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published in
Journal of Abnormal Psychology
2005

DOI (link to publisher)
10.1037/0021-843X.114.2.197

document version
Publisher's PDF, also known as Version of record

Journal of Abnormal Psychology
2005, Vol. 114, No. 2, 197–215

0021-843X/05/$12.00 DOI: 10.1037/0021-843X.114.2.197

Delta Plots in the Study of Individual Differences: New Tools Reveal Response Inhibition Deficits in AD/HD That Are Eliminated by Methylphenidate Treatment

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The authors highlight the utility of distribution-analytical techniques in the study of individual differences and clinical disorders. Cognitive deficits associated with attention-deficit/hyperactivity disorder (AD/HD) were examined by using delta-plot analyses of performance data (reaction time and accuracy) obtained through the use of a prototypical conflict task, the Eriksen flanker task. In 20 children with AD/HD (compared with matched control participants), overall performance measures indicated a marginal performance deficit. Delta-plot analyses indicated that performance deficits associated with AD/HD involve response inhibition but not automatic response activation. In a within-subjects titration study, the response inhibition deficit was eliminated by methylphenidate treatment, but these effects were highly dose specific. The beneficial effect of methylphenidate was clarified further after correcting for interindividual variation in sensitivity to medicine dosage.

Keywords: individual differences, AD/HD, inhibition, distribution analysis, methylphenidate

This article aims to point out the merits of applying distribution-analytical techniques to the study of individual differences and clinical disorders, and we illustrate the utility of these techniques by introducing delta-plot analysis to the study of attention-deficit/hyperactivity disorder (AD/HD). AD/HD is among the most prevalent and most extensively studied childhood pathologies. Mainstream theories of neurocognitive deficits associated with AD/HD currently focus on the role of impulsivity and response inhibition (e.g., Barkley, 1997; Nigg, 2001). Response inhibition is a key instrument of executive control supported primarily by frontal brain structures (e.g., Band & van Boxtel, 1999; Casey, Tottenham, & Fossella, 2002) and is invoked to suppress prepotent responses when such responses are reflex-like, premature, inappropriate, or incorrect. AD/HD-related deficiencies in the inhibition of prepotent actions have been examined widely with motor inhibition tasks (such as go/no-go tasks and stop tasks) and interference control or response conflict tasks (such as Stroop tasks, Eriksen flanker tasks, and antisaccade tasks).

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This research was supported by a grant from the Royal Netherlands Academy of Arts and Sciences to K. Richard Ridderinkhof.

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The role of frontal brain areas in resolving response conflict has been validated in studies that used neuroimaging techniques (e.g., Bench et al., 1993; Bush et al., 1998; Carter, Mintn, & Cohen, 1995; Hazeltine, Poldrack, & Gabrieli, 2000; McKeown et al., 1998; Ullsperger & von Cramon, 2001). Furthermore, a functional magnetic resonance imaging study of response conflict distinguished AD/HD adults and control participants both behaviorally and by sites of frontal cortical activation (Bush et al., 1999).

Response control is improved by methylphenidate (MPH) by enhancing frontal-lobe functioning (Mehta et al., 2000; Vaijdya et al., 1998), an effect that presumably involves a deficit associated with striato-frontal dopaminergic projections in AD/HD (e.g., Brandon, Marinelli, & White, 2003; Krause, Dresel, Krause, Kung, & Tatsch, 2000).

However, these studies have not yet been able to disentangle response inhibition processes from other processes involved in resolving response interference. Thus, to examine the role of response inhibition in AD/HD more closely, a relatively pure measure of such inhibition tasks is needed that is disentangled from other processes in response interference. Hitherto, response conflict task performance has been reported generally in terms of mean reaction times (RT), sometimes variances, but seldom in terms of higher order characteristics of reaction time distributions. AD/HD children have been shown, however, to differ from normal control participants in terms of distributional characteristics (in particular, AD/HD children show a more extended slow tail; Leth-Steensen, Elbaz, & Douglas, 2000). Here we show that such distributional features contain information highly relevant to the role of response inhibition in the neurocognitive deficits associated with AD/HD. We describe a study that uses the flanker task

(Eriksen & Eriksen, 1974) to examine AD/HD children in comparison to matched control participants (Scheres et al., 2004) as well as an MPH titration study (Scheres et al., 2003), and we report not only the results of traditional performance analyses but also of distributional analyses of RT and accuracy. We introduce into the AD/HD field a model of response activation and selective response suppression in conflict tasks, as well as the associated delta plot technique that has been shown to be sensitive specifically to automatic response activation and selective response inhibition (Ridderinkhof, 2002a). By response activation we refer to the process of building up activation for a particular response, rather than to activation states or supporting energetical mechanisms. We show how this model and the distribution-analytical techniques may provide further insights into the neurocognitive deficits associated with AD/HD and how MPH helps to restore this dysfunction.

AD/HD and Response Inhibition

Band and van Boxtel (1999) reviewed the cognitive-neuroscience literature on response inhibition and took the compiled evidence to support the notion that responses are held in check through inhibitory control, exercised by an executive system (located in prefrontal cortex) that supervises the flow of information through subordinate mechanisms (cf. Norman & Shallice, 1986; Logan & Cowan, 1984). Manifestations of inhibitory control can occur anywhere in the system (for instance in primary motor cortex, but also upstream from it, or downstream). Response inhibition can be general (serving to inhibit any ongoing motor activity, such as in stop tasks; Logan & Cowan, 1984) or selective (serving to inhibit the activation for one response but not the other), depending on where in the system the effect is exerted.

Along these lines, experimental studies that examined the nature of cognitive deficits in AD/HD have used motor inhibition tasks to study general inhibition and interference control or response conflict tasks to study selective inhibition. Substantial evidence has been amassed for the role of impulsivity and response inhibition in AD/HD. However, the picture is complex and not always entirely consistent.

Studies of motor inhibition have frequently reported that AD/HD is associated with inefficient response inhibition (for review see Nigg, 2001). However, several observations suggest that this inference is not entirely unequivocal. For instance, failures to withhold a response on no-go trials may be related to the strength of either inhibition processes, or "go" processes, or both (Schachar, Tannock, & Logan, 1993). Although this problem is addressed in the stop task (which isolates response execution processes from response inhibition processes; cf. Logan & Cowan, 1984), the specificity and magnitude of AD/HD-related deficiencies in stopping vary considerably across studies (e.g., Oosterlaan, Logan, & Sergeant, 1998), and such deficiencies are sometimes not observed at all (Daugherty, Quay, & Ramos, 1993; Jennings, van der Molen, Pelham, Debski, & Hoza, 1997; Kuntsi, Oosterlaan, & Stevenson, 2001; Pliszka, Liotti, & Woldorff, 2000; Rubia et al., 2001; Schachar, Tannock, Marriot, & Logan, 1995; Scheres, Oosterlaan, & Sergeant, 2001a, 2001b).

Studies of response conflict have also produced mixed results. AD/HD deficits in the inhibition of reflexive eye movements in antisaccade tasks have been reported in some (e.g., Castellanos et al., 2000; Munoz, Hampton, Moore, & Goldring, 1999; Rothlind, Posner, & Shaughency, 1991) but not all studies (Aman, Roberts, & Pennington, 1998). Likewise, whereas several authors have reported AD/HD deficits in interference effects on the Stroop task (e.g., Boucugnani & Jones, 1989; Houghton et al., 1999; MacLeod & Prior, 1996), others have failed to find significant effects (e.g., Bush et al., 1999; Grodzinsky & Diamond, 1992; Leung & Connoly, 1996).

Studies that examined response conflict in the Eriksen flanker task have reported AD/HD deficits more consistently (e.g., Carter et al., 1995; Crone, Jennings, & van der Molen, 2003; Hooks, Milich, & Pugzles Lorch, 1994; Jonkman et al., 1999). However, interference effects likely involve multiple component processes (such as selective attention, perceptual conflict, response execution and competition) in addition to response inhibition. Each of these components may contribute independently to the size of the interference effect (Ridderinkhof & van der Stelt, 2000), and may thus be differentially sensitive to the effects of AD/HD. Normal development in flanker task performance is characterized more by age-related improvements in processes related to response competition compared with perceptual conflict, as shown through the use of behavioral and psychophysiological approaches (Ridderinkhof & van der Molen, 1997). Likewise, Jonkman et al. (1999) used psychophysiological indices to show that AD/HD deficits in the flanker task involve response competition rather than perceptual conflict or response execution.

Dynamics of Response Activation and Response Inhibition in Conflict Tasks

Stroop, Simon, and Eriksen tasks are prototypical representatives of choice RT tasks in the conflict paradigm. In such tasks, the designated response is indicated by one aspect of the stimulus, but competing response tendencies may be elicited by other aspects of the stimulus, even if the latter are to be ignored. The typical observation is that responses are slowed when to-be-ignored stimulus features elicit the response opposite to (rather than the same response as) the one elicited by the target stimulus feature. For instance, in the arrow version of the Eriksen task that was used in the present study the participant's task is to ignore flanking arrows and to issue a discriminative response on the basis of the direction of a target arrow. Responses are typically slowed in incongruent (IG) trials, that is, when the flanking arrows point in the opposite direction from the target arrow rather than in the same direction, as in congruent (CG) trials.

Direct Activation and Selective Inhibition of Responses

In examining the mechanisms underlying interference effects in conflict tasks, many authors have reported evidence in support of a dual-route architecture of response activation (e.g., de Jong, Liang, & Lauber, 1994; Eimer, Hommel, & Prinz, 1995; Kornblum, Hasbroucq, & Osman, 1990; Ridderinkhof, van der Molen, & Bashore, 1995). A schematic representation of this type of model is depicted in Figure 1. Most significant, the controlled process of stimulus–response (S–R) translation is paralleled by a direct activation route; the two routes converge at the level of response activation processes. Note that, in contrast to winner-

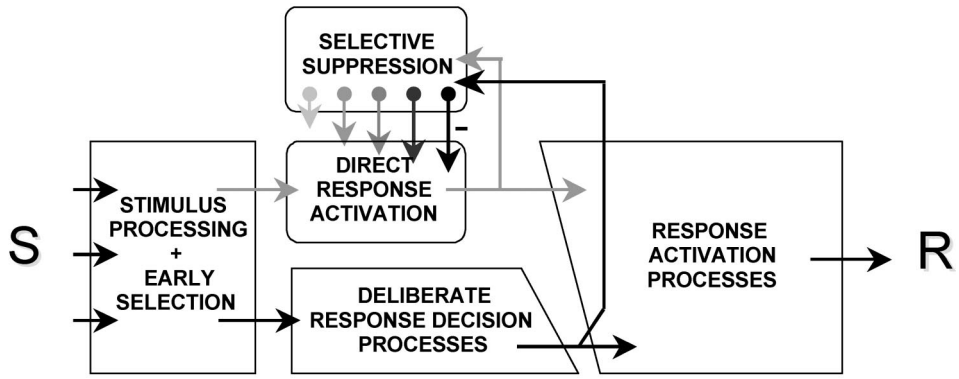

Figure 1. Elementary architecture of the dual-process model. The increasing size of the arrows from the suppression module schematically represent the operation dynamics of this module (i.e., suppression is not operational immediately and takes some time to build up). S = stimulus; R = response.

takes-all race models, response activation in this model can accumulate on the basis of inputs from both parallel routes.

The activation-suppression hypothesis (Ridderinkhof, 2002a) holds that (a) direct response activation resulting from irrelevant stimulus features is selectively suppressed, and (b) this selective inhibition takes some time to build up (see also Eimer, 1999). In Figure 1, the schematic representation of the dual-process model incorporates these selective suppression processes. Like most mental processes, both the activation of responses and the selective inhibition of direct activation are subject to variability. The time to encode and identify stimulus features and to select appropriate responses on the basis of target features varies from trial to trial and, as a consequence, the time course and strength of direct response activation vary from trial to trial. The strength, onset time, and/or build-up rate of selective inhibition of direct response activation may also vary from trial to trial. These notions are referred to as the *activation-variability premise* and the *suppression-variability premise*, respectively (Ridderinkhof, 2002b). Together, the dual-process model and the activation-suppression hypothesis (for a review see Ridderinkhof, van den Wildenberg, Wijnen, & Burle, 2004) give rise to the following sets of general predictions.

