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Inhibition in developmental disorders: A comparison of inhibition profiles between children with autism spectrum disorder, attention-deficit/hyperactivity disorder, and comorbid symptom presentation

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Abstract

Thirty to 80% of children with autism spectrum disorder (ASD) also have symptoms of attention-deficit hyperactivity disorder (ADHD). Many children with ASD and ADHD experience difficulties carrying out goal directed behaviors, particularly when it comes to inhibiting responses. The aim of the current study was to better understand the relative strengths and weaknesses across different measures of inhibition in children with ASD, ADHD, ASD+ADHD, and children who are typically developing (TD). Inhibition of distracting information, motor responses, response speed, and selections with the potential for greater loss was measured in 155 school-aged children across these four groups. Results indicate that, for children with ASD +ADHD, inhibition varied across the different outcomes assessed. Relative to TD children, children with ASD+ADHD showed greater difficulty inhibiting behavioral responses. Conversely, inhibition of distracting information and strategic slowing of response speed differed between the children with ASD+ADHD and those with either ASD or ADHD. Avoidance of potential losses did not significantly differ between the four groups. The unique pattern of inhibition abilities shown in the ASD+ADHD group suggests the need for special consideration in the context of targeted intervention.

Lay Abstract

Many children with autism spectrum disorder (ASD) also have symptoms of attention-deficit hyperactivity disorder (ADHD). Children with ASD and ADHD often experience difficulties with inhibition. This study had the goal of understanding inhibition in children with ASD, ADHD, ASD

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+ADHD, and children who are typically developing (TD) using tasks that measured several aspects of inhibition. Results indicate that children with ASD+ADHD had greater difficulty inhibiting behavioral responses than TD children. Children with ASD+ADHD also differed from children with ASD and with ADHD in their inhibition of distracting information and strategic slowing of response speed. The four groups did not differ in their avoidance of potential losses. Children with ASD+ADHD exhibit a unique profile of inhibition challenges suggesting they may benefit from targeted intervention matched to their abilities.

Autism spectrum disorder (ASD) is a developmental disorder characterized by impaired social function and communication as well as restrictive, repetitive behaviors or interests (American Psychiatric Association, 2013). There is significant variability in symptom presentation within and across individuals with ASD (Geschwind, 2009). Comorbidity (i.e., co-occurrence) with other psychiatric disorders contributes to additional variance in symptom presentation and severity (Mannion & Leader, 2016; Simonoff et al., 2008). Together, these factors make diagnosis and treatment of ASD especially difficult. To address this variability, initiatives such as the National Institute of Mental Health's Research Domain Criteria (RDoC) propose assessing patterns of symptoms along a continuum that is independent of diagnostic status (Insel et al., 2010).

Attention-deficit/hyperactivity disorder (ADHD) commonly co-occurs (i.e., is comorbid) with ASD, as approximately 30–80% of children with ASD have concurrent symptoms of inattention and hyperactivity/impulsivity (Rommelse et al., 2010). Due to this high rate of overlap, it is often questioned whether or not ASD and ADHD are qualitatively distinct disorders that commonly co-occur or if they are, in fact, manifestations of the same etiological disorder (e.g., van der Meer et al., 2012). Understanding comorbidity is central to determining the pattern of risk for such disorders, and a number of models have been proposed including (a) alternate forms of the same disorder, (b) one disorder affecting the risk for the other, (c) three independent disorders, or (d) correlated risk factors for both disorders (Neale & Kendler, 1995). Characterizing the pattern of comorbidity may offer significant insight into the best way to identify and treat developmental disorders and, potentially, reduce risk for developing them. For instance, if ASD and ADHD are truly manifestations of the same disorder, a top down approach to symptom management may be applied (i.e., targeting mechanisms underlying heterogeneous symptoms). Alternatively, if ASD and ADHD are distinct disorders (i.e., different risk factors or etiology), treatments that target distinct symptoms and behavioral outcomes, related to specific clinical symptomology, may be recommended.

In addition to shared symptomology, many children with ASD and ADHD experience deficits in executive function (EF) - a set of higher order cognitive functions that rely upon top-down control over goal-directed actions and behaviors (Barkley, 1997; Ozonoff et al., 1991; Pellicano et al., 2006). Provided the prevalence of EF deficits in ASD and ADHD, a closer examination of EF profiles may help to clarify comorbidity of these disorders by probing a basic dimension of the clinical profile and evaluating its relation to symptoms. Moreover, further characterization of the EF profile could identify separate subgroups of children or highlight similar EF deficits that are characteristic of both diagnostic groups. An

EF profile that is unique to children with comorbidity may provide information regarding symptom etiology and create opportunities for individualized interventions and treatment strategies. Different EF profiles for children with singular versus comorbid diagnoses would also potentially clarify some of the inconsistencies reported in previous studies that combined these groups, and would guide the future investigation of EF in ASD and ADHD.

Executive Function in Developmental Disorders

Executive function encompasses inhibition, working memory, and set-shifting abilities. The domains of EF affected among individuals with developmental disorders vary: relative to typically developing (TD) children, children with ASD often have difficulty with set-shifting abilities, whereas working memory and inhibition are characteristically impaired among children with ADHD (Antshel et al., 2016; Geurts et al., 2004; Gioia et al., 2010; Hovik et al., 2017; Lawson et al., 2015; Ozonoff & Jensen, 1999). Like children with ADHD, those with ASD also show deficits in working memory (Goldberg et al., 2005) and some measures of inhibition (Corbett et al., 2010; Happé et al., 2006; Panerai et al., 2016 but see Christ et al., 2007; Christ et al., 2011). However, there are a number of studies that report conflicting and/or contradictory results (see Castellanos et al., 2006; Hill, 2004; O'Hearn, et al., 2008; Russo et al., 2007 for review), suggesting that, like primary symptoms, executive dysfunction varies among individuals with developmental disorders.

Recent research has compared EF between children with a diagnosis of ASD or ADHD to children with comorbid symptom presentation (ASD+ADHD). These results indicate that inhibition and working memory are more impaired among children with combined symptomology relative to children with a singular diagnosis of ASD (Colombi & Ghaziuddin, 2017; Yerys et al., 2009) or ADHD (Cooper et al., 2014). Studies that have directly compared EF between children with ASD, ADHD, and ASD+ADHD suggest that the EF profiles of children with comorbid symptoms are additive, as children with dual symptom presentation have more severe EF deficits than children with a singular diagnosis (Andersen et al., 2013; Antshel & Russo, 2019; Craig et al., 2016; Gargaro et al., 2011; Karalunas et al., 2018; Taurines et al., 2012; Tye et al., 2014; Unterrainer et al., 2016).

Remaining Questions

Prior to the release of the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) in 2013, children could not receive a dual diagnosis of ASD and ADHD. Therefore, it is possible that previous studies of children with ASD may have included children who would also meet criteria for co-occurring ASD+ADHD. Given the significant comorbidity between these disorders (Rommelse et al., 2010), it is crucial to ensure that populations are clearly defined prior to analysis.

