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Differential response to pharmacological intervention in ADHD furthers our understanding of the mechanisms of interference control

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ABSTRACT

The deficit in "interference control" found in children with Attention Deficit Hyperactivity Disorder (ADHD) could be due to two distinct processes, which are not disentangled in most studies: a larger susceptibility to activating prepotent response impulses and a deficit in suppressing them. Here, we investigated the effect of 1/ADHD and 2/ methylphenidate (MPH), on these two components of interference control. We compared interference control between untreated children with ADHD, children with ADHD under MPH, and typically developing children performing a Simon task. The main findings were that 1/ children with ADHD were more susceptible to reacting impulsively and less efficient at suppressing impulsive actions, and 2/ MPH improved the selective inhibition of impulsive actions but did not modify the strength of response impulse. This work provides an example of how pharmacological interventions and selective responses to them can be used to investigate and further our understanding of cognitive processing.

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ADHD; interference control; methylphenidate; activation-suppression model; Simon task

Imagine that you are stopped at a traffic-light waiting for it to turn green. As soon as it turns green you prepare to accelerate, but suddenly a little boy arises running behind a balloon just in front of your car. The safest response is actually to brake. This situation therefore requires overlearned automatic actions to be overridden by controlled ones. Every day, we are forced to adapt our behaviour to unexpected environmental changes. This flexibility requires efficient cognitive control. Cognitive control refers to a set of processes which allow us to flexibly adapt to our ever-changing environment by regulating our behaviours, for example by suppressing inappropriate spontaneous actions and facilitating those which are better adapted to the context (Braver et al., 2003).

Cognitive control can be studied through tasks, called conflict tasks, that require managing interference between competing responses. Classically, in conflict tasks, there is interference between an automatic tendency to respond to an irrelevant but salient stimulus and a controlled goal-directed response to a relevant stimulus (Eriksen & Eriksen, 1974; Simon, 1969; Stroop, 1935). For example, in the Simon task, participants are required to choose between a right or a left response, depending on the colour 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). This behavioural cost is known as the Simon effect or interference effect. A widely accepted interpretation of the interference effect is proposed by the dual-route model (Kornblum, 1994; Kornblum et al., 1990). This model proposes 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 colour (which is the relevant information) must be translated into the required response according to task instructions via a slower controlled processing route (de

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Jong et al., 1994; Kornblum, 1994; Kornblum et al., 1990; Proctor et al., 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.

Conflict tasks have been investigated in children with ADHD, characterized by symptoms of inattention, hyperactivity, and impulsivity (American Psychiatric Association, 2000). Most of the studies (for an overview, see Mullane et al., 2009) but not all (Borella et al., 2013; Schwartz & Verhaeghen, 2008;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 et al., 2005), and larger interference effects (Jonkman et al., 1999) have usually been reported. Classically, the difficulties of children with ADHD in conflict tasks were considered to be due to difficulties in inhibiting inappropriate automatic and prepotent responses (Barkley, 1997; Nigg, 2001). But some more recent studies have suggested that inhibition abilities may actually be intact in children with ADHD (Coghill et al., 2014). The mixed findings may come from the fact that interference control is classically evaluated with the magnitude of the interference effect only, but this measure does not differentiate response inhibition processes from other processes involved in the conflict and its resolution. Therefore, a relatively pure measure of inhibitory processing is needed if we want to more precisely examine the role of response inhibition in cognitive control in ADHD. Moreover, this is particularly relevant if we consider as a crucial question, the question of determining whether ADHD is due to a unique deficit or rather to multiple deficits, as proposed more and more often because of the large heterogeneity of performance patterns observed in ADHD (Castellanos & Tannock, 2002; Castellanos et al., 2006; Nigg et al., 2005).