Predictions Derived from the Activation-Suppression Hypothesis

The first predicted pattern relies on the activation-variability premise. The slower the processing in the deliberate decision route, the more time is available for response activation along the direct activation route. Thus, if deliberate response decision processes were to proceed relatively quickly, then the effects of direct activation should be short-lived; on IG trials, the build-up of activation for the incorrect response along the direct-activation route would not be able to reach high amplitudes before response activation based on the deliberate route takes over. As a consequence, the correct response can be activated relatively quickly, and few errors result. If deliberate response decision processes were to proceed relatively slowly, then the effects of direct response activation should last longer; the build-up of activation for the incorrect response along the direct-activation route could attain higher amplitudes before the correct response is activated along the deliberate route. As a result, activation for the correct response starts relatively late. If deliberate response decision processes were too slow, then the activation for the incorrect response along the direct-activation route could transgress the threshold at which an overt response is emitted. Note that the result is a *fast* error; by contrast, if direct activation for the incorrect response were to stay just below the threshold for responding, the result would be a *slow* correct response.

The second predicted pattern capitalizes on the suppression-variability premise. The effects of direct response activation should be shorter lived in conditions in which selective inhibition of that activation is relatively strong compared with conditions in which selective inhibition is relatively weak. With strong inhibition, the build up of activation for the incorrect response along the direct-activation route would be able to attain a lesser magnitude before being corrected by selective suppression processes. As a consequence, the activation of the incorrect response along the direct-activation route will exceed the response threshold sooner when selective inhibition is weak compared with when it is strong. In other words, under a stronger inhibition regime, one may more often prevent incorrect activation from resulting in an overt response. Thus, with decreasing inhibitory strength, the proportion of fast IG errors would increase, and errors would occur also at increasingly longer RTs. This would occur because the influence of direct response activation would last longer before inhibition processes mounted. More important, in strong-inhibition compared with weak-inhibition conditions activation for the correct IG response should benefit (i.e., can be initiated earlier and build up more quickly) from suppression of the incorrect response activation. With weak inhibition only the slower IG responses benefit from selective inhibition; with stronger inhibition, the facilitation of IG responses will be more pronounced, and faster IG responses will also benefit from selective inhibition.

Evidence for the activation-suppression hypothesis and its predictions with respect to the dynamics of direct response activation and selective inhibition has been derived from distributional analyses of behavioral data (RT and accuracy), as will be reviewed below. The distribution-analytic approach allows for a careful examination of these temporal dynamics, as we discuss briefly in

the next section. For a more elaborate discussion of these analytical tools the reader is referred to the Appendix.

Distributional Analyses in Conflict Tasks

Several tools are available for distributional analyses. The present focus is on conditional accuracy functions (CAFs) and cumulative density functions (CDFs), followed by delta plots that provide a convenient simplification of the information present in CAFs and CDFs (delta plots show the magnitude of interference effects as a function of response speed; see the Appendix). It was argued above that IG but not CG trials are characterized by many fast direct-activation errors. Thus, in delta plots for accuracy, the slopes between the earliest quantile points will differ significantly between conditions involving strong versus weak direct response activation, whereas at later quantiles these slopes differ less and approach zero (for an illustration, the reader is referred to Figure A4 in the Appendix). It was argued further that with weak inhibition only the slower IG responses benefit from selective inhibition, whereas with stronger inhibition, the benefit for IG responses is more pronounced and extends to faster portions of the CDF (such that only the fastest responses are error prone). Thus, in delta plots for RT, the slopes between quantile points turn from positive to more negative relatively late when inhibition is weak and turn from positive to more negative progressively earlier when inhibition is stronger (for an illustration, refer to Figure A3 in the Appendix). The point of divergence between two delta plots (representing two different levels of inhibitory strength) is the critical variable in comparisons between groups or conditions.

Thus, perhaps counterintuitively, this logic leads us to look for response inhibition effects primarily in response speed and for response activation effects primarily in response accuracy (for a review see Ridderinkhof et al., 2004).

Evidence for the Activation-Suppression Hypothesis: A Brief Review

Eimer (1999; Eimer & Schlaghecken, 1998) presented masked prime stimuli prior to target stimuli. The subliminally presented primes could be congruent or incongruent to the target stimuli (i.e., associated with the same or opposite response, respectively). With short intervals between prime presentation and target presentation, performance benefits were observed for congruent compared with incongruent trials, but these benefits turned to performance costs at longer intervals. Event-related brain potentials demonstrated that the masked primes initially generated direct activation of the corresponding response in primary motor cortex, which was subsequently suppressed. At short intervals, activation of the response associated with the cue escapes suppression and is followed immediately by activation of the response associated with the target. Thus, responses to congruent cue–target pairs are facilitated compared with responses to incongruent pairs. At longer intervals, inhibition (which is slow to develop) kicks in, so that a triphasic pattern emerges: (a) activation of the response associated with the cue, (b) selective inhibition of this activation, and (c) activation of the response associated with the target. Thus, responses to congruent cue–target pairs show (a) activation of the correct response, (b) inhibition of that response, and (c) reactivation of that response, rendering the eventual reaction to be relatively slow and error-prone (as the correct response was inhibited). By contrast, responses to incongruent cue–target pairs show (a) activation of the incorrect response, (b) inhibition of that response, and (c) activation of the correct response, yielding a relative fast and accurate reaction (as the incorrect response was inhibited). Thus, these data evidenced a pattern of facilitation followed by inhibition.

Ridderinkhof (2002a) argued that this pattern of facilitation followed by inhibition would be expressed in delta plots in the leveling off or turning negative during slower segments of the response time distribution and designed a series of experiments to verify this prediction. In one experiment, Simon-task stimuli (that required a two-choice response on the basis of stimulus color) were incidentally intermixed with similar stimuli that required a response on the basis of stimulus shape; stimulus location could always be ignored (and thus location driven direct response activation could always be suppressed). In a second condition, that used the exact same stimuli, the mixed-in trials required a response on the basis of their location; thus, suppression of location driven direct response activation could be disadvantageous. Distributional analyses of the RT data from the regular Simon task (that was identical in all respects across the two contexts) revealed opposite results for the two contexts: delta plots leveled off early and turned negative for the condition in which location driven response activation could always be suppressed but not for the context in which location was sometimes relevant.

Burle and colleagues (Burle, Possamai, Vidal, Bonnet, & Hasbroucq, 2002) used electromyographic recordings to demonstrate that this delta plot effect reflects an online act of inhibitory control. In a regular version of the Simon task, these authors showed that the leveling off and turning negative of the delta plot was most prominent on those trials that contained partial errors (i.e., subthreshold activation of the muscles involved in the incorrect response prior to the threshold activation of the correct response). The operation of response inhibition is most critical on those trials on which the incorrect response is actually activated to the motor level, and this inhibitory engagement is expressed in the prominent deflection in the delta plot. Together, these studies provide behavioral and psychophysiological evidence for the expression of selective response suppression processes in RT distributions, in particular in the leveling off of delta plots.

The Present Study

Each of the patterns of results reviewed above is consistent with the predictions derived from the activation-suppression hypothesis, although competing theories of interference effects have thus far not been able to capture these distributional features. In the present study we illustrate the utility of the methodology described above in the study of clinical disorders and individual differences. Here we use delta plot analysis to explore differences between children with AD/HD and control children with respect to response inhibition in interference control and the amelioration of this difference by MPH. To that end, speed and accuracy were recorded in an arrow variety of the Eriksen task (described below). This arrow version has been used originally to study interference effects in normal young children (Ridderinkhof & van der Molen, 1995) and has been used successfully in several studies with children with AD/HD (e.g., Crone et al., 2003; Jonkman et al., 1999). The

present data were taken from a larger-scale titration study that examined effects of MPH on performance in a variety of response inhibition tasks (reported in Scheres et al., 2003, 2004). The multiple-blind crossover design of this study allowed a comparison of three MPH doses to placebo (in addition to baseline measurements in which MPH expectancy was absent). In the original report, only mean RTs were reported for the flanker task (along with several dependent measures from several other tasks). In this study, 20 children with AD/HD were matched carefully to control children in terms of age, gender, and IQ, and we report in detail the results of distribution analyses that augmented the analyses of overall performance.

One primary aim was to establish whether children with AD/HD, when matched carefully to control children in terms of age, gender, and IQ, show a deficit in response inhibition. If AD/HD does involve a response inhibition deficit, as hypothesized by current mainstream theories (e.g., Barkley, 1997; Nigg, 2001), then the slopes of (especially the slower segments of) delta plots for RT should be more negative going for control children than for children with AD/HD measured at baseline (without MPH expectation). The predicted pattern is shown schematically in the hypothetical delta plot in Figure 2A. If AD/HD involves excessive direct response activation, then the slopes of the faster segments of delta plots for accuracy should be steeper for children with AD/HD compared with control children (illustrated in Figure 2B).

Note that, although the duration of deliberate decision-making processes is obviously variable, we are not making assumptions about differential stability or variability in these processes in AD/HD children compared with control children. More specific, individual differences in delta plot slopes are not assumed to covary consistently with individual differences in the duration of deliberate decision-making processes. Although differences in these parameters are quite conceivable, here we focus on differences in response activation and inhibition processes, leaving it to other studies to examine variability in decision processes.

Another primary aim was to establish whether response inhibition deficits in children with AD/HD are reduced by MPH and to examine dose effectiveness. MPH (also known as Ritalin) is the most frequently prescribed medication for children with AD/HD (Goldman, Genel, Bezman, & Slanetz, 1998; Swanson, McBurnett, Christian, & Wigal, 1995). It has been shown to reduce symptoms of inattention, hyperactivity, and impulsivity, as observed by parents and/or teachers (e.g., Schachar & Tannock, 1993). MPH has also been observed to improve performance on tasks that measure response inhibition (e.g., Everett, Thomas, Cote, Levesque, & Michaud, 1991; Konrad, Günther, Hanisch, & Herpertz-Dahlmann, 2004; Scheres et al., 2003; Tannock, Schachar, Carr, Chajczyk, & Logan, 1989; Tannock, Schachar, & Logan, 1995). In another study (Jonkman et al., 1999) that used the flanker task, MPH was not found to reduce interference effects. Given the fact that theories on impaired response inhibition are among the most widely recognized conceptions in trying to understand the main symptoms in children with AD/HD, it is surprising that only a few studies have focused on the effect of MPH on measures of response inhibition.

If MPH does indeed serve to improve response inhibition, then the slopes of (especially the slower segments of) delta plots for RT should be more negative going for MPH compared with the placebo. In addition, delta plot slopes are hypothesized to be more negative going as MPH doses increase.

Curiously, the nature of individual patterns of response to MPH shown by children with AD/HD is usually highly idiosyncratic (Hoeppner et al., 1997; Pelham & Smith, 2000; Rapport, DuPaul, Stoner, Birmingham, & Masse, 1985). Sensitivity to different MPH doses is subject to considerable interindividual variability (whereas for some individuals performance improves optimally with high doses of MPH, other individuals may benefit more from lower doses; Clarke, Barry, McCarthy, & Selikowitz, 2002; Rapport et al., 1987). Such differences may obscure the efficacy of MPH in improving inhibitory control over inappropriate responses.