Relatedly, results pertaining to group differences in inhibition are mixed (Corbett et al., 2010; Geurts et al., 2004; Gioia et al., 2002; Goldberg et al., 2005; Happé et al., 2006; Hovik et al., 2017; Kado et al., 2012; Lawson et al., 2015; Neely et al., 2016; Nyden et al., 1999; Nydén et al., 2010; Salcedo-Marin et al., 2013; Samyn et al., 2014; Semrud-Clikeman et al., 2010; Sinzig et al., 2008, 2014; Tsuchiya et al., 2005; Xiao et al., 2012; Yang et al., 2009;

Yasumura et al., 2014). One factor that may contribute to these inconsistent results is variation in the type of inhibition measured. Nigg (2000) outlined a taxonomy of inhibition constructs that facilitates a more granular mapping to clinical disorders such as ASD and ADHD. Of these measures, interference control, reactive inhibition, proactive inhibition (i.e., proactive slowing), and motivational inhibition have been implicated in developmental disorders including ASD (Faja & Nelson Darling, 2019; Geurts et al., 2014, 2008; Mosconi et al., 2008) and ADHD (Barkley, 1997; Fosco et al., 2019; Mullane et al., 2009). Interference control is operationalized as the ability to suppress stimuli that may interfere with a response (Cragg, 2016). Behavioral inhibition – defined as the ability to stop mid-task to regulate behavior or complete a non-dominant response – is supported by independent processes that are both reactive and proactive. Reactive inhibition measures the speed of the stopping process whereas proactive inhibition, or proactive slowing, involves strategic response slowing in order to complete more challenging tasks while maintaining accuracy (Van Hulst et al., 2018; Verbruggen & Logan, 2008, 2009). Finally, motivational inhibition gauges avoidance of losses in activities that include feedback or reward contingencies (Cassotti et al., 2014).

Although previous studies have evaluated inhibition profiles of children with ASD and ADHD (Craig et al., 2016; Gargaro et al., 2018; Taurines et al., 2012), fewer have examined distinct facets of inhibition within the co-occurring ASD+ADHD group. Relative to TD children, children with ADHD and ASD+ADHD appear to have reduced reactive, but not proactive, inhibition (Van Hulst et al., 2018). On a behavioral inhibition task, participants with ADHD and ASD+ADHD made more omission errors and exhibited increased reaction time variability compared to TD children or children with ASD (Bühler et al., 2011; Karalunas et al., 2018; Takeuchi et al., 2013; Tye et al., 2014). Reports of group differences in interference control are mixed (Karalunas et al., 2018; Takeuchi et al., 2013). Other domains of inhibition (i.e., motivational inhibition) are understudied and warrant additional research.

Current Study

The aim of the current study was to compare inhibition profiles of children with ASD, ADHD, comorbid presentation of ASD+ADHD, and TD controls. Children within the age range of 7 to 11 years were sampled, as this is an age in which symptoms of ADHD often manifest and are reliably diagnosed (Applegate et al., 1997). In an effort to reduce variance that may be accounted for by inconsistency in clinical characterization and/or stimulant medication use, the current study (1) used the same inclusion criteria for ADHD symptoms across groups and (2) only included children who were not taking stimulant medications at the time of testing as the role of stimulant medication on EF outcomes is understudied and may have significant implications in characterizing EF among children with developmental disorders (Hawk et al., 2018; Hosenbocus & Chahal, 2012; Pietrzak et al., 2006; Weyandt et al., 2013).

Furthermore, to assess distinct facets of inhibition, children completed a wide-ranging, objective behavioral battery that indexed interference control, reactive inhibition, proactive inhibition, and motivational inhibition. Characterization of these distinct facets of inhibition

in children with comorbid symptom presentation is of paramount importance as different types of inhibition deficits may map closely to distinct developmental disorders or serve to distinguish clinical subgroups. Among neurodevelopmental disorders, dissociative profiles of inhibition may be used to improve diagnostic outcomes and inform specific treatment strategies. Provided that some inhibitory deficits are more common among a subgroup or subgroups, more precise characterization of inhibition outcomes may be used to understand etiology and catalog behavioral phenotypes of commonly comorbid disorders (Nigg, 2000).

Based on prior research assessing inhibition in these groups (see Craig et al., 2016; Gargaro et al., 2011; Taurines et al., 2012 for review), we hypothesized that children with co-occurring ASD+ADHD would have an inhibition profile that was more severely impaired relative to TD children or children with a singular diagnosis of ASD or ADHD. Specifically, we presumed that reactive and motivational inhibition would be more impaired among children with singular (ADHD group) and comorbid diagnosis of ADHD (ASD+ADHD), relative to TD children and children with a singular diagnosis of ASD (Bühler et al., 2011; Karalunas et al., 2018; Sonuga-Barke, 2002; Tye et al., 2014). Due to mixed findings and lack of prior evidence, we did not have specific hypotheses for group differences in interference control or proactive inhibition.

Methods

Participants

As part of a larger study, 209 children provided data that were used in the current analyses. Seven additional children were tested but not included in this study due to missing data on the behavioral battery (see Figure 1). Children were recruited from a hospital in New England and a university in the Pacific Northwest. The TD group included children without clinical concerns whereas the ASD and ADHD groups included children with existing diagnoses.

Exclusionary criteria included neurological disorders of known etiology, history of serious head injury, physical impairments that would limit participation in the experimental tasks, and caregivers with insufficient English language ability to complete measures. All procedures were approved by the Human Subjects Division of each institution. Prior to testing, caregivers provided informed written consent and children provided assent.

Group status (ASD, ADHD, ASD+ADHD, and TD) was based on an existing clinical diagnosis (or lack of diagnosis for the TD group) as reported by the child's caregiver. Diagnostic status was then confirmed via standardized questionnaires and/or assessment by a licensed clinician. Existing ASD diagnoses (for children in the ASD groups) were confirmed via direct observation (Autism Diagnostic Observation Schedule, Second Edition Module 3; ADOS-2; Lord et al., 2012) and caregiver-report of symptoms (Autism Diagnostic Interview-Revised; ADI-R; Rutter et al., 2015). Existing ADHD diagnoses (ADHD group) were confirmed via caregiver ratings (Conners-3 Comprehensive Behavior Rating Scales; Conners, 2008) using diagnostic criteria (symptom counts ≥ 6) for the Inattention/Hyperactivity or Inattention scales.

Continuous ADHD symptoms were also assessed across all groups using the ADHD subscale of the Child Behavior Checklist (CBCL; Achenbach & Rescorla, 2001). Children with a confirmed diagnosis of ASD and T-scores ≥ 65 on the ADHD subscale of the CBCL were classified as having clinically significant ADHD symptoms and were included in the ASD+ADHD group. Because there is little consensus on the best way to quantify ADHD symptoms in children with ASD, a T-score of 65 was used to as the cut-point to identify children within a 'borderline clinical range' of ADHD (Achenbach & Rescorla, 2001), consistent with other studies (Andersen et al., 2013; Cremone-Caira et al., 2019). To ensure consistent symptom levels across our ADHD and ASD+ADHD groups, we excluded children with a confirmed diagnosis of ADHD who had T-scores < 65 on the ADHD subscale of the CBCL.

