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Sluggish Cognitive Tempo as a Possible Predictor of Methylphenidate Response in Children With ADHD: A Randomized Controlled Trial

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Abstract

Objective: To examine whether sluggish cognitive tempo (SCT) symptomatology moderates dose response to methylphenidate, and whether the impact of SCT on medication response is distinct from attention-deficit/hyperactivity disorder (ADHD) subtype effects.

Methods: Stimulant-naïve children with ADHD predominantly inattentive type (ADHD-I; n=126) or ADHD combined type (ADHD-C; n=45) aged 7–11 years were recruited from the community from September 2006 to June 2013 to participate in a prospective, randomized, double-blind, 4-week crossover trial of long-acting methylphenidate. ADHD diagnosis and subtype were established according to DSM-IV criteria using a structured interview and teacher ADHD symptom ratings. SCT symptoms were assessed using a teacher-rating scale with two factors (Sluggish/Sleepy and Daydreamy). Primary outcomes included: 1) categorization of children as methylphenidate responders, non-responders, or placebo responders by two blinded physicians, and 2) parent and teacher ratings of child behavior on the Vanderbilt ADHD Diagnostic Rating Scales while on placebo and three methylphenidate dosages (low, medium, high).

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Results: Increased SCT Sluggish/Sleepy factor scores were associated with being a methylphenidate non-responder or placebo responder rather than a methylphenidate responder (p=0.04). Sluggish/Sleepy scores were also linked to diminished methylphenidate dose response on parent- and teacher-rated inattention symptoms (Sluggish/sleepy*dose p=0.004). SCT Daydreamy symptoms and ADHD subtype (ADHD-I versus ADHD-C) were not associated with methylphenidate responder status and did not moderate methylphenidate dose response on inattention symptoms.

Conclusions: SCT Sluggish/Sleepy symptoms, but not SCT Daydreamy symptoms or ADHD subtype, predicted methylphenidate non-response. This novel finding, if replicated, may have important implications for assessing SCT as part of ADHD care.

Trial registration: https://clinicaltrials.gov/ct2/show/NCT01727414.

Keywords

ADHD; Methylphenidate; Attention; Subtype; sluggish cognitive tempo

INTRODUCTION:

Attention-deficit/hyperactivity disorder (ADHD) is a prevalent childhood neurobehavioral condition associated with substantial impairments in academic, social, and family functioning.[1] Psychostimulants have the largest effect size and highest response rate among ADHD medications,[2] and methylphenidate is the most commonly prescribed ADHD treatment worldwide.[3] Nonetheless, only a minority achieve normalization of function with methylphenidate treatment, and there is wide variability in optimal dose. As no factors have been identified that consistently predict methylphenidate response, gradual escalation titration is recommended to achieve optimal dosing,[4] but this can be a prolonged and expensive process.

One phenotypic factor that has received little attention in prior methylphenidate response studies is referred to as sluggish cognitive tempo (SCT). The SCT phenotype incorporates symptom dimensions not captured by ADHD DSM criteria, and is characterized by daydreaming, seeming to be “in a fog,” mental confusion, and underactivity.[5] A recent meta-analysis indicates that SCT symptoms are empirically distinct from, yet strongly related to, ADHD symptoms in factor analyses. [6] Although SCT symptoms are more closely linked to inattentive than hyperactive-impulsive symptoms, high levels of SCT symptomatology can be seen in both ADHD-combined type (ADHD-C) and ADHD-inattentive type (ADHD-I). [7–9] Despite the elevated SCT scores of many children with ADHD (estimated to occur in approximately 50%[7]), only one study has examined whether SCT predicts methylphenidate response: in Ludwig et al.’s naturalistic study of children with ADHD-I, SCT symptoms *based upon a unidimensional measure* did not predict methylphenidate response.[10] It is particularly important to evaluate whether different SCT dimensions have discrete effects on methylphenidate response given evidence that specific SCT dimensions may differentially predict functioning among youth with ADHD.[11–13] Some studies have found that SCT symptoms separate into cognitive (e.g., daydreaming, inconsistent alertness, mental confusion) and behavioral (e.g., slowness, lethargy, drowsiness) dimensions,[7, 12, 14] and