We examine this effectiveness by using the distribution analytic techniques described above. In an attempt to correct for this variability, and thus obtain a less obscure picture of the beneficial effects of MPH, additional procedures were designed to establish *dose effectiveness* for each dose and for each individual separately, and to reanalyze the data accordingly. For each participant, the optimum dose, the least optimal dose, and the intermediate dose was determined operationally by rank ordering the interference effect on mean RT, as induced by incongruent compared with congruent flankers. For any given participant, the optimum dose thus was that MPH dose that resulted in the smallest interference effect. Although this data-driven operational definition is obviously rather arbitrary and has clear limitations in terms of its predictive power (as to dose effectiveness in general), it does provide us with a clearer view on the mechanisms (in particular the deployment of inhibitory capabilities) through which MPH helps to optimize the resistance to flanker interference. In other words, the role of response inhibition in the remedial effects of MPH on the sensitivity to interference effects can now be studied under relatively pure conditions, that is, after controlling for individual differences in dose-dependent differences in sensitivity with respect to these interference effects.

Method

Participants

In the studies reported by Scheres et al. (2003, 2004), 23 boys with AD/HD (age: $M = 8.7$, $SD = 1.7$; range: 6–12 years; IQ: $M = 97.6$, $SD = 14.7$) and 22 normal control boys (age: $M = 9.6$, $SD = 1.8$; range: 6–12; IQ: $M = 104.7$, $SD = 19.1$) participated. Selection procedures are reported in detail in Scheres et al. (2004), but will be reviewed briefly below for completeness. Intelligence was assessed individually by administering four subtests of the Wechsler Intelligence Scale for Children—Revised (WISC–R). IQ as estimated by the Vocabulary, Arithmetic, Block Design, and Picture Arrangement subtests correlates (.90) with the full-scale IQ (Groth-Marnat, 1997). Each of the tested children had an IQ score of 70 or higher.

Selection procedure for the AD/HD group. Children in the AD/HD group were referred to pediatricians and child psychiatrists and were all identified as meeting the *Diagnostic and Statistical Manual of Mental Disorders* (4th ed.; *DSM–IV*; American Psychiatric Association, 1994) criteria for AD/HD by their physician and/or a multidisciplinary team of professionals. All children diagnosed with AD/HD were advised treatment with MPH; none of them had used MPH previously. Parents of all the children who were diagnosed with AD/HD were administered the Diagnostic Interview Schedule for Children—Parent version (DISC–IV; Schaffer, Fisher, Lucas, Dulcan, & Schwab-Stone, 2000). The DISC–IV is a structured interview that generates *DSM–IV* diagnoses. If children met the

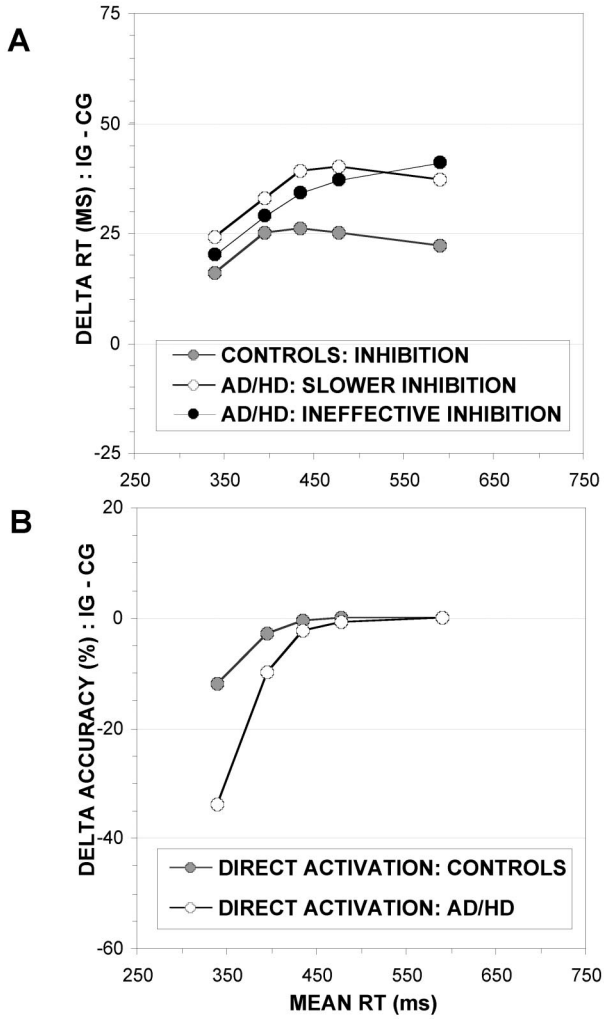

Figure 2. Schematic illustration of potential delta plot effects, showing hypothetical examples of deficient response inhibition (A) and excessive direct response activation (B). A: Delta plots for response speed. Delta plots show effect size (i.e., in this instance the magnitude of the Eriksen flanker effect) as a function of response speed (as expressed in reaction time [RT] quintile scores). Efficient response inhibition is expressed in the leveling off and turning negative of the delta plot at slower segments (CONTROLS: INHIBITION). In control children inhibition may affect all responses except the fastest, whereas with weaker inhibition in children with attention-deficit/hyperactivity disorder (AD/HD) only the slower responses may benefit. In this case, the slope is equally negative going (indicating efficient response suppression) in the slower segments of the delta plots, but the point in time at which delta plots start to level off is later for the weaker-inhibition condition (AD/HD: SLOWER INHIBITION). Alternatively, children with AD/HD might not be able to approach the level or efficiency of response suppression obtained in control children, not even in the slowest responses. In that case, slopes in the slower segments of the delta plots differ between groups (AD/HD: INEFFECTIVE INHIBITION). Thus, deficiencies in response suppression may be expressed in the point of divergence of the delta plots, or in the slopes of the slowest segments, or both. B: Delta plots for accuracy. Excessive direct response activation results in reduced response accuracy for fast responses to incongruent but not congruent stimuli and is thus expressed in a greater interference effect in faster segments. As a consequence, the stronger the direct response activation, the steeper the fast segments of the delta plot. CG = congruent condition; IG = incongruent condition.

criteria for AD/HD on the DISC–IV, they entered the study. For all children who were diagnosed with AD/HD and referred to this study, the DISC–IV confirmed the *DSM–IV* diagnosis. DISC-IV results further indicated that 11 children with AD/HD also met criteria for a diagnosis of oppositional defiant disorder (ODD), and 1 child with AD/HD met criteria for conduct disorder (CD).

Parents and teachers of the children who were diagnosed with AD/HD on the DISC–IV also completed the Disruptive Behavioral Disorder Rating Scale (DBD; Pelham, Gnagy, Greenslade, & Milich, 1992) and the *DSM–IV* screener (Hartman et al., 2001). The DBD consists of four subscales (Hyperactivity/Impulsivity, Inattention, ODD, and CD), each of which is composed of specific *DSM–IV* items. The *DSM–IV* screener was developed to assess syndromes of childhood psychopathology on the basis of the *DSM–IV*. Descriptives for the AD/HD group on the DBD and the *DSM–IV* screener can be found in Scheres et al. (2003); scores on these scales conformed to the DISC–IV scores and were not used as additional exclusion criteria.

Data from 1 of the 23 children with AD/HD were excluded from data analysis because the child failed to perform at acceptable levels in most tasks in the Scheres et al. (2004) study and showed extremely slow and variable responses in the task reported here. A second child performed at chance-level accuracy in the placebo condition whereas accuracy was above 90% in all other conditions; data from this child were also disregarded. Data collection in the present task was incomplete for 1 further child with AD/HD. Thus, the AD/HD group in the present analyses consists of 20 boys (age: $M = 9.0$, $SD = 1.6$; range 7–12; IQ: $M = 100.7$, $SD = 12.7$). On the basis of DISC–IV scores, 1 of these children met criteria for AD/HD hyperactive/impulsive type, 7 children were of the inattentive type, and the remaining 12 children met criteria for the combined type.

Selection procedure for the normal control group. The normal control children were selected from regular schools in Amsterdam and its vicinity. Parents of all children in the age range of 6–12 years in three schools ($N = 403$) received information on the study. Parents who were willing to have their child participate ($n = 98$) signed an informed-consent form and completed the DBD questionnaire and the *DSM–IV* screener. Initial inclusion criteria for the normal control group were met if scores on the parent DBD were below the 80th percentile for the Hyperactivity/Impulsivity and Inattention subscales, and below the 90th percentile for the ODD and CD subscales ($n = 40$). The DBD and the *DSM–IV* screener were completed by the teachers for each of the remaining children. Inclusion criteria were met if scores on the teacher DBD were below the 90th percentile for each subscale ($n = 31$). Finally, for the present analyses we carefully selected children from the control group to match the 20 children with AD/HD on the basis of age, gender, and IQ. This selection procedure yielded a control group of 20 boys (age: $M = 9.4$, $SD = 1.7$; range 6–12; IQ: $M = 107.4$, $SD = 17.1$). One-way analyses of variance (ANOVAs) showed that the AD/HD and control groups did not differ significantly (at $\alpha = .05$) with respect to either age or IQ, $F(1, 38) = 0.57$ and 1.93, respectively.

Group descriptives. Groups differed on the parent and teacher DBD scales, which were used as the criterion measures for the normal control group. In addition, the groups differed from one another on all *DSM–IV* screener scales. Elevated scores in the AD/HD group on all scales were expected, because correlations between the syndrome scales range from .32 to .78 (Hartman et al., 2001). However, only scores on the AD/HD scales were above the 95th percentile for the AD/HD group.

Stimuli and Apparatus

Participants were seated 40 cm in front of an IBM-compatible personal computer that was used for stimulus presentation and response registration. Responses could be indicated by pressing one of two push buttons. All stimuli were presented in white against a black background. The stimulus array on each trial consisted of five stimuli: a target stimulus surrounded on

each side (to the left and to the right) by two distractor stimuli (flankers). Target stimuli were arrows (2.0 × 1.0 cm) pointing to the right or to the left, presented at the center of the computer screen. The direction of the target arrow indicated whether the child had to press the left or the right response button (left-pointing arrow, left-hand response, and vice versa). The flankers were either arrows (2.0 × 1.0 cm) or rectangles (2.0 × 0.6 cm). Combination of target and flankers yielded three types of stimulus arrays: neutral (NEU), congruent (CG), and incongruent (IG). A neutral array consisted of the target arrow flanked by rectangles (□ □ → □ □ or □ □ ← □ □). A congruent array consisted of the target arrow flanked by arrows that pointed in the same direction as the target (→ → → → → or ← ← ← ← ←). An incongruent array consisted of a target arrow flanked by arrows pointing in the opposite direction (→ → ← → → or ← ← → ← ←).

A trial started with the presentation of a small fixation cross at the center of the screen. After 500 ms, the stimulus array was presented for 1,000 ms, after which the screen turned black for 1,500 ms. The order of stimuli was determined randomly but with the restriction that each stimulus appeared equally often.

Task and Procedure

The participant's task was to make a rapid discriminative response on the basis of the direction of the target arrow and to ignore flanking stimuli. It was explained that the flankers could be NEU, CG, or IG, in equal proportions. Responses were to be given as fast as possible keeping error rates below 10% on average.

After the experimenter had verified that all instructions were understood, participants first performed four practice blocks of 45 trials each (15 trials per stimulus type), to familiarize them with the task and procedure and to allow them to optimize and stabilize their performance. Depending on the percentage of correct responses in each practice block, children were encouraged to (a) work as fast as possible (when the percentage of errors was between 0 and 5%), (b) work as accurately as possible (when the percentage of errors was higher than 10%), or (c) work as fast and accurately as possible (when the percentage of errors was between 5 and 10%). Next, six experimental blocks were presented, each consisting of 60 trials (20 trials per stimulus type). Blocks of trials were separated by 2-min intermissions. No incentives or rewards were used. Children received a small present after participation, but they were not made aware of this at any time before or during task performance.