Finally, children with significant, confounding clinical traits were excluded from analyses. Children in the ADHD group were screened for ASD symptoms via the Social Responsiveness Scale, Second Edition (SRS-2; Constantino & Gruber, 2014) using a threshold of SRS-2 Total T-score > 75. TD children whose CBCL ADHD subscale T-score was ≥ 65 (to rule out significant ADHD symptoms) and/or SRS-2 Total T-score was > 75 (to rule out significant ASD symptoms) were excluded from analyses.[1] All children had a Full Scale IQ > 85, confirmed via the Wechsler Abbreviated Scale of Intelligence, Second Edition (WASI-2; Wechsler, 1999) to ensure that EF challenges were not due to borderline intellectual disability.

Long-acting stimulant medications are typically active for 8 to 12 hours after intake (Brams et al., 2010). As such, children in the ADHD group were asked to discontinue stimulant medication use at least 12 hours prior to data collection (last dose of medication taken 24 hours before participation). Those who could not discontinue stimulant medications were excluded from the study. Children in the ASD groups were not taking stimulant medications at the time of participation. Medication use was exclusionary for children in the TD group.

Although not used as an exclusionary criterion for this study, it is worth noting that 7 children in the final ASD group (14.3%), 3 in the ADHD group (14.3%), and 6 in the ASD +ADHD group (22.2%) were taking non-stimulant medications and were included in analyses.[2] Importantly, the proportion of children taking non-stimulants did not differ between the clinical groups tested (χ^2 (2, n = 97) = 0.891, p = 0.640). Medications used to treat symptoms of other co-occurring conditions (e.g., risperidone, sertraline, fluticasone) were not exclusionary for participation except within the TD group. One child in the TD group (1.7%) was taking melatonin to alleviate difficulties with sleep. Eleven children in the ASD group (22.4%), 5 children in the ASD+ADHD group (18.5%), and 2 children in the ADHD group (9.5%) were taking medications for symptoms of other co-occurring

[1]Evidence indicates that an SRS-2 T-score cutoff of 75 has the strongest psychometric properties for detecting social deficits in children with ADHD (Bölte et al., 2011). In an effort to use the same inclusion criteria across groups, we used a cut-off of 75 (indicative to clinically significant social deficits) for both the ADHD and TD groups. Notably, however, there were two children in the TD group who had SRS-2 Total T-scores between 60 and 65, which may be indicative of mild to moderate deficits in social interactions.

[2]To explore the effects of medication type (stimulant, non-stimulant, combined stimulant and non-stimulant) on inhibition outcomes in this sample, we included children taking stimulants (clinical groups only) and ran exploratory analyses with medication type as a factor in the primary ANCOVA models. The main effect of medication type was not significant in models predicting inhibition outcomes of interest ($ps \geq 0.216$).

conditions (e.g., depression, anxiety, sleep difficulties).[3] The proportion of children taking these non-exclusionary medications did not differ between groups (χ^2 (3, n = 155) = 6.377, p = 0.095).

The final sample included 155 children. Forty-nine children were included in the ASD group (4 females, 8.2%) and 21 in the ADHD group (2 females, 9.5%). Twenty-seven children with an existing diagnosis of ASD and clinically significant symptoms of ADHD were included in the ASD+ADHD group (6 females, 22.2%). Fifty-eight children in the final sample did not have an existing clinical diagnosis and were included in the TD control group (9 females, 15.5%). Descriptive information for each of these groups is provided in Table 1.

Measures

Inhibition Battery—Three computer-based tasks were designed to measure four domains of inhibition: interference control, reactive inhibition, proactive inhibition, and motivational inhibition. We elected to use objective, computer-based assessments of EF because these tasks are 'algorithmic' and map to specific cognitive and behavioral outcomes throughout development (Toplak et al., 2013). In contrast, subjective reports of EF (i.e., rating scales and questionnaires) are 'reflective' and susceptible to potential confounds such as reporter-bias and the halo effect. Tasks were presented on a PC laptop via E-Prime 2 with an external keyboard to facilitate button presses. The keyboard was covered so that only the keys used for each task were available.

Stroop Task: The Stroop Task (Perlstein et al., 1998; Stroop, 1935) measures interference control and has been used in developmental samples with ASD and ADHD (Goldberg et al., 2005). Prior to task administration, children completed colorblindness-screening items to ensure validity of results (see Supplemental Figure 1). During the 96-trial task, words were presented in congruent, incongruent, or neutral trials depending on the word and color of the font the word was presented in (see Perlstein et al., 1998). The difference in correct response time (cRT) between congruent and incongruent trials indexed interference control, such that larger values represented more difficulty suppressing responses to incongruent trials and, consequently, more difficulty with interference control.

Stop-Change Task: The Stop-Change Task (De Jong et al., 1995) measures reactive inhibition and proactive inhibition (i.e., proactive slowing) and has been adapted for use in children with developmental disorders (Geurts et al., 2004). Children completed a version of this task with *either* an auditory or a visual stop signal.[4] In the dominant task - during which children were presented with "go trials" - children were asked to quickly press one of two

[3]Specifically, 10 children (8 ASD, 1 ASD+ADHD, 1 ADHD) were taking anxiety medications, 2 children (1 ASD, 1 ASD+ADHD) were taking antipsychotics, and 7 children (1 TD, 2 ASD, 3 ASD+ADHD, 1 ADHD) were taking melatonin. As these medications are not directly linked to EF, they were not exclusionary for the current study.

[4]A larger proportion of children completed the visual version of the task (55.3%). To determine if the type of stop-signal (auditory versus visual) altered results, we ran exploratory univariate ANCOVAs for the Stop-Change Task outcomes of interest (reactive inhibition and proactive inhibition) and included stop-signal type as a factor in the model. In the model predicting reactive inhibition, the main effect of group persisted (F(3,135) = 3.06, p = 0.031, η_p^2 = 0.064), suggesting that signal type did not contribute to group differences. The main effect of signal type and group by signal type interactions were not significant ($ps \geq 0.055$). In the model predicting proactive inhibition, the main effect of group remained significant (F(3,136) = 2.80, p = 0.043, η_p^2 = 0.058) whereas the main effect of signal type and group by signal type interactions were not ($ps \geq 0.089$).

buttons (left/right) to indicate the location of an image on the left or right side of the screen. In contrast, during "change trials" (25% of trials), a stop signal (either a beep or a color change to a central image) indicated that children were to stop the dominant response and press a third button (i.e., the change response).

Prior to completing experimental test blocks, children completed three training blocks. For the first of three training blocks, children practiced only the go (left/right) task. For the second training block, practice was provided with the stop signal, which preceded a subset of items. Children were instructed to suppress their go responses when the stop signal occurred (i.e., stop but not change). In the final training block, the change response was introduced with a fixed warning duration, and children were instructed to press a different button when the stop signal occurred.