In 2002, Ridderinkhof extended the dual-route model by proposing the "activation-suppression" model of interference control which incorporates the temporal dynamics of cognitive control and allows two components of it to be dissociated. This model keeps the idea that, in incongruent trials corresponding to a conflict situation, conflicting stimulus information (based on stimulus position), directly activates an incorrect action impulse that conflicts with the selection of the appropriate response (based on stimulus colour). This first process, which we will call impulse capture, is assumed to reflect the degree to which the response system is susceptible to activating location-driven automatic responses. The model further asserts that, upon detecting the activation of an incorrect response, an inhibition mechanism is engaged to selectively suppress this incorrect response activation, reducing then interference between automatic and deliberate response activations. This second process, which we will call selective inhibition, is assumed to reflect inhibitory control, which is progressively built up to suppress interference induced by the incorrect action impulse. The "activation-suppression" model proposes a set of distributional analytic tools (conditional accuracy functions and delta plots) that can isolate and quantify the relative strength of impulse capture and the proficiency of inhibitory control (Ridderinkhof, 2002; see also Van den Wildenberg et al., 2010). Indeed, it is proposed that the two dynamic processes, impulse capture and its subsequent selective inhibition, can be analytically dissociated by respectively analyzing accuracy rates and interference effects across the full range of the RT distribution.

The first aim of the present study was then to disentangle the contribution of the two processes of interference control using these distributional analytic tools which allow to separately quantify the effect of ADHD on intensity of impulse capture and on selective inhibition efficiency.

Furthermore, the symptoms of ADHD are usually improved under Methylphenidate (MPH) (which is one of the most frequently prescribed treatments for ADHD), as reported by parents and/or teachers of children (for review, see Wilens, 2003). Some studies have suggested that MPH could improve performance in some tasks that measure response inhibition (Konrad et al., 2004; Scheres et al., 2003; Tannock et al., 1989, 1995), but concerning conflict tasks, data are not consistent since some studies reported that MPH was not found to reduce interference effects (Jonkman et al., 1999, 2007; Scheres et al., 2003) while a few others reported a positive effect of MPH on interference control (Chou et al., 2015; Langleben et al., 2006; Ridderinkhof et al., 2005). However, these studies, except one (Ridderinkhof et al., 2005), have not yet been able

to disentangle response inhibition processes from other processes involved in interference control. Therefore, the second aim of the study was to more purely explore the effect of MPH on inhibitory processes by using analytic tools that allow us to separately quantify the effects of MPH on the intensity of impulse responses and on the ability to inhibit them.

Dynamic analyses of performance and interference control

The "activation-suppression" 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. Therefore, the model enables two predictions.

First, if the suppression of impulse 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 on incongruent compared to congruent trials. Hence, the strength of impulse capture should be reflected in the proportion of errors on incongruent trials at the shortest RTs (fast errors). These can be evaluated by plotting accuracy rates against RT (known as conditional accuracy functions, CAF; Suarez et al., 2015a; Van den Wildenberg et al., 2010; Van Wouve et al., 2016; Wylie et al., 2010, 2012, 2013). On the other hand, inhibitory control should be more evident during slower responses when the inhibition of the response impulse 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-plot function). The interference effect decrease in the longest RTs can be considered a reliable measure of the efficiency of the inhibition (Suarez et al., 2015a, 2015b; 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 delta-plot function 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). For a more elaborate presentation and discussion of these distributional analytic tools, the reader is referred to previously cited references (Ridderinkhof, 2002; Ridderinkhof et al., 2004; Van den Wildenberg et al., 2010).

To summarize, the aim of the present study was to understand cognitive mechanisms involved in interference control and their dissociability by using dynamic analyses of performance, which allow for the separate investigation of the intensity of impulse capture and the efficiency of selective inhibition in children with ADHD. We explored differences between three groups of children: Children diagnosed with ADHD who had never received medication, children diagnosed with ADHD while under MPH, and control children (typically developing peers), with respect to impulse capture and response inhibition in interference control. If ADHD does involve a response inhibition deficit, as hypothesized by current mainstream theories (e.g., Barkley, 1997; Nigg, 2001), then the slope of the delta-plot function at the longest RTs should be more negative going for control children than for children with ADHD without medication. If ADHD involves excessive direct impulse capture, then children with ADHD without medication should commit more fast errors (indicated by the first point of the distribution analysis of the accuracy rate in incongruent trials) compared with control children. And if MPH does indeed serve to improve response inhibition and reduce impulse capture, then the last slope of the delta-plot function at the longest RTs should be more negative going for children with ADHD under MPH compared with children with ADHD without medication, and children under MPH should also commit fewer fast errors than children without MPH. Moreover, if it is found that, instead of affecting both processes, MPH affected one and not the other then their separate pharmacological susceptibility would constitute further evidence of the independence of the two cognitive processes. This would show how differential responses to pharmacological intervention can be used to investigate and further our understanding of cognitive processes.