Experimental Design

Between-subjects design: AD/HD versus matched control participants. Prior to any of the MPH or placebo sessions (and prior to any medication), the children diagnosed with AD/HD were tested at baseline (thus, no MPH expectation was present). The baseline session took place within 2 weeks after the DISC–IV and WISC–R assessment. Half of the AD/HD children and half of the matched control children were tested in the morning; all of the other children were tested in the afternoon. The data collected during this baseline session were used for between-subjects comparisons with matched control children (see above), who received a baseline session only.

Within-subjects design: Placebo and three different doses of MPH. Within a week after the baseline assessment, the children with AD/HD started the titration stage. A pseudorandomized, multiple-blind, placebo-controlled crossover design was used in which all participants received each of four treatment conditions: placebo, 5 mg of MPH, 10 mg of MPH, and 20 mg of MPH. Medication and placebo were prepared by the hospital pharmacy and packed in identical tablets (placebo tablets contained only a base granulate). The highest dose never exceeded 0.9 mg per kg body weight. Each treatment condition was administered during 7 days, twice daily, at breakfast (around 7:30 a.m.) and at lunch (around 12:30 p.m.). The titration procedure (for protocol details refer to Scheres et al., 2003) allowed for assessment of the child under the four treatment conditions on a fixed weekday. The order of the weeks was balanced using a Latin square design. All test sessions were in the afternoon. Medication compliance was verified throughout the medication period. During the assessments, the experimenter administered the tablet to the child 1 hr prior to testing. The experimenter was blind to the type of tablet.

Analytical Design

Several sets of analyses were designed to examine the effects of AD/HD (i.e., AD/HD children at baseline vs. matched control children) and of MPH treatment (i.e., placebo, low dose, medium dose, and high dose for AD/HD children). For all analyses, effect sizes (ES) will be reported as partial eta squared.

Baseline analysis. For each participant, mean RT and overall accuracy were determined for CG, IG, and NEU conditions (the first two trials in each experimental block were considered warm-up trials and were not included in the analyses) from the data collected at baseline (i.e., prior to the MPH and placebo sessions). Initial ANOVAs were conducted on mean RTs and accuracy scores and included the effects of the within-subjects variable congruence (CG vs. IG vs. NEU) and the between-subjects variable AD/HD (AD/HD vs. matched control children).

Next, for each participant, reaction times of all responses (including both correct and incorrect responses; response omissions were observed only incidentally) were rank ordered for each condition and then divided into five equal-size speed bins (quintiles). Mean RT and accuracy were determined for each quintile in each condition separately. Delta plots for accuracy and RT were constructed by plotting interference effect size (accuracy or mean RT in the IG condition minus accuracy or mean RT in the CG condition) as a function of response speed (the average of mean RTs in the CG and IG conditions per quintile). Overall, mean RT and accuracy were mathematically equivalent to the average of the mean RTs and accuracies of the five quintiles. Slopes were computed for the delta plot segments connecting the data points of Quintiles 1 and 2, Quintiles 2 and 3, Quintiles 3 and 4, and Quintiles 4 and 5. A second set of ANOVAs was conducted on the slopes of each of the delta plot segments (Q1–2, Q2–3, Q3–4, Q4–5) for RT, and on the slope of the first segment (Q1–2) for accuracy (incorrect flanker-driven response activation failed to be corrected only on very fast trials; hence, the effects of direct activation are revealed only in the initial segment of conditional accuracy functions). These analyses included the between-subjects variable AD/HD (AD/HD vs. matched control children).

MPH analysis. For each participant, mean RT and overall accuracy were determined for each congruence condition in each of the four MPH sessions. Initial ANOVAs were conducted on mean RTs and accuracy scores and included the effects of the within-subjects variables congruence (CG, IG, NEU) and treatment (placebo, low dose, medium dose, high dose).

Next, for each participant and condition, reaction times of all responses were rank ordered per condition and then divided into quintiles. Mean RT and accuracy were determined for each quintile in each condition separately. Delta plots for accuracy and RT were constructed as before. A second set of ANOVAs was conducted on the slopes of each of the delta plot segments (Q1–2, Q2–3, Q3–4, Q4–5) for RT, and on the slope of the first segment (Q1–2) for accuracy. These analyses involved the within-subjects variable treatment (placebo, low dose, medium dose, high dose).

MPH reanalysis. To correct for interindividual variability in sensitivity to different MPH doses, dose effectiveness was established for each dose and for each individual separately, and the data were reanalyzed accordingly. For any given participant, the optimum dose was that MPH dose that resulted in the smallest interference effect. The optimum dose, the least optimal dose, and the intermediate dose were determined operationally for each participant by rank ordering the interference effect on mean

RT, as induced by incongruent compared with congruent flankers. The number of children for whom the low, medium, and high dose was the optimum dose was 4, 5, and 11, respectively. ANOVAs were conducted on mean RTs and accuracy scores and included the effects of the within-subjects variables congruence (CG, IG, NEU) and optimum dose (placebo, inferior dose, intermediate dose, optimum dose). A second set of ANOVAs was conducted on the slopes of each of the delta plot segments (Q1–2, Q2–3, Q3–4, Q4–5) for RT, and on the slope of the first segment (Q1–2) for accuracy. These analyses involved the within-subjects variable optimum dose (placebo, inferior dose, intermediate dose, optimum dose).

Results

Baseline Analyses

Overall performance. The first set of ANOVAs focused on the effects of AD/HD and congruence on mean RTs and accuracy scores. Compared with matched controls, AD/HD children were slightly slower (547 ms vs. 568 ms) and less accurate (97.0% vs. 96.2%), but both effects failed to approach statistical significance, $F(1, 38) = 0.61$, ES = .016, and $F(1, 38) = 2.00$, ES = .050, respectively. Congruence produced its typical effect on RT, $F(2, 76) = 67.81$, $p < .001$, ES = .641, and on accuracy, $F(2, 76) = 26.07$, $p < .001$, ES = .407. IG responses (581 ms) were slower than were NEU responses (545 ms), $F(1, 38) = 108.86$, $p < .001$, ES > .999, and were also slower than CG responses (548 ms), $F(1, 38) = 91.49$, $p < .001$, ES > .999, whereas CG and NEU responses did not differ from each other, $F(1, 38) = 0.83$, ES = .368. Similarly, IG trials yielded more errors (5.3%) than did NEU trials (2.6%), $F(1, 38) = 28.39$, $p < .001$, ES = .428, or CG trials (2.1%), $F(1, 38) = 31.95$, $p < .001$, ES = .457, whereas accuracy for CG and NEU responses did not differ from each other, $F(1, 38) = 2.61$, ES = .064.

It is important to note that the congruence effects on RT tended to be modulated by AD/HD, $F(2, 76) = 2.64$, $p < .078$, ES = .078, such that the difference in RT between IG and CG trials was larger for children with AD/HD compared with control children, $F(1, 38) = 4.14$, $p < .049$, ES = .098 (see Figure 3A and B). The congruence effects on accuracy were not influenced by AD/HD, $F(2, 76) = 0.98$, ES = .025.

Thus, overall performance measures suggest that compared with matched control children, children diagnosed as AD/HD are somewhat more sensitive to interference effects on response speed (but not accuracy) in the present conflict task. These patterns could not be explained in terms of speed–accuracy trade-off. We now turn to distributional analyses to explore the effects of AD/HD on response activation and inhibition in greater detail.

Distributional analyses. Delta plots for speed and accuracy were constructed as described above in the analytic design section. The second set of ANOVAs focused on the effects of AD/HD on the slopes of the delta plots through the use of simple contrasts between groups at each quintile segment. For RT, the delta plots for children with AD/HD and control children were observed to diverge at the slower end of the RT distributions, whereas delta leveled off for control children earlier than for children with AD/HD (see Figure 3C). Consistent with these visual impressions, delta plot slopes did not differ statistically for either the early segments, Q1–2: $F(1, 38) = 0.76$, ES = .020; Q2–3: $F(1, 38) = 0.79$, ES = .020, or for the slowest segment, Q4–5: $F(1, 38) = 0.21$, ES = .006, but the slopes began to diverge at the point where the positive-going delta plot leveled off for normal control children, Q3–4: $F(1, 38) = 4.44$, $p < .042$, ES = .105. This pattern suggests that response inhibition is slower to operate in children with AD/HD (cf. the hypothetical patterns in Figure 2A). For accuracy, the delta plots for children with AD/HD and control children appear to converge across the entire RT distribution (see Figure 3D). Indeed, the initial segment (reflecting the effects of direct flanker-driven response activation) did not differ between groups, $F(1, 38) = 0.05$, ES = .001. Thus, AD/HD children do not appear to display excessive direct response activation (cf. the hypothetical patterns in Figure 2B). We now turn to the effects of MPH on the performance of children diagnosed with AD/HD.

MPH Analyses

Overall performance. One set of ANOVAs focused on the effects of treatment (three doses of MPH plus placebo) and congruence on mean RTs and accuracy scores of AD/HD children. Congruence once more produced its typical effect on RT, $F(2, 38) = 53.36$, $p < .001$, ES = .737, and on accuracy, $F(2, 38) = 24.12$, $p < .001$, ES = .559. IG responses (496 ms) were slower than NEU responses (472 ms), $F(1, 38) = 58.37$, $p < .001$, ES = .754, and also slower than CG responses (473 ms), $F(1, 38) = 54.36$, $p < .001$, ES = .741, whereas CG and NEU responses did not differ from each other, $F(1, 38) = 0.63$, ES = .032. Similarly, IG trials yielded more errors (5.3%) than did NEU trials (2.5%), $F(1, 38) = 24.56$, $p < .001$, ES = .564, or CG trials (2.3%), $F(1, 38) = 25.75$, $p < .001$, ES = .575, whereas accuracy for CG and NEU responses did not differ from each other, $F(1, 38) = 0.24$, ES = .028.

Response time decreased as a function of MPH, $F(3, 57) = 6.18$, $p < .001$, ES = .246 (513, 472, 472, and 464 ms in placebo, low dose, medium dose, and high dose sessions, respectively), but treatment did not affect overall accuracy, $F(3, 57) = 0.24$, ES = .013 (96.3, 96.8, 96.7, and 96.7%). It is important to note that MPH treatment was effective in modulating the effect of congruence on RT, as reflected in the Treatment × Congruence interaction effect, $F(6, 114) = 2.61$, $p < .021$, ES = .121. In particular, the difference in RT between IG and CG trials decreased monotonically as a function of increasing dosage, $F(3, 57) = 3.21$, $p < .030$, ES = .144. The most pronounced difference appeared to occur between placebo and nonplacebo (see Figure 4A), as confirmed by simple contrast analyses (placebo vs. high dose: $F(1, 19) = 7.48$, $p < .013$, ES = .282; placebo vs. medium dose: $F(1, 19) = 5.92$, $p < .025$, ES = .238; placebo vs. low dose: $F(1, 19) = 2.09$, ES = .099, *ns*). MPH failed to modulate the congruence effects on accuracy, $F(6, 114) = 0.82$, ES = .041 (see Figure 4B).

Thus, the analyses of overall response speed suggest that the sensitivity to interference effects in AD/HD children is reduced considerably by MPH. To examine the medicinal effects on response activation and inhibition in greater detail, we now turn to the delta plot analyses.

