errors.

2.1.2. Accuracy rates

As seen in Figure 2b, which represents accuracy rates for the three groups of children, treated and untreated children with ADHD did not submit fewer correct responses than the control children (untreated ADHD: 95.4%, SD = 2.9; ADHD-MPH: 95.4%, SD = 3.4; Controls: 96.9%, SD = 2.4) ($F_{2, 62} = 0.94$; $p = 0.39$).

As classically observed, accuracy rates were smaller in the IGs (94.3%; SD = 3.9) than in the CGs (97.4%; SD = 2.5) ($F_{1, 62} = 20.16$; $p < 0.0001$). The difference between IGs and CGs that is, the interference effect—tended to vary between groups, as indicated by the marginally significant Group x Congruency interaction ($F_{2, 62} = 2.51$; $p = 0.08$). The interference effect was larger in the untreated ADHD children (3.7%; SD = 3.8) compared with the control children (2.1%; SD = 2.6) ($t_{43} = 1.98$; $p < 0.05$; effect size: Cohen's $d = 0.51$). However, the interference effects for control children and ADHD children taking medication (3.2%; SD = 3.2) were not significantly different ($t_{38} = 1.62$; $p = 0.11$; effect size: Cohen's $d = 0.4$), as between the two groups of children with ADHD ($t_{43} = 1.02$; $p = 0.3$; effect size: Cohen's $d = 0.15$).

2.2. Dynamic analysis of performance

2.2.1. Dynamic analysis of the interference effect

Figure 3a displays delta plots, representing the size of the interference effect as a function of quintiles for the control, untreated ADHD, and MPH-ADHD groups. The evolution of the Simon effect size with the quintiles tended to be different between groups (Group x Congruency x Quintiles: $F_{8,248} = 2.06$, $p < 0.05$). The interference effect decreased with the longest RTs for the control group, whereas it remained globally stable across quintiles for children with ADHD not taking medication. Very interestingly, the interference effect also decreased with increasing RT for children with ADHD under MPH.

The comparison of the slope values of the delta plot's last segments (Control *versus* untreated ADHD: $t_{43} = 2.14$; $p < 0.05$; effect size: Cohen's $d = 0.59$ / Control *versus* MPH-ADHD : $t_{38} = 1.08$; $p = 0.28$; effect size: Cohen's $d = 0.17$ / MPH-ADHD *versus* untreated ADHD : $t_{43} = 1.85$; $p = 0.06$; effect size: Cohen's $d = 0.52$) confirms that the interference

effect similarly decreased for the longest RTs in the control group and MPH-ADHD group but did not decrease for children with ADHD who were untreated.

Figure 3. Distributional analyses. (a) Delta plots showing Simon effect size as a function of response speed, expressed in reaction time (RT) quantile scores for untreated ADHD group (squares), MPH-ADHD group (triangles), and control group (circles). (b) Conditional accuracy functions (CAF) for congruent (white symbols) and incongruent (black symbols) trials for untreated ADHD group (squares), MPH-ADHD group (triangles), and control group (circles).

2.2.2. Dynamic analysis of accuracy

Figure 3b displays distributional analyses for accuracy rates of the two types of trials (CG and IG) and the three groups of children. As expected, low responses on IG as well as both fast and slow responses on CG trials were all above 95% of accuracy and the accuracy rate value was lower for the first point of IGs in all groups. When comparing the accuracy rate values for the first quintile in IGs, measuring the fast errors rate, the analysis revealed differences between groups ($F_{2,62} = 3.08$; $p < .05$; Control *versus* untreated ADHD : $t_{43} = 2.21$; $p < 0.05$; effect size: Cohen's $d = 0.53$; Control *versus* MPH-ADHD : $t_{38} = 1.86$; $p = 0.06$; effect size: Cohen's $d = 0.41$; untreated ADHD *versus* MPH-ADHD : $t = 0.95$; $p = 0.34$; effect size: Cohen's $d = 0.12$). Children with ADHD, with and without treatment, tended to commit more fast errors in IGs than control children, suggesting a higher vulnerability to response impulse (Figure 3b).

3. Discussion

The aim of the present study was twofold: we investigated the effect of 1/ ADHD and 2/ MPH on the expression and suppression of impulse actions. These two effects will be discussed separately.

3.1. ADHD and interference control: Comparison between untreated children with ADHD and control children

The comparison of overall performance (mean RT and accuracy rate) between untreated children with ADHD and control children has revealed that children with ADHD presented weak performance compared with control children. First, they were slower without committing less errors, which excludes an explanation in terms of speed-accuracy trade-off.