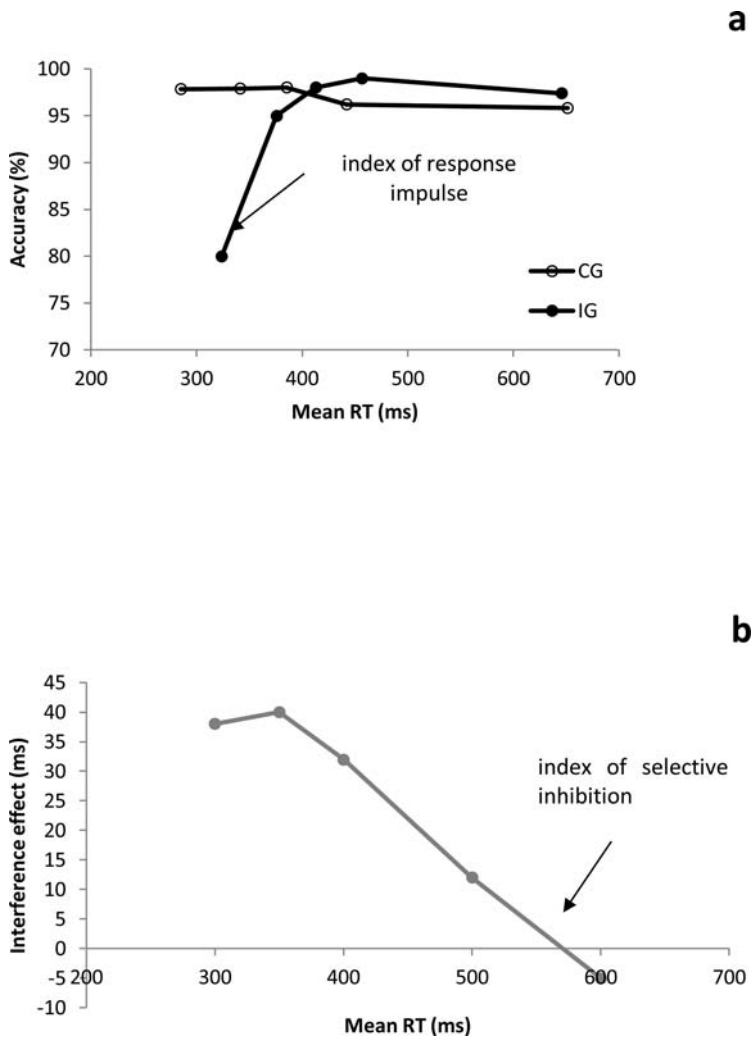

Figure 1. Example of a distributional analysis of performance with five quantiles. (a) Response impulse. Conditional accuracy functions (CAF) for congruent (white circles) and incongruent (black circles) trials. (b) Response inhibition. Delta plot representing the interference effect as a function of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

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.

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-

Table 1. Demographic variables for the three groups (mean and standard error of the mean, SEM).

	Untreated ADHD children (n = 25) Mean (sem)	ADHD children with MPH (n = 20) Mean (sem)	Control group (n = 20) Mean (sem)	Untreated ADHD children *versus* Control t_{43} =	MPH-ADHD children *versus* 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

Note: IQ = Intellectual quotient; Attention symptoms and Impulsivity/Hyperactivity symptoms were assessed by using the Conner's Parent Rating scales.

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 et al., 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 behavioural 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 in 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, including 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 children with ADHD. 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 et al., 2006). RTs were recorded at the nearest millisecond.