Distributional analyses. Delta plots for speed and accuracy were constructed as before, separately for each drug dose (see Figure 4C and D). Visual inspection suggests that for RT, the delta plots diverge already at early segments, with the slopes being less positive as drug dose increases. At placebo the delta plot does not level off until the last segment. This pattern suggests that the operation of response inhibition is speeded up by higher doses of

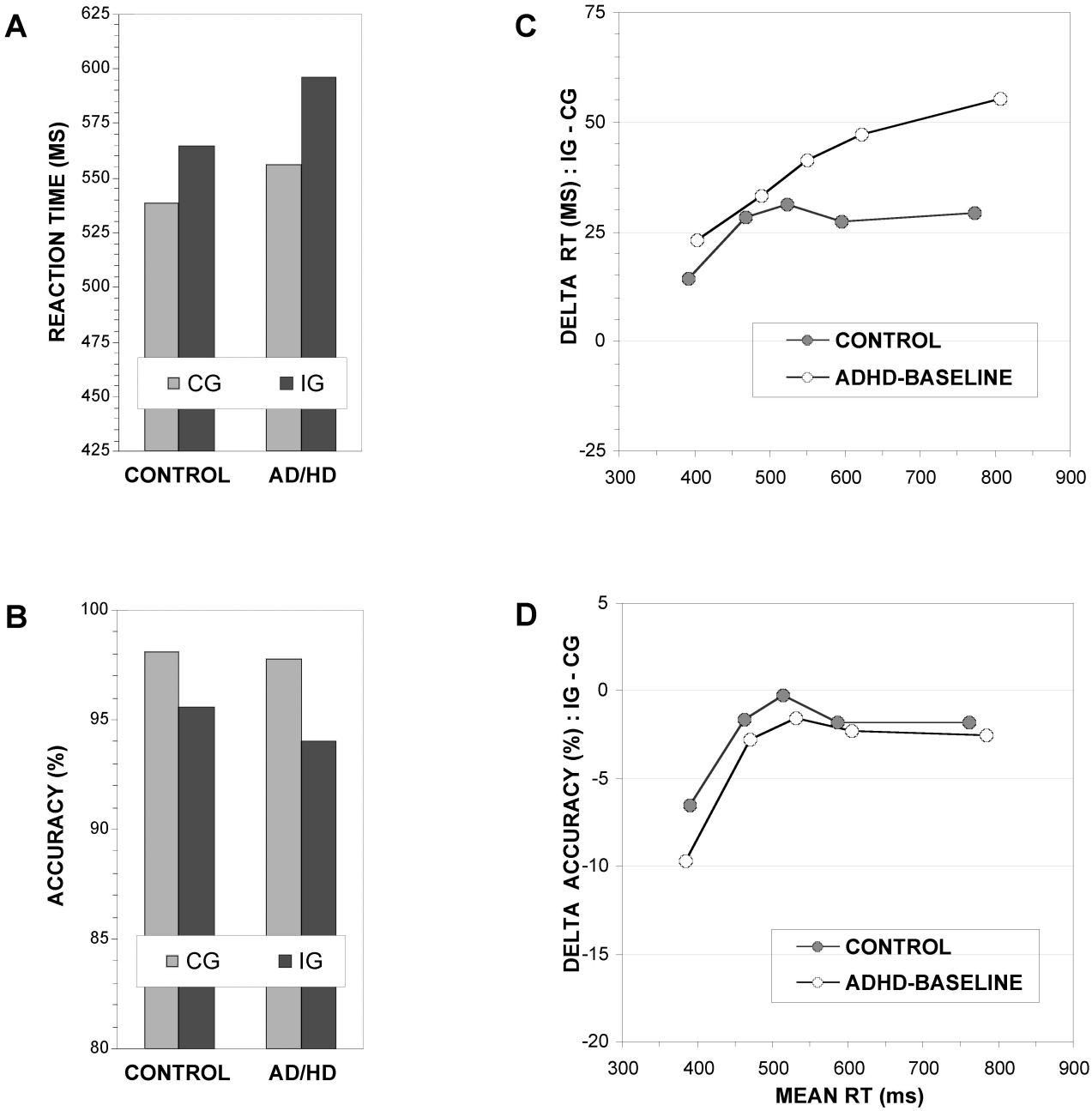

Figure 3. Children with attention-deficit/hyperactivity disorder (AD/HD) versus matched control children: overall effects (A and B) and delta plots (C and D) for reaction time (RT; A and C) and accuracy (B and D). Delta plots display effect size (i.e., in this instance the magnitude of the flanker congruence effect) as a function of response speed (as expressed in RT quintile scores). CG = congruent condition; IG = incongruent condition.

MPH (cf. the hypothetical patterns in Figure 2A). For accuracy, systematic patterns are less apparent, although the slope of the initial segment tends to become less negative as a function of drug dose. Thus, AD/HD children appear to show less direct response activation under the highest MPH dose (cf. the hypothetical patterns in Figure 2B).

To corroborate these observations, the next set of ANOVAs focused on the effects of MPH on the slopes of the delta plots. Delta plot slopes for RT tended to differ for the early segments, Q1–2: $F(3, 57) = 2.64$, $p < .058$, ES = .122; Q2–3: $F(3, 57) = 2.25$, $p < .093$, ES = .106, but not for the later segments, Q3–4: $F(3, 57) = 0.87$, ES = .044; Q4–5: $F(3, 57) = 0.80$, ES = .040. Simple contrast analyses showed that the tendencies observed for the early segments capitalized on the differences between placebo and the higher drug doses, Q1–2: placebo vs. medium dose, $F(1, 19) = 7.36$, $p < .014$, ES = .279; Q2–3: placebo vs. medium dose,

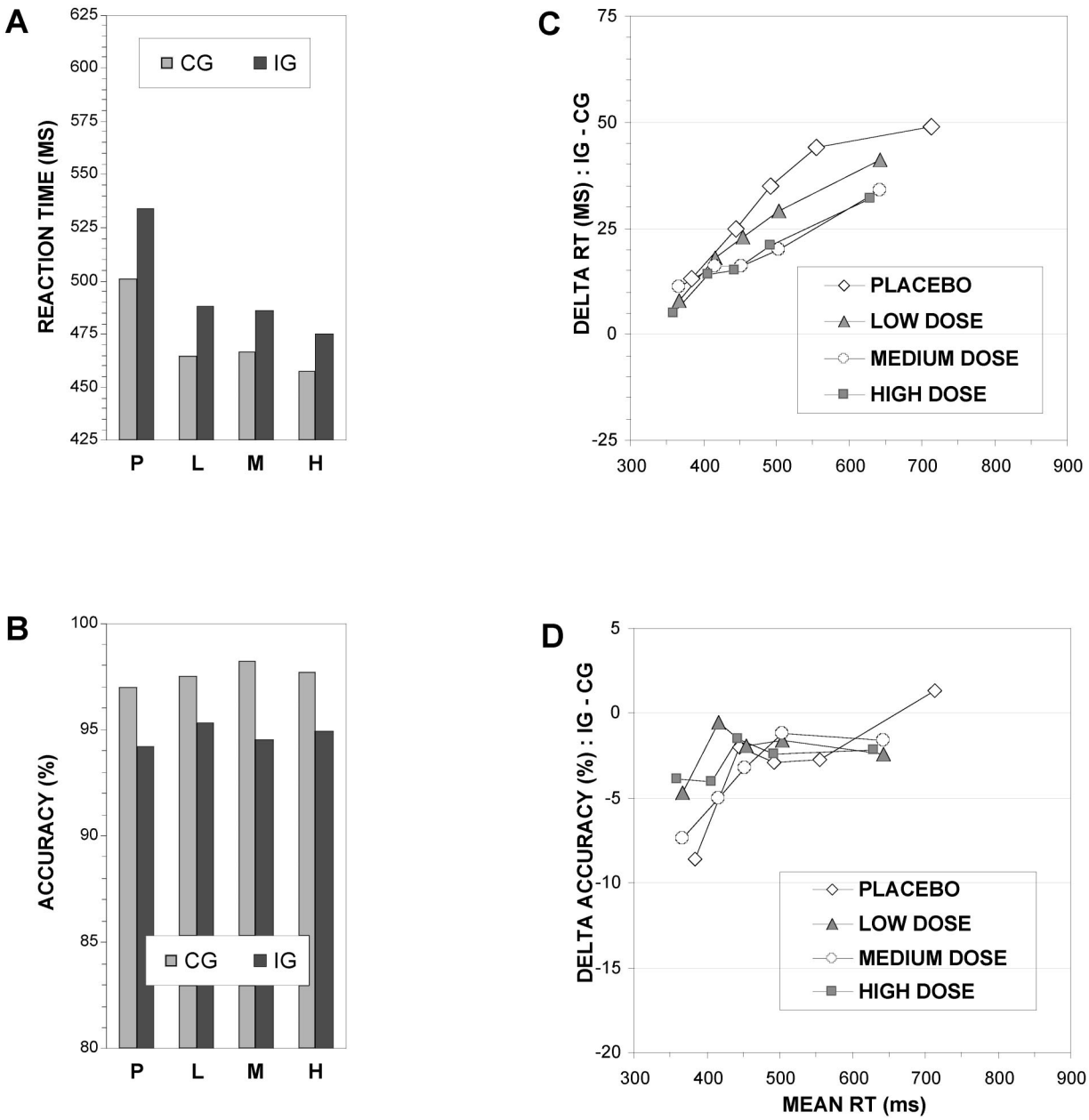

Figure 4. Effects of methylphenidate: overall effects (A and B) and delta plots (C and D) for reaction time (RT; A and C) and accuracy (B and D). Delta plots display the magnitude of the flanker congruence effect as a function of response speed (as expressed in RT quintile scores). CG = congruent condition; IG = incongruent condition; P = placebo; L = lowdose; M = medium dose; H = high dose.

$F(1, 19) = 4.15$, $p < .056$, ES = .179; placebo vs. high dose, $F(1, 19) = 4.24$, $p < .054$, ES = .182. Delta plot slopes for accuracy also tended to differ for the earliest segment, Q1–2: $F(3, 57) = 2.78$, $p < .049$, ES = .128. Simple contrast analysis showed that this tendency capitalized on the differences between placebo and the highest drug dose, $F(1, 19) = 11.02$, $p < .004$, ES = .367, whereas all other contrasts failed to approach significance. To explore these dose-dependent MPH effects further, we turn to a reanalysis of dose effectiveness.

MPH Reanalyses

To correct for interindividual variability in sensitivity to different MPH doses, the optimum dose, the least optimal dose, and the intermediate dose were determined operationally for each participant by rank ordering the interference effect on mean RT, as induced by incongruent compared with congruent flankers. ANOVAs were conducted on mean RTs and accuracy scores and included the effects of the within-subjects variables congruence

(CG, IG, NEU) and optimum dose (placebo, inferior dose, intermediate dose, optimum dose). For obvious reasons the main effects of congruence are necessarily identical to those in the previous analysis and will not be reiterated here. A second set of ANOVAs was conducted on the slopes of the delta plot segments and involved the within-subjects factor optimum dose (placebo, inferior dose, intermediate dose, optimum dose).

Overall performance. Response time varied as a function of optimum dose, $F(3, 57) = 6.24$, $p < .001$, ES = .247. As in the previous analysis, RT was faster in each of the MPH conditions compared with placebo but did not differ between drug doses (513, 473, 464, and 472 ms in placebo, inferior dose, intermediate dose, and optimum dose, respectively). Optimum dose did not affect overall accuracy, $F(3, 57) = 0.28$, ES = .014 (96.3%, 96.6%, 96.9%, and 96.7% for placebo, inferior dose, intermediate dose, and optimum dose, respectively).

Optimum dose was determined on the basis of congruence effects on RT per dose. Thus, for trivial reasons, optimum dose modulated the effect of congruence on RT, $F(6, 114) = 7.06$, $p < .001$, ES = .271. The difference in RT between IG and CG trials decreased monotonically as a function of dose, $F(3, 57) = 13.39$, $p < .001$, ES = .413, with the most pronounced difference occurring between placebo and optimum dose (see Figure 5A), as confirmed by simple contrast analyses (placebo vs. optimum dose, $F(1, 19) = 19.51$, $p < .001$, ES = .507; placebo vs. intermediate dose, $F(1, 19) = 4.32$, $p < .051$, ES = .185; placebo vs. inferior dose, $F(1, 19) = 0.13$, ES = .007). Optimum dose failed to modulate the congruence effects on accuracy, $F(6, 114) = 0.23$, ES = .012 (Figure 5B).