After completion of the training blocks, children completed four test blocks. Each test block contained 64 trials (16 trials with stop signals presented at random). Stop signal timing was adjusted to account for individual differences in response time by computing the mean cRT from go trials in the previous block. Stop signals occurred equally at 50, 200, 350, and 500 ms before each child's anticipated dominant response (e.g., go trial cRT – 50 ms).

Each trial began with a fixation point presented for 350 ms. The go image was presented for 1500 ms equally on the right and left side of the screen and disappeared when a response was registered. Each trial had a 1000 ms inter-trial interval. The four stop intervals were also presented equally within a block. Children were instructed to respond as quickly and accurately as possible. Feedback was not provided.

Two outcome variables were derived from the Stop-Change Task. Reactive inhibition was indexed by stop signal reaction time (SSRT). SSRT was computed via the mean method as a measure of the time required to inhibit a go response when a stop signal was presented (Band et al., 2003; Crone & Van der Molen, 2004; Logan et al., 1984; Verbruggen et al., 2019). Proactive inhibition was calculated as the difference in mean cRT to first 24 go trials during the first test block (i.e., go trials when change trials were interspersed) minus the mean cRT to the 24 trials of first practice block (i.e., go trials only). Longer SSRTs and lower proactive inhibition latencies indicated reduced reactive and proactive inhibition, respectively.

Hungry Donkey Task: The Hungry Donkey Task (Crone & Van der Molen, 2004) is an adaptation of the Iowa Gambling Task that captures affective decision-making and inhibition in response to feedback. Similar versions of the Iowa Gambling task have been used with children who have ASD and ADHD (Garon et al., 2006; South et al., 2014). In the current study, the Hungry Donkey Task was used to probe motivational inhibition. Children fed apples to a donkey by opening four doors with varying gains and losses. Two doors were advantageous and resulted in a net gain whereas two doors were disadvantageous and resulted in a net loss. One of the advantageous doors provided higher magnitude and lower frequency gains while the other advantageous door provided lower magnitude but higher frequency gains. Similarly, the two disadvantageous doors provided high versus low frequency losses. Risk avoidance was measured by computing the number of selections from

both doors with high frequency losses (one advantageous and one disadvantageous) during the final 40 trials of the 100-trial task (to capture inhibition after receiving feedback).[5] Lower scores marked avoidance of frequent losses (Cassotti et al., 2014) and may represent the ability to integrate reward contingencies into response selections (i.e., better motivational inhibition).

Procedure

Information pertaining to child eligibility was collected during an initial phone screening-interview by trained research staff (i.e., health and demographic information, medication use). The ADI-R and ADOS-2 (ASD group) and Conners-3 (ADHD group) were collected to confirm existing diagnoses. Because children with ASD are particularly susceptible to order effects (Jones et al., 2013), experimental tasks (Stroop Task, Stop-Change Task, and Hungry Donkey Task) were collected in one of two fixed orders, and administered to the child by a research assistant, while caregivers completed the CBCL and SRS assessments. Breaks were taken between tasks to maintain the child's attention and task engagement. If the child was unwilling/unable to complete a task, the task was skipped and/or that experimental visit was terminated. In some instances, incomplete or skipped tasks from the first experimental visit were re-administered during the second experimental visit to avoid data loss. For participation, caregivers were provided a small monetary incentive and children selected an age-appropriate prize.

Statistical Analyses

Four separate univariate analysis of covariance (ANCOVA) models examined group differences in inhibition. In these models, outcomes derived from the aforementioned inhibition battery were entered as dependent variables. Group (ASD, ADHD, ASD+ADHD, TD) was entered as the independent variable. Due to expected and significant group differences in IQ (see Results below), IQ was entered as a covariate in all models (Full Scale IQ from the WASI-2). If a significant main effect of group was detected, post-hoc analyses were run to examine group differences. The *p*-values reported for pairwise comparisons are Bonferroni adjusted for multiple comparisons ("The calculation of Bonferroni-adjusted p-values," 2018). In all analyses, z-scores were used to aid in the comparison and visualization of group differences across tasks with different metrics (e.g., response time versus frequency of responses). Z-scores were computed relative to the TD group for all outcome variables using the following algorithm:

$$Z - score = \frac{(Individual\ Score\ on\ Outcome - Average\ Score\ for\ the\ TD\ Group\ on\ Outcome)}{Standard\ Deviation\ for\ the\ TD\ Group\ on\ Outcome}$$

Raw RT scores for the Stroop and Stop-Change Tasks are plotted for each task condition and group in Supplemental Figure 2A and 2C.

[5]Groups did not differ when the advantageous and disadvantageous doors were evaluated separately (main effect of group: $ps \geq 0.146$).

Missing Data

Pairwise deletion (i.e., available case analysis) was used to account for missing data in the current study. Children who (1) failed task-specific screening criteria, (2) refused to participate in specific tasks, (3) were unable to complete a task due to a missed experimental visit, fatigue, or time constraints (i.e., visits running late or ending early due to family scheduling concerns) were missing data. Invalid data (i.e., not enough data to compute specific variables needed for analysis, computer/experimenter error) were also marked as missing. Final samples, accounting for missing data for each task, are outlined in Supplemental Figure 1.

Results

Age ($F(3,151) = 0.389$, $p = 0.761$) and sex distribution (χ^2 (3, $N = 155$) = 3.430, $p = 0.330$) did not significantly differ by group (Table 1). Full Scale IQ significantly differed by group ($F(3,151) = 6.834$, $p \leq 0.001$, $\eta_p^2 = 0.120$, Table 1). Post-hoc analyses indicated that the TD group had significantly higher IQ than the ASD and ASD+ADHD groups ($ps \geq 0.004$). The ADHD group also had a higher IQ than the ASD+ADHD group ($p = 0.052$).

Stroop Task

The Stroop Task was used to index interference control. Controlling for IQ (main effect of IQ was marginally significant, $p = 0.059$), the main effect of group was significant ($F(3,131) = 4.575$, $p = 0.004$, $\eta_p^2 = 0.095$, Figure 2A). Post-hoc comparisons indicated that interference control was significantly different between the ASD and ASD+ADHD groups ($p = 0.007$), with a larger condition-related difference in cRT observed for children with ASD. Interference control was also marginally different between the ADHD and ASD +ADHD groups ($p = 0.058$), with a larger difference observed for children with ADHD. All other pairwise comparisons were not significant ($ps \geq 0.213$).

An exploratory multivariate ANCOVA was run to aid in interpretation of this finding. In this model, cRTs for congruent and incongruent trials were evaluated separately. The main effect of group was significant only for cRT to incongruent trials ($F(3,131) = 4.100$, $p = 0.008$, $\eta_p^2 = 0.086$; congruent trials: $F(3,131) = 1.319$, $p = 0.271$). Post-hoc comparisons indicated that the TD group responded to incongruent trials significantly faster than the ASD group ($p = 0.011$; all other comparisons were not significant: $ps \geq 0.089$; Supplemental Figure 2A). Moreover, paired samples t-tests indicated cRT did not differ between trial types in the ASD +ADHD group ($t(23) = -0.914$, $p = 0.370$), whereas all other groups responded significantly faster to congruent versus incongruent trials, demonstrating the expected advantage for congruent trials ($ps \leq 0.01$).