Second, they presented a larger interference effect than control children. These findings are quite consistent with results from other studies involving different types of conflict tasks, which report that children with ADHD present difficulties in dealing with conflicts between automatic and controlled responses, providing further arguments for an interference control deficit in children with ADHD (for a review, see Mullane, Corkum, Klein, & McLaughlin, 2009).

Interference control deficits in subjects with ADHD have mainly been interpreted as deficits in inhibitory processes (Barkley, 1997; Nigg, 2001). But these deficits can be caused by either 1/ a higher vulnerability in activating the automatic response triggered by the location of the stimulus, or 2/ a deficit in the ability to suppress automatic responses. The observation of dynamic analyses of the performance only can help with investigating these two processes separately.

Delta-plot analyses revealed that the interference effect decreased for the longest RTs for the control group, whereas it remained stable for children with ADHD. Based on the activation-suppression model (Ridderinkhof, 2002), these results indicate that children with ADHD had difficulties in suppressing response impulse. The dynamic analysis of the accuracy revealed that children with ADHD committed more fast errors in IGs than control children. These results suggest that children with ADHD also present a stronger propensity to activate automatic responses. Therefore, our data suggest that children with ADHD present both a larger vulnerability to response impulse and more difficulties in suppressing them.

Our results are partially consistent with those presented in the only study (to our knowledge) using a dynamic analysis to investigate the performance of children with ADHD engaged in a conflict task (Ridderinkhof, Scheres, Oosterlan & Sergeant, 2005). The authors reported children with ADHD had difficulties in suppressing response impulse but did not

report a larger vulnerability to response impulse. But at least two differences between the two experiments may be noted. First, concerning the response impulse, the authors have drawn their conclusions based on the analysis of delta plots for accuracy, while we directly compared the accuracy rates for the IG trials at the fastest responses, which seem a better indicator of response impulse, as suggested by more recent articles (Ridderinkhof, Wylie, & van den Wildenberg, 2011; Van Wouve et al., 2016; Van den Wildenberg et al., 2010; Wylie et al., 2012, 2013). Second, the children performed a flanker task and the nature of the interference is different in the Simon task (motor interference) and the flanker task (perceptive interference). Data from a recent study comparing the two tasks have suggested that the control of inappropriate responses is more difficult to evidence and less stable in the flanker task (Burle, Spieser, Servant, & Hasbroucq, 2014).

The inhibition deficit has often been considered the core deficit in different models of ADHD (Barkley, 1997; Nigg, 2001). According to these models, behavioral inhibition is the process behind the correct functioning of the executive system, and an impairment of this system would explain deteriorated performance of subjects with ADHD in various tasks that evaluate executive functions. But our data suggest that symptoms observed in children with ADHD—such as impulsivity and hyperactivity—may be explained as well by a larger vulnerability to response impulse and by difficulties in inhibition. In the Simon task, the vulnerability to response impulse suggests that children with ADHD would present difficulty ignoring the position of the stimulus, even if it is an irrelevant parameter. This inability to ignore the position of the stimulus, considered a distractor, could be the result of their inattention. Lapses of attention could prevent these children from focusing their attention on the relevant characteristic of the stimulus, the color, which requires controlled attention and the association between the location of the stimulus and the ipsilateral response could be

stronger for these children, who might be more prone to select the response that is used most often (that is, the ipsilateral one).

Our results seem in line with the recent neuroenergetic theory (NeT) of ADHD (Killeen, 2013; Killeen, Russell, & Sergeant, 2013) which proposes that an effortful response is impaired in ADHD because of an insufficient neuronal energy supply, leading to neuronal fatigue. The inhibition of the prepotent response (the response ipsilateral to the stimulus location), which requires effortful control, could then be impaired in ADHD. These findings are in line with those recently obtained by Huang-Pollock and colleagues (2017). By using computational modeling, they found—in a go/no-go task—that the increased task engagement among children with ADHD, due to faster event rates (which increased neuronal energy consumption), was unable to counteract the concurrent slowing of processing speed in “no-go” decisions. In the context of a go/no-go task, the preferential slowing of drift in the no-go decision relative to the go decision is consistent with the idea that fatigue would affect processes that require greater effort.

3.2. MPH treatment and interference control

MPH medication not only significantly improved the response speed of children with ADHD (even if they remained slower than control children) but also reduced interference effects. These data confirm results obtained by Ridderinkhof and collaborators (2005) with the flanker task but do not support data obtained in an earlier study (also using the flanker task), in which MPH was not found to reduce the interference effect (Jonkman et al., 1999).