1.2.2. Task and procedure

The children's task was to respond as quickly and accurately as possible on the basis of the colour 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 controlateral 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 colour, red or green, of the circle. The colour-response mapping was balanced across participants.

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

1.3. Dynamic analysis of performance

1.3.1. Impulse capture: dynamic analysis of accuracy

The dynamic analysis of accuracy 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 (Ridderinkhof, 2002; Ridderinkhof et al., 2004; Van den Wildenberg et al., 2010).

1.3.2. Selective response inhibition: 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 et al., 2002; Ridderinkhof, 2002; Suarez et al., 2015a, 2015b). The slope of the last segment of the delta-plot was used as an index of the efficiency of the inhibition of automatic responses (Ridderinkhof, 2002; Ridderinkhof et al., 2004; Van den Wildenberg et al., 2010).

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 factor 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 IG CAF which have been proposed to be the most sensitive measure of impulse 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 CAF 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 Quintiles. 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 2(a) 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 $d = 0.73$).

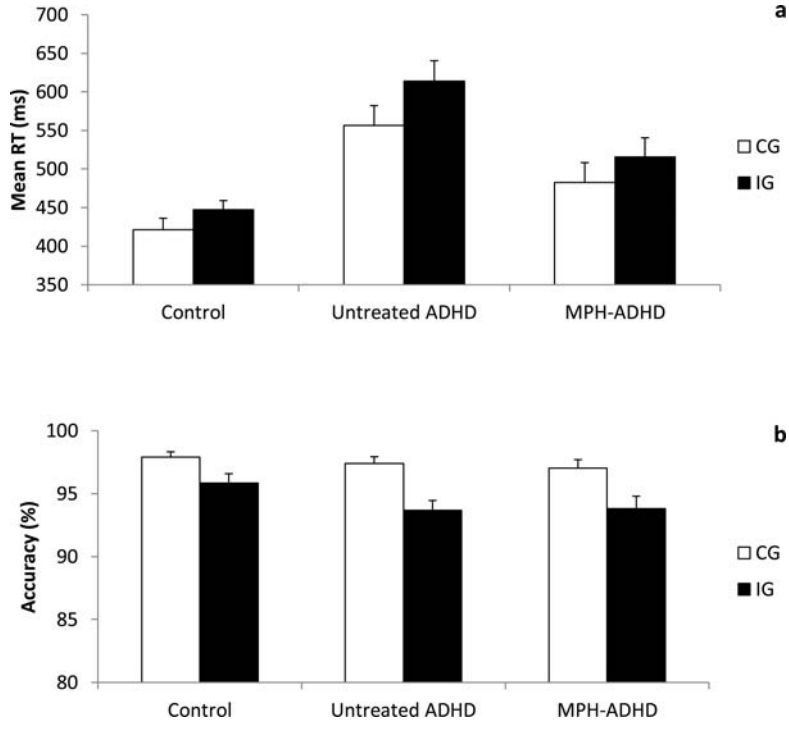

Figure 2. Simon task performance. Overall mean RT (a) and accuracy rate (b) for congruent (white bars) and incongruent (black bars) trials for control children, untreated children with ADHD, and children with ADHD under MPH. Error bars are mean standard errors.

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).

2.1.2. Accuracy rates

As seen in Figure 2(b), which represents accuracy rates for the three groups of children, treated and untreated children with ADHD did not produce 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. Impulse capture: dynamic analysis of accuracy