there is some indication that the daydreamy cognitive dimension is uniquely associated with increased peer problems, while the slowness/sleepy behavioral dimension is uniquely associated with depression and learning/organization problems.[7, 12, 15, 16] It is also essential to investigate whether SCT and subtype effects are distinct, and to determine the role of SCT symptoms in MPH response across ADHD subtypes.

The current study's objective is to examine whether specific SCT dimensions moderate methylphenidate dose response curves while considering and incorporating the contribution of ADHD subtype. In evaluating the possible role of SCT, our study builds on the Ludwig et al. study[10] by using a randomized titration design, including children with both ADHD-C and ADHD-I, and considering different dimensions of SCT.

METHODS

Participants and Procedures

Stimulant-naïve children ages 7–11 were recruited for the Attention Deficit Disorder Medication Response Study (https://clinicaltrials.gov/ct2/show/NCT01727414) via advertisements distributed to local schools, pediatricians' offices, and hospitals from September 2006 to June 2013. All parents/caregivers and participants provided written and informed consent/assent according to the Institutional Review Board-approved protocol. ADHD diagnosis and subtype were determined using methodology similar to the Multimodal Treatment Study of Children with ADHD.[17] Children were considered to meet criteria for a symptom domain (i.e., inattention and/or hyperactivity/impulsivity) if the parent/caregiver on the Diagnostic Interview Schedule for Children [DISC][18] and the teacher on the Vanderbilt ADHD Diagnostic Teacher Rating Scale[19] reported 6 non-overlapping DSM-IV symptoms in a symptom domain and both parent and teacher each reported at least 4 symptoms in that domain. The sample was limited to ADHD-I (n=126) or ADHD-C (n=45). Subtype was defined as follows: if parents endorsed ≥6 hyperactive-impulsive symptoms OR parents endorsed ≥4 hyperactive-impulsive symptoms and teachers endorsed ≥2 additional non-overlapping hyperactive-impulsive symptoms, children were classified as ADHD-C; all others were classified as ADHD-I. Children with ADHD-I were oversampled to allow adequate power for examination of medication response in ADHD-I specifically. All participants also met ADHD DSM-IV onset age, pervasiveness, and impairment criteria. A trained clinician (pediatrician or psychologist) interviewed families to confirm the diagnosis and provide a Clinical Global Impression[20] rating of functional severity of at least "moderately ill."

Children were also evaluated for psychiatric comorbidities using the DISC, and those with mania/hypomania were excluded. Comorbid oppositional defiant, conduct, depression, and anxiety disorders were allowed unless determined to be the primary cause of ADHD symptomatology or necessitating different treatment. Children with Wechsler Abbreviated Scale of Intelligence[21] IQ <80 and Wechsler Individual Achievement Test—2nd edition[22] word reading and numerical operations subtests <80 were excluded, as were children whose medical history suggested significant brain injury.

A total of 194 children met all study inclusion criteria, and among these 171 entered the medication trial (See Supplemental Figure). Non-participants differed on race/ethnicity (i.e., smaller proportion of non-Hispanic whites; p=0.007) and IQ score (i.e., mean IQ of 99 vs. 107; p=0.04) from participants, but these groups did not differ on sex, academic achievement scores, presence of comorbid mental health conditions, or parent or teacher ADHD symptom scores (all *p*s>0.20).

Medication Trial

Participants underwent a 4-week, double-blind, crossover trial of long-acting osmotic-release oral system methylphenidate (Concerta®), during which they were randomized equally to one of six dosing schedules comprised of three active dosage weeks (18mg, 27mg, 36mg for children ≤25kg; 18mg, 36mg or 54mg for children >25kg; sample mean maximum dose=1.57 mg/kg/day) and one week of placebo (see prior publication[23] for dosing schedules). Study pills were identical capsules filled with either an inert white powder (placebo) or the prescribed dose of MPH over-encapsulated to preserve the blind.