Stop-Change Task

The Stop-Change Task was used to measure both reactive inhibition and proactive inhibition. In the ANCOVA assessing group differences in reactive inhibition, the main effect of group was significant ($F(3,138) = 3.448$, $p = 0.018$, $\eta_p^2 = 0.070$, Figure 2B) controlling for IQ ($p = 0.524$). Post-hoc comparisons indicated that the ASD+ADHD group required significantly longer warning durations relative to the TD group ($p = 0.042$). All other pairwise

comparisons were not significant ($ps \geq 0.176$). Although cRT on go trials (i.e., dominant task) did not significantly differ by group ($p = 0.201$), groups did differ on accuracy for change trials ($p = 0.004$) such that the clinical groups (ASD, ASD+ADHD, and ADHD) had lower accuracy than the TD group ($ps \leq 0.031$).

In the model evaluating proactive inhibition, the main effect of group was significant ($F(3,139) = 3.015$, $p = 0.032$, $\eta_p^2 = 0.061$, Figure 2C). Again, the main effect of IQ was not significant ($p = 0.658$). Post-hoc comparisons indicated that proactive inhibition was significantly decreased in the ASD+ADHD relative to the ADHD group ($p = 0.021$). All other pairwise comparisons were not significant ($ps \geq 0.242$).

Because it is possible that slower cRT during the test block resulted from the dual task demands of performing both the dominant and the Stop-Change task, compared to the singular demand of responding only to go trials during the first practice block, a separate ANCOVA was run to examine changes in accuracy during the practice block and the first 24 go trials of the test block (i.e., those used to generate cRT for proactive inhibition). If slowing was due to dual task demands of the more difficult test condition, accuracy would also be expected to decrease (Verbruggen & Logan, 2009). Instead, the main effect of group was not significant ($F(3,138) = 0.278$, $p = 0.841$). The main effect of IQ was also not significant ($p = 0.564$).

Exploratory, multivariate ANCOVAs were also run to assess group differences in accuracy and cRT during the dominant task (i.e., go trials when change trials were interspersed) and while practicing the dominant task (i.e., only go trials), separately. The main effects of group were not significant ($ps \geq 0.177$; Supplemental Figures 2B and 2C).

Hungry Donkey Task

The Hungry Donkey Task was used to gauge motivational inhibition via risk avoidance. In this ANCOVA, the main effect of group was not significant ($F(3,141) = 1.400$, $p = 0.245$, Figure 2D). The main effect of IQ, however, was significant ($F(1,141) = 5.845$, $p = 0.017$, $\eta_p^2 = 0.040$).

An exploratory bivariate correlation between IQ and risk avoidance (collapsed across diagnostic groups), indicated that children with higher IQ picked from doors with high frequency losses less frequently ($r = -0.195$, $p = 0.019$), therefore demonstrating a more mature strategy of risk avoidance.

Discussion

The aim of the current study was to compare inhibition profiles between children with ASD, ADHD, comorbid presentation of ASD+ADHD, and TD controls. Children with ASD +ADHD had a greater impairment in reactive inhibition, relative to TD children, consistent with previous reports (Karalunas et al., 2018; Takeuchi et al., 2013; Tye et al., 2014). Yet, counter to our hypothesis and the results of other studies (see Craig et al., 2016; Gargaro et al., 2011; Taurines et al., 2012 for review), the ASD+ADHD group did not demonstrate an additive impairment (relative to other groups) across the facets of inhibition assessed.

Rather, our results indicated that inhibition difficulties in this group were task-dependent: the ASD+ADHD group demonstrated a unique profile of inhibition outcomes that assessed response time (interference control and proactive inhibition) relative to children with singular diagnoses of ASD or ADHD.

The profile observed for interference control, reactive and proactive inhibition suggests a quantitatively unique pattern of performance for children with co-occurring ASD and ADHD symptoms (ASD+ADHD). Given that inhibition deficits varied across groups of children with ASD, ADHD, and ASD+ADHD, the results of the current study suggest that detailed measurement of inhibition may serve to differentiate qualitatively distinct disorders. Further, as the same pattern of inhibition deficits were not observed for all clinical groups, measuring multiple aspects of inhibition may be useful in isolating unique clinical groups rather than dimensional manifestations of the same disorder. These findings have important clinical implications: As children with comorbid symptoms experienced reduced sensitivity to incongruent information, delayed reactivity to a stop-signal, and less strategic slowing to adjust to task demands, relative to other clinical groups, children with ASD+ADHD might benefit from interventions that differentially target selective, reactive, and strategic inhibition (see Implications).

Evidence of Unique Inhibition Profiles in ASD, ADHD, and ASD+ADHD

Consistent with prior work (Karalunas et al., 2018; Takeuchi et al., 2013; Tye et al., 2014), children with ASD+ADHD exhibited impaired reactive inhibition. Relative to the TD group, the ASD+ADHD group required more time to inhibit responses to the stop signal and correctly shift to a non-dominant response during the Stop-Change Task. Reactive inhibition scores for the ASD and ADHD groups fell between the TD and ASD+ADHD groups and did not differ from either (see Figure 2B). This suggests that reactive inhibition challenges may be additive for children with ASD+ADHD.

Comparatively, interference control differed between children with ASD+ADHD and those with a singular diagnosis of ASD or ADHD, in contrast with previous literature (Karalunas et al., 2018). To better understand this unique profile among children with ASD+ADHD, we examined cRT to congruent and incongruent trials of the Stroop Task, separately. As expected, children in the TD, ASD, and ADHD groups took longer to respond to trials with conflicting information (i.e., increased cRT to incongruent versus congruent trials). Children in the ASD+ADHD group, however, did not demonstrate an advantage in efficiency for the congruent trials, suggesting that they may not be attending to the stimulus dimensions in the same way.

The ASD+ADHD group also used less strategic slowing of responses during the Stop-Change Task, as indexed by reduced proactive inhibition. In this task, children should strategically slow their response times during test blocks (relative to practice blocks) in an effort to effectively prepare for the possibility of change trials when the stop signal is presented (see Verbruggen & Logan, 2008, 2009). Smaller differences in cRTs to go trials during the practice block versus test blocks suggest that children in the ASD+ADHD did not implement this strategy, as cRTs were comparable during go trials that did not include a stop signal (i.e., practice). This finding contrasts Van Holst and colleagues (2018) who reported

reduced reactive, but not proactive, inhibition among children with ADHD and ASD +ADHD relative to TD controls. Taken together, these findings provide evidence of both proactive and reactive response time difficulties among children with comorbid symptom presentation.

Results of exploratory ANCOVAs also ruled out the possibility of widespread differences in RTs, as cRTs of children with ASD+ADHD did not differ from other groups when specific conditions were assessed separately (i.e., congruent or incongruent trials of the Stroop Task or go trials during the dominant or practice blocks of the Stop-Change Task). Thus, cRTs of children with ASD+ADHD only differed from the other clinical groups when difference score measures were evaluated (i.e., incongruent-congruent trial difference score or dominant-practice task difference score). Further, accuracy during the same set of trials did not differ by group, which is consistent with strategic rather than dual task slowing.