Thus, our classification procedure for rank ordering MPH (in terms of modulatory effects on flanker interference in RT) specifically and selectively produced the anticipated effect, without influencing overall RT or accuracy and without influencing interference effects on accuracy. Hence, our reanalysis is not obfuscated by unintended covariances in the latter factors; any specific effects of our reclassification on direct response activation or on response inhibition is uncorrelated with (and therefore cannot be explained in terms of) effects on overall performance. We can now examine the extent to which the beneficial effects of MPH involve response inhibition more directly because the obscuring effects of individual differences in dose sensitivity have been reduced.

Distributional analyses. Delta plots for speed and accuracy were constructed as before, separately for each optimum drug dosage (see Figure 5C and D). Visual inspection suggests that for RT, the delta plots for placebo and the two most effective doses already diverge at early segments, whereas the most effective dose begins to diverge from the intermediate dose at later segments. The delta plot for the optimum dose in fact shows negative slopes at later segments, resulting in near-zero overall interference effects. These patterns suggest that the operation of response inhibition is speeded up by MPH, and that the most effective MPH dose is the most successful in increasing the level of response inhibition (resulting in higher asymptote levels; cf. Figure 2A). The delta plot for the least-effective dose runs parallel with that for placebo in the early segments, but the former appears to be more positive going in the later segments, indicating counterproductive effects (less effective response inhibition) of this drug dose. For accuracy, the slope of the initial segment appears to be less steep for the two most effective doses compared with placebo and the least effective dose. Thus, children with AD/HD appear to show less direct response activation under more effective MPH doses (cf. Figure 2B).

These impressions were largely confirmed by ANOVAs focusing on the effects of optimum dose on the slopes of the delta plots. Delta plot slopes for RT did not differ between doses in the earliest segment, $F(3, 57) = 1.89$, ES = .091, but differed (marginally to significantly) at later segments, Q2–3: $F(3, 57) = 3.46$, $p < .022$, ES = .154; Q3–4: $F(3, 57) = 2.68$, $p < .055$, ES = .124; Q4–5: $F(3, 57) = 2.30$, $p < .087$, ES = .108. Simple contrast analyses (comparing placebo with each of the other doses) confirmed that for placebo, the slopes were more positive compared with the optimum dose at the second and third segments, Q2–3: $F(1, 19) = 6.52$, $p < .019$, ES = .256; Q3–4: $F(1, 19) = 3.76$, $p < .067$, ES = .165, more positive compared with the intermediate dose at the second segment, Q2–3: $F(1, 19) = 5.39$, $p < .032$, ES = .221, and less positive compared to the inferior dose at the fourth segment, Q4–5: $F(1, 19) = 3.93$, $p < .062$, ES = .171.

Note that the slope differences in delta plots between MPH conditions do not likely result from MPH-dose-related differences in speeding up or in eliminating slow responses. As can be seen in Figure 5, the most effective dose did not differ in RT from the intermediate or least effective doses, either in terms of mean RT or in terms of the fastest or slowest RT quintiles.

Delta plot slopes for accuracy tended to differ for the earliest segment, Q1–2: $F(3, 57) = 2.28$, $p < .090$, ES = .107. Simple contrast analysis showed that this tendency held for the optimum dose, $F(1, 19) = 4.03$, $p < .059$, ES = .175, and for the intermediate dose, $F(1, 19) = 3.51$, $p < .076$, ES = .156, but not for the inferior dose, $F(1, 19) = 0.35$, ES = .018.

Discussion

Response Inhibition in Children With AD/HD Versus Control Children

At baseline, overall performance analyses revealed a marginally significant interaction effect that reflected a greater difference in RT between IG and CG trials for children diagnosed with AD/HD than for matched control children. This finding is more or less consistent with other reports of flanker interference in children with AD/HD (Carter et al., 1995; Crone et al., 2003; Hooks et al., 1994; Jonkman et al., 1999), but tells us little about the role of response inhibition in this effect. Delta plot analyses (Ridderinkhof, 2002a) were applied to examine the (differential) engagement of response inhibition in flanker interference. These analyses revealed that the leveling off in the positive-going delta plots for RT was more pronounced and was manifest earlier in the distribution for control children than for children with AD/HD. In the context of the activation-suppression model, these findings indicate that AD/HD children (compared with normal control children) show a deficiency in the selective inhibition of responses as activated on the basis of the flankers.

No differential patterns were observed in the delta plots for accuracy, indicating that AD/HD children do not display a stronger tendency for direct activation of responses on the basis of prepotent distractors. However, it should be noted that because error rates were generally low, small group differences in accuracy may have resulted in relatively large differences in response speed (as

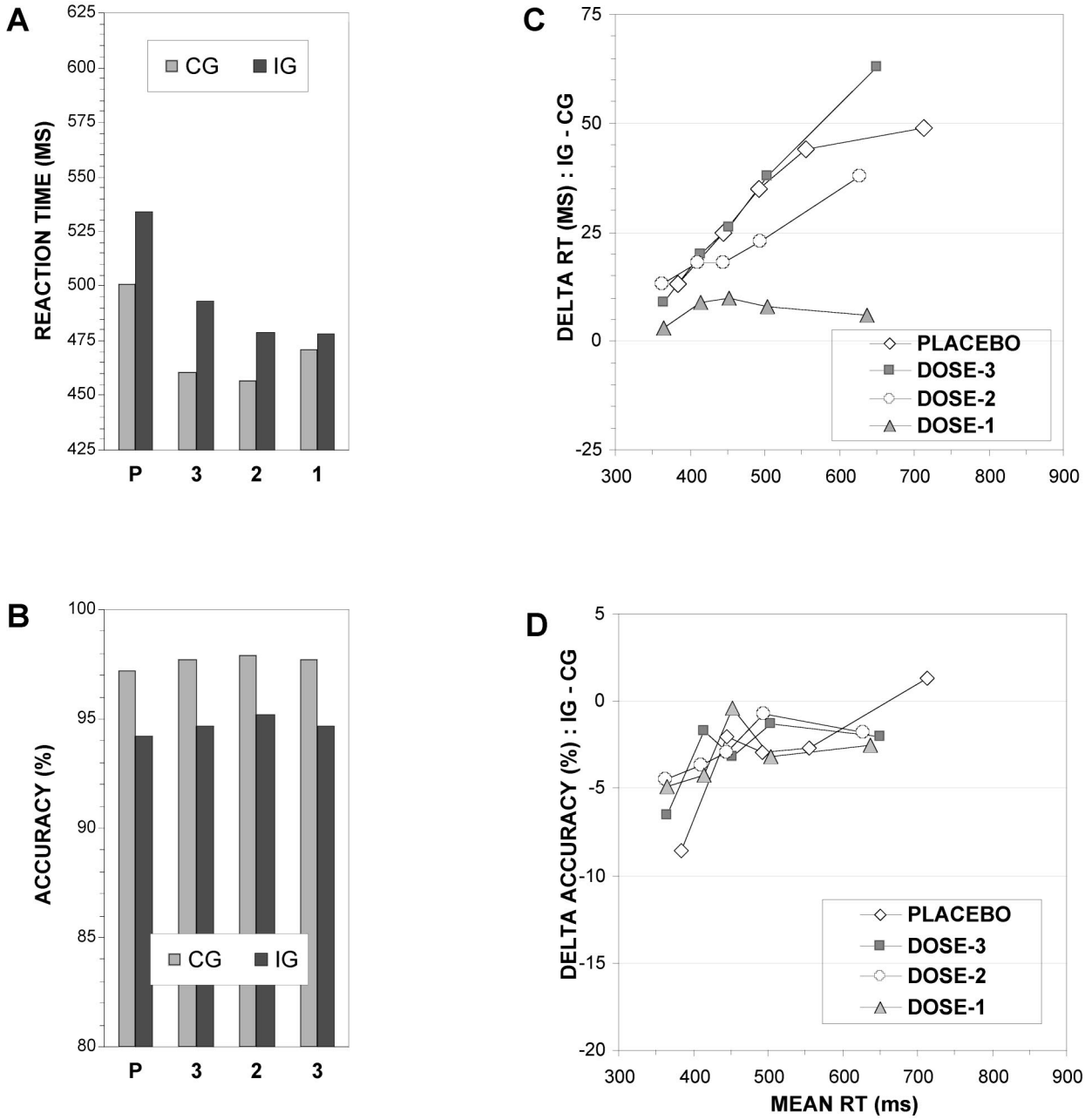

Figure 5. Reanalysis of effects of MPH according to optimum dose: overall effects (A and B) and delta plots (C and D) for RT (A and C) and accuracy (B and D). Delta plots display the magnitude of the flanker congruence effect as a function of response speed (as expressed in RT quintile scores). 1 = optimum session; 2 = intermediate dose session; 3 = inferior dose session; P = placebo; CG = congruent condition; IG = incongruent condition.

can be seen in the conditional-accuracy functions presented in the Appendix). Even with a difference in accuracy (between children with AD/HD children and control children) of less than 1%, and in the absence of any interaction effect on accuracy involving AD/HD, we acknowledge that such a difference may, in theory, be associated with more substantial differences in response speed. It is important to note that we have shown previously (Band, Ridderinkhof, & van der Molen, 2003) that the efficiency of response inhibition, as expressed in delta plot slopes, is not affected by differences in (instructed) accuracy levels. Thus, our inferences regarding response suppression in AD/HD are not severely threatened by the minimal differences in near-ceiling accuracy. We acknowledge also that differences in response activation might be more pronounced if performance accuracy were less close to ceiling. Nonetheless, it may be noted that accuracy was not overemphasized in our instructions to the participants, and the present accuracy results

are not atypical against the backdrop of the larger literature. Thus, the conditional accuracy function results do allow us to demonstrate the utility of this method in examining individual differences in the strength of direct response activation and to draw some cautious inferences about response-activation differences between groups.

Although sometimes effect sizes in the present analyses caution against overinterpretation of the outcomes, the present results provide thus far unique evidence for theories that emphasize response inhibition as a fundamental neurocognitive deficit in AD/HD (e.g., Barkley, 1997; Nigg, 2001—although some children with AD/HD in our sample were of different subtypes than the combined subtype addressed in Barkley's theory). Note that these conclusions could not possibly have been obtained when analyses were confined to overall performance. These findings highlight the usefulness of the delta-plot technique in clinical research.

Beneficial Effects of MPH Treatment

In the only published MPH study that uses the flanker task, MPH was not found to reduce interference effects in AD/HD children (Jonkman et al., 1999). In the present study, MPH did serve to reduce the interference effects incurred by incongruent distractors for RT but not for accuracy. These remedial effects were more pronounced for higher doses of MPH. Reclassification of MPH doses in terms of effectiveness in reducing flanker interference effects on RT yielded similar but more pronounced and more reliable outcomes.

Distributional analyses demonstrated that for higher drug doses the delta plots for RT and accuracy tended to be less positive in early segments of the RT distributions. These patterns were magnified when MPH doses were reclassified in terms of dose effectiveness. In accordance with the activation-suppression model, the remedial influence of MPH on the interference effects incurred by incongruent distractors involves two processes: (a) a slight reduction in the strength of prepotent distractors to activate responses directly, as reflected in the increase in accuracy for fast IG responses, and (b) a pronounced strengthening of the efficiency of the selective inhibition of responses (as activated by distractors), as reflected in the gradually more negative-going delta plots for RT as a function of optimal drug dose.

Note that though in the conventional MPH analysis responses were fastest in the highest dose (both for CG and IG trials), in the reanalysis, responses in the optimum dose appeared to be slightly slower rather than faster compared with the next-optimal dose (although statistically there was no significant difference). At first sight, the pattern shown in Figure 5A might suggest a selective slowing down of responses to CG trials. A more intuitive interpretation of this observation, although necessarily speculative, could be that in the optimum dose all responses are slightly slowed down, but slowing in IG trials is canceled out by the benefits of optimal response inhibition, with the latter being suggested by the delta plots in Figure 5C.