Figure 3(a) 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

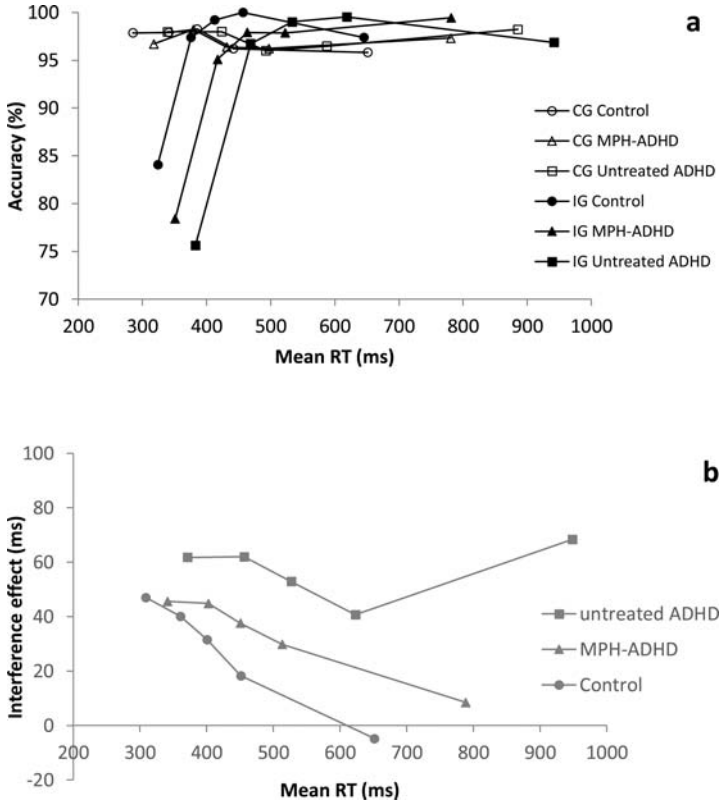

Figure 3. (a) Response impulse. Conditional accuracy functions (CAF) for congruent (white symbols) and incongruent (black symbols) trials for untreated ADHD group (squares), MPH-ADHD group (triangles), and control group (circles). (b) Response inhibition. Delta plots showing Simon effect size as a function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

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 3(b)).

2.2.2. Selective response inhibition: dynamic analysis of the interference effect

Figure 3(b) 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.

3. Discussion

The aim of the present study was to investigate the effect of ADHD and MPH on the expression and suppression of impulse actions to better understand

cognitive processes involved in interference control in children with ADHD. 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 revealed that children with ADHD exhibited weaker performance than control children. First, they were slower without committing fewer 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 a cognitive control deficit in children with ADHD (for a review, see Mullane et al., 2009).

Cognitive control deficits in children with ADHD have mainly been interpreted as deficits in inhibitory processes (Barkley, 1997; Nigg, 2001). But the use of dynamic analyses of performance data can help to more precisely investigate cognitive control by allowing the impulse capture and the subsequent selective inhibition of automatic responses to be dissociated. Two main results were obtained. First, the dynamic analysis of the accuracy revealed that children with ADHD committed more fast errors in IGs than control children. These results revealed that children with ADHD presented a stronger propensity to impulse capture. In other words, it indicates that children with ADHD were more prone to activate responses which are ipsilateral to the stimulus position, which suggests that they have more difficulty not being influenced by salient yet irrelevant information. This could come from difficulties in ignoring the irrelevant feature of the stimulus, its position, and/or in maintaining attention on the relevant feature, its colour. Second, delta-plot analyses revealed that the interference effect decreased for the longest RTs for the control group, as classically observed in control populations (Burle et al., 2005; Wijnen & Ridderinkhof, 2007). In contrast, it remained stable for untreated children with ADHD. Based on the "activation-suppression" model (Ridderinkhof, 2002), these results indicate that children with ADHD had difficulties in suppressing response impulse, that is the response automatically activated in response to the position of the stimulus.

Therefore, our data suggest that difficulties in interference control observed in children with ADHD are due to both a larger vulnerability to response impulses and more difficulties in suppressing them. Our data thus confirm an inhibition deficit in children with ADHD, but also suggest that their difficulties in cognitive control cannot be explained by an inhibition deficit only. The inhibition deficit has often been considered the core deficit in different models of ADHD (Barkley, 1997; Nigg, 2001). According to these models, behavioural inhibition is the key process underlying the correct functioning of the executive system, and an impairment of this system would explain impaired performance of individuals with ADHD in various tasks that evaluate executive functions. But our data suggest that difficulties in cognitive control observed in children with ADHD are also explained by a greater propensity to activate automatic responses, something which is rarely considered in most studies. If we consider, as proposed by DeYoung (2013), that impulsive responses entail at least the two processes we investigated: a response impulse, whose strength can depend on the context, and a lack of inhibition, our data suggest that symptoms observed in children with ADHD—such as impulsivity and hyperactivity—may also be explained by a larger vulnerability to response impulse. In other terms, impaired inhibitory control would be not sufficient to account for ADHD symptoms alone. It must be rather envisaged that these symptoms could also be due to a larger vulnerability to response impulse, that is to premature motor responses to information that turns out to be irrelevant.