Counter to the group differences reported for response time measures, children with ASD, ADHD, ASD+ADHD, and TD did not differ on the motivational inhibition task that featured reward contingencies, consistent with other studies that have compared similar outcomes in these groups (Crone et al., 2003; Geurts et al., 2006; Karalunas et al., 2018). It is possible that the lack of group differences in this reward-based task reflects intact hot excutive function (see Zelazo & Carlson, 2012; Zelazo & Muller, 2002) among school-aged children with comorbid symptoms of ASD and ADHD. Subjective examiniation of group averages on this outcome indicate that children with ASD+ADHD performed more like children with ADHD (see Figure 2D). As reward processing is a central impairment in ADHD, that is also common in ASD (Sonuga-Barke, 2002), inhibitory deficits associated with reward or motivation may be more closely linked to ADHD symptomology. Alternatively, our participants may not have been sufficiently motivated by the rewards provided in the Hungry Donkey Task, as they were simulated and not tangible.

Collectively, it is worth noting that behavioral outcomes were task-dependent and varied across the facets of inhibition assessed regardless of diagnostic group. Consistent with proposals by Nigg (2000) and other researchers (Carlson, 2003; Christ et al., 2007), our results reiterate the importance of utilizing multiple outcome measures in order to adequately assess inhibition among children with developmental disorders. If only one outcome were assessed (i.e., reactive inhibition), we may have come to different a conclusion regarding the difference in inhibition between children with across diagnostic groups. Moreover, by comparing various inhibition outcomes between children ASD +ADHD to groups of children with singular diagnosis of ASD or ADHD, our results highlight aspects of inhibition related to inhibition that may be unique to children with comorbidity (Karalunas et al., 2018; van der Meer et al., 2012).

Implications

Identifying specific inhibition impairments in subgroups of children with ASD, ADHD, and ASD+ADHD may inform treatment and intervention strategies. Accumulating evidence suggests that distinct types of inhibition are supported by different neural networks (see Nigg, 2000 for review). For example, an experimental study in adults found that stimulation of the inferior frontal gyrus – an area of the prefrontal cortex that supports inhibition -

impaired reactive inhibition but did not affect interference control (Chambers et al., 2007). Interference control is supported by areas of parietal cortex in addition to prefrontal structures (Adleman et al., 2002). Inhibition tasks use rewards or incentives (i.e., motivational inhibition) are also distinct, as they elicit activation of the striatum and the amygdala (Paulsen et al., 2015). Notably, however, there is a paucity of studies exploring the neural mechanisms of inhibition taxonomy in children with developmental disorders. If the networks supporting distinct types of inhibition are truly unique, and they contribute to meaningful behavioral outcomes among subgroups - namely, interference control, reactive and proactive inhibition - then neural activity could be a target of neurofeedback (Coben et al., 2010) or non-invasive brain stimulation (Ameis et al., 2017) as a means of intervention.

Beyond differences in underlying neurobiology, subgroup-specific inhibition profiles could also inform behavioral intervention. For example, Applied Behavior Analysis (ABA) is an effective behavioral intervention commonly used to alleviate core symptoms of ASD. This therapy uses rewards to facilitate behavioral change (Makrygianni et al., 2018). Thus, subgroups of children with differences in motivational inhibition may have contrasting responses to reward contingencies. Conversely, cognitive training approaches, which often target impulsivity and task-related attention, are typically recommended for ADHD symptom management (see Sonuga-Barke & Cortese, 2018 for review), and may be particularly useful for subgroups of children that experience difficulty with interference control as well as reactive and proactive inhibition. Taken together, the results of the current study suggest that children with comorbid presentation of ASD and ADHD may benefit from cognitive interventions.

Limitations and Future Directions

To our knowledge, the current study was the first to compare multiple aspects of inhibition across children with ASD, ADHD, and ASD+ADHD. As such, ‘trending’ or marginally significant differences ($ps \leq 0.08$) were reported for transparency. However, these results should be interpreted with caution. Relatedly, the samples tested were relatively small and there were an unequal number of children in each group. The sample tested was also predominantly composed of Caucasian males with high socioeconomic status (annual household income) and IQ. Further testing with larger and more diverse samples is needed to infer generalizability.

IQ significantly differed between groups tested. Many researchers deliberately match IQ across groups (by excluding children with high or low IQs) to alleviate this confound. We elected to maintain larger samples and increase power by controlling for IQ in our statistical analyses (via ANCOVA). Nonetheless, it is important to acknowledge that IQ difficulties are inherent to many developmental disorders (particularly ASD) and are difficult to ‘match’ in comparison groups (Dennis et al., 2009). Furthermore, the average IQ for children in the TD and ADHD groups was high (approximately 1 standard deviation greater than the population mean), which may limit the generalizability of these results. In an attempt to address this limitation, all analyses were also conducted without IQ as a covariate, and the group differences in inhibition outcomes were largely identical except that the ASD group

exhibited a significantly larger difference between incongruent and congruent conditions of the Stroop (i.e., interference control) relative to the TD group.

A main effect of IQ was only detected when assessing group differences in motivational inhibition. As this variable was derived from performance on the last 40 trials of a 100-trial task, it is possible that children with lower IQ had more difficulty learning the pattern of gains and losses attributed to the different doors. If this is the case, they may not have been prepared to make 'advantageous' selections during the last 40 trials used to compute risk avoidance in the current study. Additional research is needed to test this hypothesis further.

Lastly, although (1) ADHD group characterization was based on two, objective caregiver-report measures (Conners-3 and CBCL ADHD subscale) and (2) the same measure was used to characterize ADHD symptoms across groups (CBCL ADHD subscale), ADHD symptoms and diagnosis were not confirmed via psychosocial interviews as is preferred in the field. Clinical characterization of ADHD outcomes should be confirmed with gold standard assessments in future work. Additionally, although children in the ADHD were not taking medications at the time of experimental testing, the impact of long-term use of stimulant medication on EF is unknown (Pietrzak et al., 2006). It is also possible that by asking children with ADHD to withhold medications, their performance was impacted indirectly (e.g., change in routine, increased distractibility, reduced persistence, etc.). Because other medications (e.g., anxiety and sleep medications) were not expected to impact EF, they were not exclusionary for the current study. Nonetheless, replication in a more representative sample of children using these types of medications is needed to increase external validity.