Note further that for the least effective drug dose, response inhibition in fact tended to be worse than under placebo, as expressed in the more positive slope for the slowest segment of the delta plot. Thus ineffective dosage, as indexed by the present effect measure, comprises a cost rather than a benefit. This finding may perhaps explain why MPH does not always produce the expected benefits (e.g., Jonkman et al., 1999).

Concluding Comments

MPH has been observed previously to improve performance on tasks that involve response inhibition (e.g., Everett et al., 1991; Konrad et al., 2004; Scheres et al., 2003; Tannock et al., 1989; Tannock, Schachar, & Logan, 1995). We show here that in terms of the activation-suppression model (Ridderinkhof, 2002a, 2002b), the patterns of results appear to reflect MPH effects on two processes: (a) a reduction in the strength for direct activation of responses by prepotent distractors and (b) an increase in the efficiency of the selective suppression of responses. If our findings can be independently replicated, this would suggest that, as indicated in Figure 1, two factors are involved in AD/HD deficits in interference effects: the direct response activation process and the selective response inhibition process.

Two further points need to be noted from the present results. First, in contrast to what a general "impulsivity" model of AD/HD would predict (cf. Barkley, 1997), the fast, early segments of the delta plots did not differentiate children with AD/HD from control children, and MPH had its locus of effect in the middle segments not in the early segment. Second, contrary to what one would have predicted from the distribution analyses of Leth-Steensen et al. (2000), the range of the response speed distribution that differentiated children with AD/HD from control children and in which MPH exerted its differential effects was not restricted to the slowest segments. The findings here indicate that the effects occur just past some optimal point and not at an extreme point in performance (slowest segment). These results emphasize the need for distributional analyses of performance data, and they suggest that careful analysis of performance distribution and electrophysiological measures is required to determine where in the distribution a suboptimal state commences and terminates in AD/HD children. Solving to this issue could explain the inherent variability repeatedly observed in AD/HD (Castellanos & Tannock, 2002; Sergeant & van der Meere, 1990).

Finally, the observed group differences in response inhibition might be related to differences in speed/accuracy balance, with children with AD/HD favoring speed over accuracy in comparison to control children. We have recently used delta-plot analysis (as well as event-related brain potential methodology) to examine the role of direct response activation and selective response suppression as instrumental tools in achieving shifts in speed–accuracy balance (Band et al., 2003). Thus, differences between children with AD/HD and control children (or between MPH doses) in the efficiency of response suppression may either reflect inherent inhibitory deficiencies, or functional inhibitory deficiencies that result from differences in speed–accuracy balance. The present analytical approach itself does not discriminate between these two possibilities (it merely highlights the inhibitory deficits); however, it could well be used as a tool in further studies of speed–accuracy tradeoff differences in AD/HD.

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Appendix

Cumulative Density Functions (CDFs)

CDFs plot the cumulative probability of responding as a function of response speed. Figure A1 (A) shows the sigmoid-shaped CDFs associated with ex-Gauss distributed RTs (here, we have plotted RT decile scores) for two hypothetical conditions *x* and *y* where one condition is associated with slower RTs than is the other. The typical pattern is that the proportional difference in RT between the two conditions is similar across response speed quantiles/quintiles; as a result, the absolute difference in RT between the two conditions increases from fast to slower quantiles (cf. Luce, 1986).

In addition to these "standard" differences in CDFs between faster and slower conditions, CG and IG conditions display further differences ac-

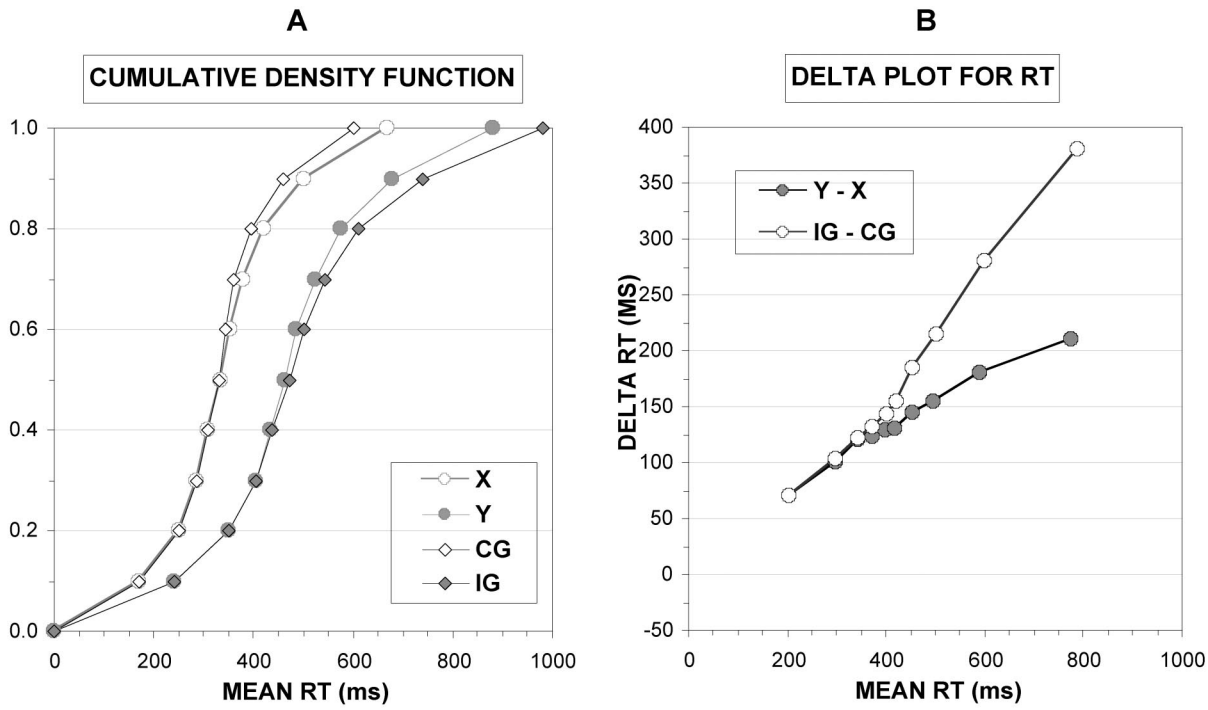

Figure A1. A: Cumulative density functions (CDFs) for two arbitrary hypothetical conditions *x* and *y* (where condition *y* is associated with slower reaction times [RTs] than is condition *x*) as well as for hypothetical congruent (CG) and incongruent (IG) trials in a flanker task. Conditions CG and IG resemble conditions *x* and *y*, respectively, but they also reflect the additional direct-activation effects of irrelevant location in a flanker task. Slow IG trials are affected more by the negative effects of direct activation for the incorrect response than fast IG trials. Slow CG trials benefit more from the positive effects of direct activation for the correct response than fast CG trials. CDFs were approximated by plotting, for each condition separately, the cumulative probability of responding as a function of mean RT for each of 10 response speed deciles. B: Delta plots for response speed for the hypothetical *x* and *y* conditions and the hypothetical congruence effects as derived from the cumulative density functions plotted in Panel A. Delta plots plot effect size (i.e., in this instance the magnitude of the flanker congruence effect) as a function of response speed. Response speed is expressed in RT decile scores.

cording to the predictions made by the activation-suppression model (as outlined in the main text). It was argued that slow IG trials would be affected (i.e., slowed) more by the negative effects of direct activation for the incorrect response than fast IG trials. Likewise, it was argued that slow CG trials would benefit (i.e., speed up) more from the positive effects of direct activation for the correct response than would fast CG trials. These patterns are illustrated in the CDFs in Figure A1A.

Conditional Accuracy Functions (CAFs)

CAFs plot accuracy of responding as a function of response speed (see Figure A2A; here, accuracy is plotted as a function of RT; data points are represented as decile scores). If responses are so fast that they could not be based on information available in the stimulus display, then the result is a fast guess with near-chance accuracy. The slower the response, the greater the chance of it being correct, reaching asymptote accuracy for the slowest responses. The smaller the incidence of fast guesses, the flatter the CAFs. Figure A2A shows the CAF patterns for the two hypothetical conditions *x* and *y* from Figure A1, where one condition is associated with slower RTs and higher error rates than the other. The typical pattern is that asymptote accuracy is attained for slow responses in both conditions, whereas faster responses are associated with more errors in the more difficult condition.

According to the predictions derived from the activation-suppression model (see the main text), CG and IG conditions should display differences in CAFs in addition to these "standard" differences between faster and slower conditions. It was argued that IG trials would be characterized by relatively many fast location-driven errors. No such argument could be made for CG trials. These patterns are illustrated in the CDFs in Figure A2A (which uses the RT decile scores plotted in Figure A1).

Delta Plots

Delta plots (also referred to as *distributional plots*) are used to plot effect size (the magnitude of the factor effect on the dependent variable) as a function of response speed. They can be derived directly from the CDFs (when plotting RT effects) or the CAFs (when plotting accuracy effects). For each RT quantile, the difference in RT or accuracy between conditions *a* and *b* is plotted on the *y*-axis against the mean of the RTs of conditions *a* and *b* in that quantile. Figure A1B shows delta plots for congruence effects on RT, as derived from the CDFs in Panel A. Figure A2B shows delta plots for correspondence effects on accuracy, as derived from the CAFs in Panel A.

De Jong et al. (1994) introduced the use of delta plots in a particular variety of the Simon task (Hedge & Marsh, 1975), and asserted that the slopes between quantile points in delta plots for RT reflect the relative time course of two different types of direct activation (unconditional vs. conditional automatic activation), which they argued to occur in the reversal of the Simon effect reported by Hedge and Marsh. Zhang and Kornblum (1997) argued that the slope of the delta plot reflects the relationship between the variability parameters of the underlying CDFs. Positive and negative delta plot slopes may result from differential time courses, but they may also result from (intended or unintended) manipulation of vari-

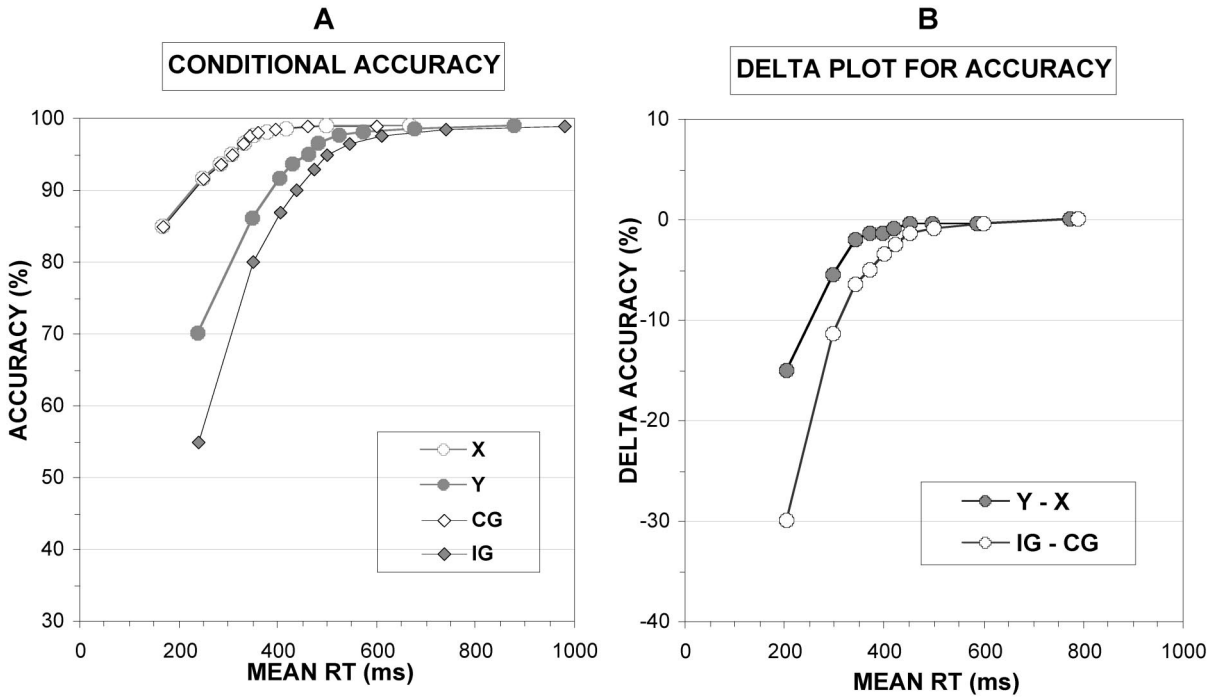

Figure A2. A: Conditional accuracy functions (CAFs) for two arbitrary hypothetical conditions *x* and *y* (where condition *y* is associated with slower reaction times [RTs] than is condition *x*) as well as for hypothetical congruent (CG) and incongruent (IG) trials in a flanker task. Conditions CG and IG resemble conditions *x* and *y*, respectively, but they also reflect the additional direct-activation effects of irrelevant location in a flanker task. IG trials (more than CG trials) are characterized by relatively many fast location-driven errors. CAFs were approximated by plotting, for CG and IG conditions separately, accuracy as a function of mean RT for each of 10 response speed deciles. B: Delta plots for response accuracy for the hypothetical *x* and *y* conditions and the hypothetical congruence effects as derived from the conditional accuracy functions plotted in Panel A. Delta plots plot the magnitude of the flanker congruence effect as a function of response speed. Response speed is expressed in RT decile scores.