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 difficulties in maintaining sustained attention (Friedman-Hill et al., 2010; Heaton et al., 2001; Huang-Pollock et al., 2006). Fluctuations in sustained attention could produce attentional lapses which would prevent

these children from focusing their attention on the relevant characteristic of the stimulus, the colour. Therefore, 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). This seems consistent with neuropsychological models of ADHD which propose that ADHD could be due to a nonoptimal activation state regulation (Sergeant et al., 1999; van der Meere, 1996). According to this hypothesis, children with ADHD might be unable to modulate their levels of arousal and activation according to task and situational demands, yielding to attentional lapses. This also seems in line with the recent neuroenergetic theory (NeT) of ADHD (Killeen, 2013; Killeen et al., 2013) which proposes that all effortful tasks could be impaired in ADHD because of an insufficient neuronal energy supply, leading to neuronal fatigue.

To summarize, our observations in children with ADHD therefore suggest that difficulties in cognitive control could come from difficulties in response inhibition but also from difficulties in maintaining sustained attention, probably responsible for the greater vulnerability to impulse capture. Interference control likely involves multiple component processes in addition to response inhibition. Each of these components may contribute independently to the size of the interference effect and may thus be differentially sensitive to the effects of ADHD. These conclusions should lead to a better understanding of attentional difficulties in explaining ADHD deficit as well as a better understanding of the role of attention in cognitive control. Moreover, it has to be noted that these conclusions could not have been obtained when analyses were limited to evaluating overall performance. These findings highlight the usefulness of the distributional analytic tools provided by the "activation-suppression" model.

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 et al. (2012) 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 selectively modified the delta-plot function. In both the control children and the ADHD children receiving MPH, the slope of the last segment was negative. These data suggest that MPH improved interference control for slower RTs, and hence the findings reveal improved effectiveness in the inhibition of automatic responses. Our findings thus confirm previously reported data suggesting that MPH globally improves performance in tasks that involve response inhibition (Konrad et al., 2004; Ridderinkhof et al., 2005; Scheres et al., 2003; Tannock et al., 1989, 1995). This is consistent with the putative effects of MPH on the fronto-striatal dopaminergic system (Madras et al., 2005; Rubia et al., 2011; Volkow et al., 1995, 2001) also known to be involved in inhibition (Aron, 2007; Aron et al., 2004, 2016).

In contrast, the dynamic analysis of the accuracy rate did not reveal a positive effect of MPH on the vulnerability to impulse capture: 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. This indicates that the vulnerability to prepotent distractors (such as the stimulus location), which trigger automatic responses, was not reduced under MPH. To summarize, our findings showed that MPH improved interference control by reducing the inhibition deficit without decreasing the vulnerability to impulse capture. In other words, the global improvement of the interference effect observed under MPH was essentially due to an improvement in inhibition efficiency.

The observation that MPH improved inhibitory processes but had no effect on the susceptibility to impulse capture also suggests that the two processes are independent. Accordingly, our data confirm data obtained in previous studies which have revealed that these two components of interference control can be differently impacted in certain cases (Fluchère et al., 2015, 2018; Ramdani et al., 2015). For example, it has been shown that subthalamic nucleus stimulation delivered to patients with Parkinson disease

selectively impairs selective suppression of response impulse but does not modify the strength of impulse capture (Fluchère et al., 2018). This dissociation also suggests that these functions are probably associated with different brain systems as already suggested by some data from neuroimaging studies (Forstmann et al., 2008). Therefore, it seems of importance to have analytical tools allowing the two processes to be dissociated when investigating cognitive processes underlying cognitive control because this dissociation could have important implications for refining explanations of ADHD but also for classifying patients according to different symptoms and for determining individualized treatments.