Conclusions

The current study assessed distinct facets of inhibition among school-aged children with ASD, ADHD, comorbid presentation of ASD+ADHD, and no clinical concerns (TD). Children with comorbid symptoms presented with significant deficits in response time measures that probed interference control, reactive inhibition, and proactive inhibition. Reactive inhibition was more impaired among children with ASD+ADHD relative to TD children. Interference control and proactive inhibition in the ASD+ADHD group differed relative to other clinical groups. Motivational inhibition, as indexed by risk avoidance, did not significantly differ between groups assessed, although children with ASD+ADHD responded comparably to children with ADHD. Collectively, the results of this study indicate that children with ASD+ADHD have a unique profile of task-dependent deficits that vary across distinct aspects of inhibition.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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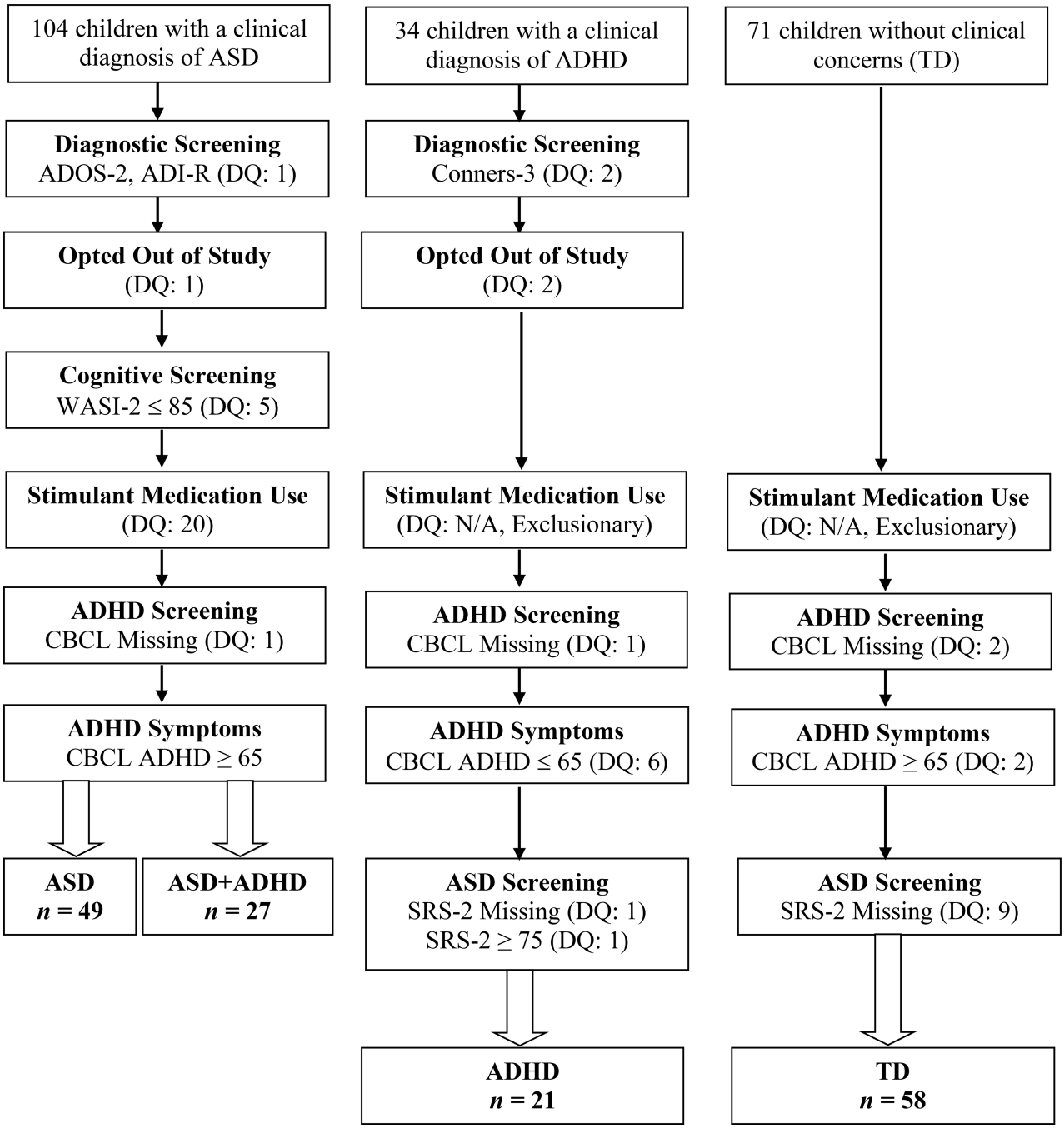

Figure 1.

Group sample sizes after filtering for eligibility and inclusion criteria.

Notes: ASD = autism spectrum disorder; ADHD = attention-deficit/hyperactivity disorder; TD = typical development; DQ = disqualified from study; ADOS-2 = Autism Diagnostic Observation Study, Second Edition; ADI-R = Autism Diagnostic Interview-Revised; WASI-2 = Wechsler Abbreviated Scale of Intelligence, Second Edition; CBCL = Child Behavior Checklist; SRS-2 = Social Responsiveness Scale, Second Edition; N/A = not applicable