(*Appendix continues*)

ability parameters. Zhang and Kornblum therefore argued that, due to this confounding, delta plot slope in itself is difficult to interpret. However, by designing experimental manipulations specifically so as to influence the variability parameters in a meaningful way, one can validly study the effects of these manipulations on delta plots (thus, delta plot slopes should be analyzed relative to each other rather than in terms of their absolute values). Thus, in evaluating the use of delta plots (and, by inference, CDFs and CAFs) in conflict tasks, one must be able to explain why correspondence effects involve the variability effects leading to the observed delta plot slopes and formulate a priori predictions about the effects of experimental conditions on delta plots. Without a model that generates such predictions, the interpretation of delta plots is post hoc and vulnerable to alternative interpretations in terms of factors that were not necessarily under experimental control. As demonstrated previously, the dual-process model and the activation-suppression hypothesis together provide a theoretical framework that generates unique predictions concerning delta plots for RT and accuracy in Simon tasks (Ridderinkhof, 2002a). Processing dynamics can be explored validly and meaningfully by examining the points in time where delta plots converge and diverge between conditions that are thought to differ in terms of the factors that influence RT variability, such as inhibitory demands in conflict tasks.

CDFs and Delta Plots for RT

In conditions in which selective inhibition is relatively strong, the effects of direct activation should be shorter-lived than in conditions in which selective inhibition is relatively weak; the build-up of activation for the incorrect response along the direct-activation route would be able to attain a lesser magnitude before being corrected by selective inhibition processes. As a consequence, activation for the correct response should be initiated earlier in strong-inhibition compared to weak-inhibition conditions. Thus, with weak inhibition only the slow IG responses benefit from selective inhibition; the stronger the inhibition, the earlier in the RT distribution will responses benefit from selective inhibition. This is illustrated in the hypothetical CDFs in Figure A3A. Note that inhibition strength and inhibition rise-time have similar effects and cannot be disentangled post hoc from observed RT distributions.

On CG trials, these effects work in the opposite direction, although the effects on CG trials are typically much less pronounced compared with the effects on IG trials. If deliberate response decision processes proceed relatively fast, then the build-up of activation for the (correct) response along the direct-activation route would be only small by the time the deliberate route produced its output. Thus, with stronger inhibition, fast CG responses would benefit less from direct activation; with weaker inhibition, fast responses would benefit more, and slower responses would also begin to benefit somewhat from direct activation (see Figure A3A).

Figure A3B displays the manifestations of weaker versus stronger selective inhibition in delta plots for RT. Most noteworthy, the slopes between quantile points turn from positive to negative relatively late when inhibition is weak and progressively more early when inhibition is stronger. The point of divergence between two delta plots (representing two different levels of inhibitory strength) is the critical variable in these comparisons.

CAFs and Delta Plots for Accuracy

It was shown that, as a result of natural variability in response speed, IG trials yield more fast errors than CG trials. That is, deliberate response decision processes are sometimes so slow that the activation for the incorrect response along the direct-activation route may exceed the threshold at which an overt response is emitted. It can be argued that in

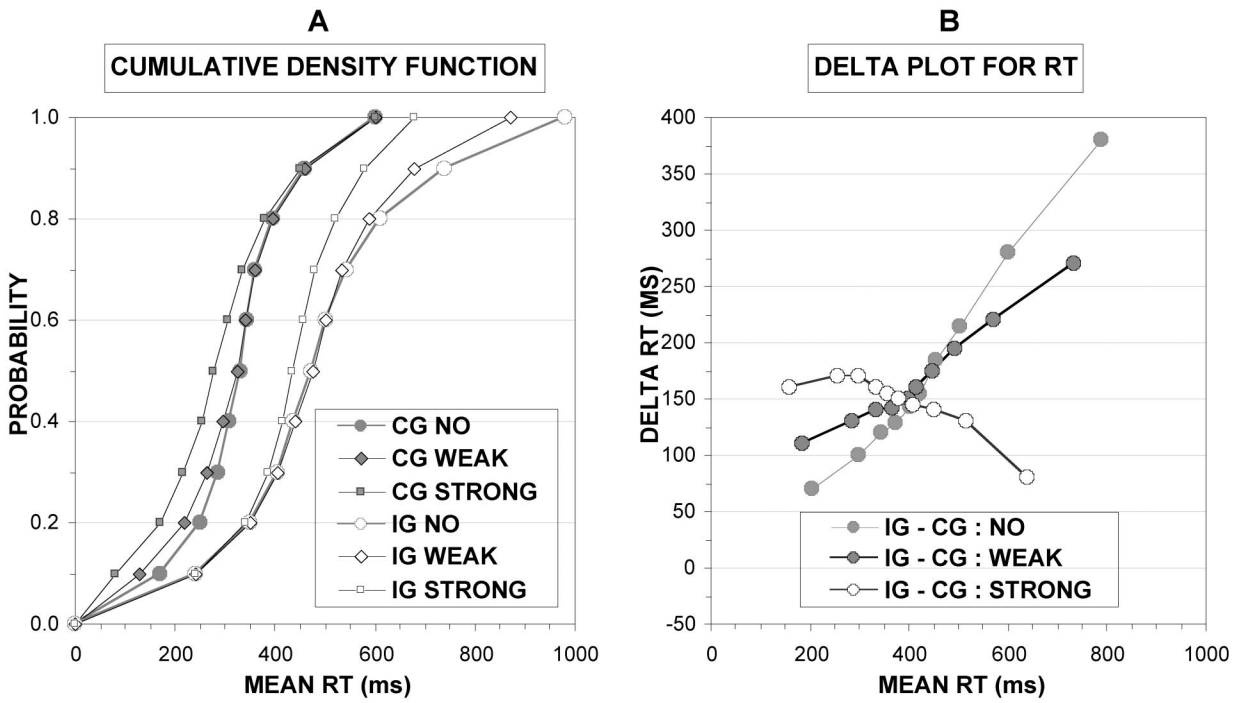

Figure A3. A: Cumulative density functions (CDFs) for three hypothetical conditions, one involving strong inhibition, one involving weak inhibition, and one involving no inhibition at all (see Appendix text). CDFs plot the cumulative probability of responding as a function of response speed. Response speed is expressed here in RT decile scores. B: Delta plots for response speed for the hypothetical congruence effects as derived from the CDFs in Panel A. Delta plots plot the magnitude of the flanker congruence effect as a function of response speed. CG = congruent condition; IG = incongruent condition.

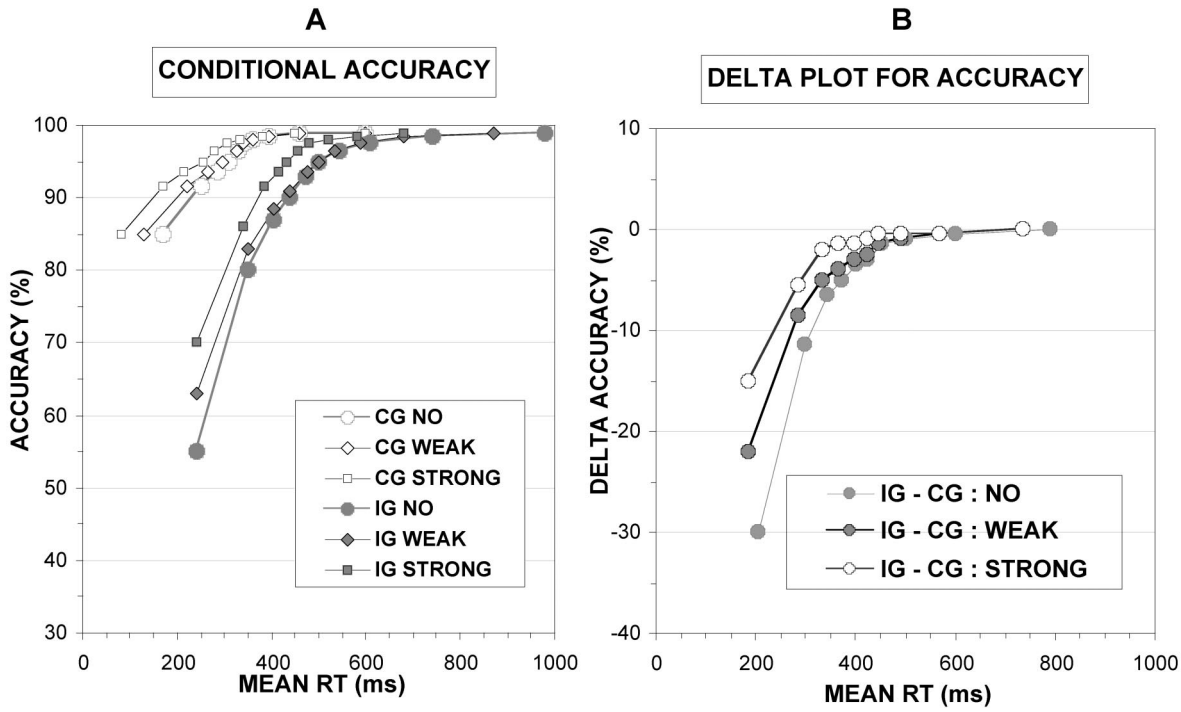

Figure A4. A: Conditional accuracy functions (CAFs) for three hypothetical conditions, one involving strong inhibition, one involving weak inhibition, and one involving no inhibition at all (see Appendix text). CAFs plot the probability of correct responding as a function of response speed. Response speed is expressed here in reaction time (RT) decile scores. B: Delta plots for accuracy for the hypothetical congruence effects as derived from the CAFs in Panel A. Delta plots plot the magnitude of the flanker congruence effect as a function of response speed.CG = congruent condition; IG = incongruent condition.

conditions in which selective inhibition is weak (or slow, or both), the activation for the incorrect response along the direct-activation route will exceed the response threshold sooner than when selective inhibition is strong (in other words, under a stronger inhibition regime, one may more often prevent incorrect activation from resulting in an overt response). Thus, in going from weak to strong inhibition, fewer fast IG errors would occur. This is illustrated in the hypothetical CAFs in Figure A4A. Straightforward effects of inhibition strength on conditional accuracy in CG trials are not anticipated.

Figure A4B displays the manifestations of weaker versus stronger selective inhibition in delta plots for accuracy. Most noteworthy, only the slopes between the earliest early quantile points differ significantly between strong and weak inhibition conditions, whereas at later quantiles these slopes differ less and approach zero.

Received September 23, 2002
Revision received June 11, 2004
Accepted June 16, 2004 ■