3.3. Conclusions

This study provides a good example of how pharmacological interventions can be used to investigate the nature and dissociability of cognitive functions. Differential responses to pharmacological interventions such as those we have reported here can provide greater understanding of the component processes used in complex task, based on a similar logic as that used in traditional cognitive neuropsychological research. Here, we found that MPH modulated inhibitory control but not impulse capture, which demonstrate that at least two dissociable cognitive processes are involved in cognitive control.

More specifically, two main conclusions may be drawn from our data. First, the difficulties in interference control resolution observed in untreated children with ADHD can be explained not only by a deficit in inhibitory control engaged to suppress automatic responses but also by a larger vulnerability to impulse capture. Second, MPH reduced these difficulties by only improving inhibitory processes, without reducing the strength of the impulse capture. These 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 et al., 2005). The authors reported children with ADHD had difficulties in suppressing response impulse but did not report a larger vulnerability to response impulse. Furthermore, their data revealed a positive effect of MPH on both the impulse capture and the efficiency of inhibitory processes. The partial discrepancies between both studies could be due to several differences between studies. First, concerning the response impulse, Ridderinkhof et al. (2005) drew 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 and by Ridderinkhof himself (Ridderinkhof et al., 2012; 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 (perceptual interference). Data from a recent study comparing the two tasks have suggested that the control of inappropriate responses is more difficult to identify and less stable in the flanker task (Burle et al., 2014). Third, the effect of MPH was investigated in a within-subject titration study, which is not the case in the present study (in which the dose of MPH was optimal for each child). Lastly, it is possible that our findings differed from those previously reported by Ridderinkhof et al. (2005) because the population of children with ADHD were not strictly equivalent. Indeed, in our study, all children who participated to the experiment met the criteria for the combined subtype in order for the ADHD groups to be as homogeneous as possible. In Ridderinkhof et al's study, on the basis of the DSM IV scores, one child met the criteria for ADHD hyperactive/impulsive subtype, seven children were of the inattentive type, and twelve children were of the combined subtype. We cannot exclude that the different subtypes of ADHD could be associated with different effects on inhibitory processes and/or response capture. We have no bases for addressing this issue in the present study since we chose to include only combined subtypes but it has already been proposed that only approximately half of children and adolescents with ADHD show deficits in inhibitory control (Bedard et al., 2003; Biederman et al., 2004; Nigg et al., 2005). This question merits then further investigation by using more precises measure of inhibitory processes.

Our data have also revealed that children with ADHD presented a larger vulnerability to impulse responses which may be explained by more difficulties in maintaining attention on relevant information and then in ignoring distractors. This suggests that difficulties in cognitive control observed in some

populations such as in children with ADHD could also come from attentional difficulties (Stocco et al., 2017). Cognitive control could, thus, be a form of executive function implemented by sustained and selective attention (Perri, 2020). Sustained attention level could modulate the vulnerability to impulse response and selective attention could increase inhibitory processes. The hypothesis of a link between inhibition and selective attention has received support from several studies. Event-related potentials studies have indicated that the higher the selective attention, the larger the component considered to be associated with inhibition (Joliot et al., 2009). The role of selective attention in interference control has also been hinted at in some studies investigating the role of selective attention in the Simon task (Suarez et al., 2015b; Ward et al., 2005). Moreover, in the literature, it has been proposed that MPH could improve ADHD symptoms by indirectly influencing other cognitive processes, such as selective attention (Hanisch et al., 2004; Konrad et al., 2004; Volkow et al., 2005). The improvement of inhibitory processes observed in children with ADHD under MPH could, therefore, also be explained by increased selective attention. If we consider that cognitive control and attentional processes are closely connected, it is important to consider the deficits in cognitive control as possible deficits in attention. As a consequence, this would suggest that treatment of hyperactivity and impulsivity may benefit from stimulating specific forms of attention. Further studies are needed to more precisely investigate the links between attentional processes and cognitive control of impulsivity before proposing new ways to explain ADHD.

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