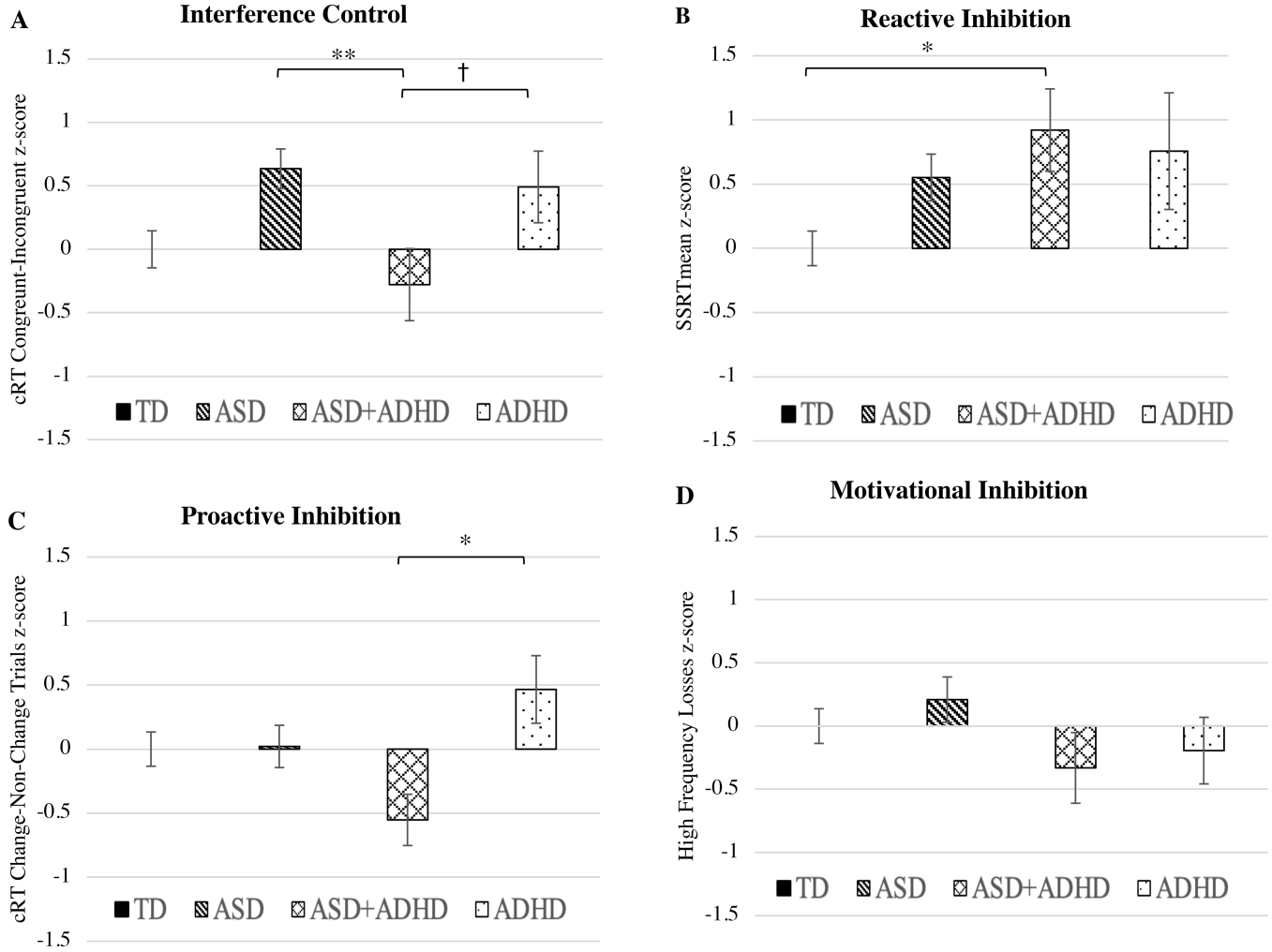

Figure 2.

Group performance on tasks measuring distinct types of inhibition, namely (**A**) interference suppression measured by the difference in cRT between congruent and incongruent trials on the Stroop Task, (**B**) reactive inhibition measured by SSRT (the time required to inhibit a go response when a stop signal was presented) during the Stop-Change Task, (**C**) proactive inhibition measured by the difference in cRT to go trials during practice and test blocks of the Stop-Change Task (where the number of trials in the practice and test blocks were comparable), and (**D**) motivational inhibition measured by the number of selections from doors with high frequency losses during the final 40 trials of the 100 trial Hungry Donkey Task.

Notes: Z-scores were computed relative to the TD group; means are adjusted for IQ; error bars represent standard error; TD = typical development; ASD = autism spectrum disorder; ADHD = attention-deficit/hyperactivity disorder; cRT = correct response time; SSRT = stop signal reaction time; ms = milliseconds

† $p \leq 0.08$; * $p < 0.05$; ** $p < 0.01$

Table 1.

Descriptive information for final samples.

	TD M (SD)	ASD M (SD)	ASD+ADHD M (SD)	ADHD M (SD)	Significance
Number of Participants	58	49	27	21	–
Age (Years)	8.78 (1.40)	8.65 (1.30)	8.85 (1.51)	8.48 (1.03)	NS
Range	7 to 11	7 to 11	7 to 11	7 to 10	
Sex (Male: Female)	49:9	45:4	21:6	19:2	NS
Race [a] (Caucasian: Non-Caucasian)	45:12	37:10	21:3	13:8	NS
Ethnicity [b] (Non-Hispanic: Hispanic)	53:5	43:6	22:4	17:4	NS
Average Household Income [c] (%)					
< $20,000	N/A	4.1%	N/A	4.8%	
$21,000 – $35,000	3.4%	10.2%	7.4%	4.8%	
$36,000 – $50,000	3.4%	6.1%	3.7%	N/A	
$51,000 – $65,000	1.7%	6.1%	7.4%	N/A	NS
$66,000 – $80,000	8.6%	8.2%	18.5%	14.3%	
$81,000 – $100,000	13.8%	14.3%	25.9%	9.5%	
$101,000 – $130,000	22.4%	12.2%	11.1%	14.3%	
$131,000 – $160,000	20.7%	8.2%	7.4%	14.3%	
> $160,000	19.0%	28.6%	11.1%	38.1%	
Non-Stimulant ADHD Medications (Total #)	N/A	7	6	3	NS
CBCL ADHD (T-score)	51.53 (2.61)	57.16 (3.69)	70.44 (3.99)	73.10 (3.56)	$F = 325.71^{**}$
WASI-2 FSIQ	117.66 (12.06)	109.06 (13.77)	106.74 (13.34)	116.62 (11.50)	$F = 6.83^{**}$
WASI-2 VCI	116.72 (13.62)	108.06 (15.48)	105.41 (14.32)	116.95 (11.30)	$F = 6.29^{**}$
WASI-2 PRI	115.41 (13.75)	108.37 (14.02)	107.15 (15.88)	112.10 (15.60)	$F = 2.99^{*}$

	TD M (SD)	ASD M (SD)	ASD+ADHD M (SD)	ADHD M (SD)	Significance
SRS-2 Total [d]	49.22 (7.15)	68.17 (9.51)	73.67 (10.42)	61.95 (6.23)	$F = 67.28^{**}$
Vineland-II Communication	111.76 (12.76)	94.51 (10.17)	87.11 (9.15)	94.24 (14.16)	$F = 36.10^{**}$
Vineland-II Daily Living	103.10 (9.53)	89.88 (9.06)	86.33 (9.62)	98.90 (14.18)	$F = 24.01^{**}$
Vineland-II Socialization	104.59 (9.88)	83.22 (10.32)	78.04 (7.63)	89.38 (13.55)	$F = 57.95^{**}$
Vineland-II Adaptive Behavior Composite	105.66 (9.40)	87.29 (8.09)	81.93 (7.08)	92.52 (11.72)	$F = 57.95^{**}$
ADOS-2 Total Calibrated Severity Score	N/A	8.61 (1.57)	8.15 (1.85)	N/A	NS
ADI-R Social	N/A	18.02 (5.48)	18.70 (4.55)	N/A	NS
ADI-R Communication	N/A	16.71 (4.25)	15.48 (4.34)	N/A	NS
ADI-R RRB	N/A	7.98 (2.50)	8.04 (2.23)	N/A	NS

Notes: M = mean; SD = standard deviation; N/A = not applicable; NS = non-significant ($p > 0.05$); TD = typical development; ASD = autism spectrum disorder; ADHD = attention-deficit/hyperactivity disorder; $ = US Dollars; CBCL = Child Behavior Checklist; WASI-2 = Wechsler Abbreviated Scale of Intelligence, Second Edition; FSIQ = Full Scale Intelligence Quotient (four subtests); VCI = Verbal Comprehension Index; PRI = Perceptual Reasoning Index; SRS-2 = Social Responsiveness Scale, Second Edition; ADOS-2 = Autism Diagnostic Observation Schedule, Second Edition; ADI-R = Autism Diagnostic Observation Schedule-Revised; RRB = Restricted, Repetitive and Stereotypes Behaviors and Interests

[a] due to missing data or field marked as 'unknown', reduced TD, ASD, and ASD+ADHD samples (ns = 57, 47 and 24, respectively)

[b] due to missing data, reduced ASD+ADHD sample size (n = 26)

[c] due to missing data, reduced TD, ASD, and ASD+ADHD sample size (ns = 54, 48, and 25, respectively)

[d] due to missing data, reduced ASD and ASD+ADHD sample size (ns = 46 and 24, respectively)

* $p < 0.05$

** $p \leq 0.001$.