The dynamic analysis of the interference effect revealed that MPH modified the delta plots. The slope of the last segment was negative as observed for control children. These data suggest that the MPH improved interference control for slower RTs, and hence they prove the

efficiency of the selective inhibition of automatic responses. In contrast, the dynamic analysis of the accuracy rate did not reveal a positive effect of MPH on the vulnerability to response impulse: The accuracy rate measured for the shortest RTs (first quintile) in IGs tended to remain larger in children who took MPH compared with control children, and there was no significant difference between both groups of children with ADHD, indicating that, even under MPH, children with ADHD still committed more fast errors in IGs. It seems that the vulnerability to prepotent distractors (such as the stimulus location), which trigger automatic responses, was not reduced under MPH. Our findings then suggest that the global improvement of the interference effect was essentially due to an improvement in inhibition efficiency. These data only partially confirm those reported by Ridderinkhof and collaborators (2005), who have shown an effect of MPH on both the efficiency of the selective suppression of automatic responses and the strength of the direct activation of responses by irrelevant information. Again, this discrepancy could be due to some differences between the two studies. In addition to the differences previously mentioned, it should be added that the effect of MPH was investigated in a within-subject titration study, which is not the case in the present study.

Our results confirm that MPH globally improves performance in tasks that involve response inhibition (Konrad, Günther, Hanisch & Herpertz-Dahlmann, 2004; Scheres et al., 2003; Tannock, Schachar, Carr, Chajczyk & Logan, 1989; Tannock, Schachar, & Logan, 1995; Ridderinkhof, Scheres, Oosterlan & Sergeant, 2005) but more precisely, they showed that MPH improves interference control by reducing the inhibition deficit without decreasing the vulnerability to response impulse.

From a neurobiological point of view, the resolution of the conflict is known to involve different brain areas. It has been reported in an fMRI study that individual differences

in the susceptibility to activate automatic prepotent responses in the Simon task (that is, in fast error rate) are associated with stronger activation in the pre-supplementary motor area (pre-SMA), whereas adults who presented a larger ability to suppress impulsive actions in the Simon task (that is, with a steeper negative slope in delta plot) showed greater activation of the right inferior frontal cortex (rIFC) (Forstmann, Van den Wildenberg, & Ridderinkhof, 2008). These findings were in line with models describing a central role for the rIFC and its efferent projections to the basal ganglia in inhibitory action control (Aron, 2007). Therefore, our data—which revealed differential effects of MPH on the activation of automatic response and inhibitory control engaged to suppress interference produced by this capture—suggest that MPH could modulate DA brain levels in the rIFC. This is quite consistent with the results of a meta-analysis of fMRI studies, which shows that the most consistent effect of MPH is the increased activation of the rIFC (Rubia et al., 2014). The latter is also considered the most replicated neurocognitive dysfunction area of ADHD (for a review, see Dickstein, Bannon, Castellanos, & Milham, 2006). Our data then support the idea that MPH would improve clinical symptoms, including reducing impulsivity and hyperactivity by increasing rIFC activation.

Nonetheless, it has also been proposed that MPH could improve ADHD symptoms by indirectly influencing other cognitive processes, such as attention. Data coming from a PET study aimed at investigating MPH action mechanisms have suggested that the dopaminergic signal amplification induced by MPH could improve the perception of stimulus or task salience and then lead subjects to deeper engagement in the task (Volkow, Wang, Fowler, & Ding, 2005). This attention increase, associated to a decrease in distractibility, may contribute to an improvement in performance. An increased selective attention level may help children to quickly detect the stimulus and then to shorten the time of all subsequent processes,

explaining why children with ADHD under MPH were faster than children with ADHD who were medication-free. The role of attention in interference control has also been hinted at in one study, which showed that the reduction of the interference effect for longest RTs could be disrupted when the Simon task was performed under a reduced level of attention (Suarez, Vidal, Burle, & Casini, 2015). Therefore, the improvement of executive control under MPH could also be secondary to an increase in attention level.

In conclusion, our data suggest that 1/ the interference control deficit observed in ADHD could be caused by both a larger vulnerability to response impulses and a deficit in inhibitory control engaged to suppress them, and 2/ MPH reduced this deficit by only improving inhibitory processes, without reducing the strength of the impulse capture. These findings contribute to a better understanding of ADHD and also of MPH action. Nonetheless, because of the large heterogeneity of ADHD, further studies are still needed to really understand this developmental disorder. For example, the question as to whether ADHD is due to a central deficit or rather to multiple deficits, as proposed more and more often (Castellanos & Tannock, 2002; Castellanos, Sonuga-Barke, Milham, & Tannock, 2006; Nigg, Willcutt, Doyle, & Sonuga-Barke, 2005), should be a crucial question. It could be very helpful to separately investigate impulse capture and proficiency of inhibition framework to tackle this question.

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Disclosure of interest

The authors report no conflict of interest.

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