Measures

ADHD Symptom Scores.—At baseline and at the end of each trial week, the Vanderbilt ADHD Diagnostic Parent Rating Scale (VADPRS)[24] and Vanderbilt ADHD Diagnostic Teacher Rating Scale (VADTRS)[19] were completed by parents and teachers, respectively. Inattentive, hyperactive-impulsive, and total symptom scores were calculated for each rater individually as follows: scores from the nine inattention symptoms were summed to derive the inattentive symptom score; a hyperactive-impulsive symptom score was generated by totaling scores from the nine hyperactive-impulsive symptoms; a total symptom score was created by summing the inattentive and hyperactive-impulsive symptom scores. In the present sample, internal consistency of the VADPRS and VADTRS was excellent. At baseline, Cronbach's alphas for the VADPRS (VADTRS) inattention, hyperactive-impulsive, and ADHD total scores were .84 (.88), .92 (.94), and .89 (.91), respectively. Internal consistency was also excellent during the four-week titration trial, with all alphas >.90 across both the VADPRS (range: .91 to .95) and the VADTRS (.93 to .96). Concurrent validity of the VADPRS with the DISC is high (r=0.79).[24]

Responder Status.—Following trial completion, parent and teacher behavior and side effect ratings from the 4 titration weeks were graphed and two blinded study physicians (TF, WB) independently judged the optimal week. The physicians discussed and resolved discrepancies while still blind to dose conditions. Children were then classified as being a non-responder (*n*=10, no week judged to be better than pre-trial baseline), placebo responder (*n*=26, placebo week judged to be "best week"), or methylphenidate responder (*n*=132, a methylphenidate dose week determined to be "best week"), with 3 children having insufficient data to determine "best week." In order to increase power, children judged to be non- and placebo responders were combined into a single non-responder/placebo responder group (*n* = 36) for responder analyses.

Sluggish Cognitive Tempo (SCT).—At baseline, teachers completed a 12-item SCT rating scale, with each item rated on a four-point scale (0=*rarely/never,* 1=*sometimes*,

2=*often*, 3=*very often*). SCT items were identical or very similar to items used in previous SCT studies.[7, 25, 26] Teacher ratings were used since teachers may be somewhat better able than parents to distinguish SCT from ADHD symptoms,[8, 27] and because teacher-rated SCT uniquely predicts impairment in both school and home contexts.[28]

We conducted an exploratory factor analysis of the 12 symptoms using maximum-likelihood extraction, and an oblique promax rotation yielded two factors with Eigenvalues >1.0 (Factor 1: 6.33 [53% of variance]; Factor 2: 1.38 [12% of variance]). Similar to recent SCT measurement studies,[7, 12, 25] these two factors were termed *Daydreamy* (7 items; α=.88; i.e., "Seems to be 'in a fog,'" "Is easily confused," "Daydreams, stares into space, or gets lost in his/her thoughts," "Seems not to hear, needs things repeated," "Is absentminded, forgets things easily," "Seems to be unaware of his/her surroundings (for example, doesn't notice wet pain or a dangerous situation)," "Has trouble making up his/her mind") and *Sluggish/Sleepy* (5 items; α=.90; i.e., "Is sluggish, slow to respond," "Is drowsy or sleepy," "Is underactive, slow moving, or lacks energy," "Is apathetic or unmotivated," "Is lethargic"). The SCT Daydreamy and SCT Sluggish/Sleepy factors were significantly correlated, r=.63, p<.001. Each item had a primary factor loading >.40 on its respective factor, absolute factor loading <.20 on the alternative factor, and a factor loading difference of >.30 on the primary factor compared to the alternative factor. Regression-based factor scores for the two SCT dimensions were produced and used in analyses. Mean and standard deviation of SCT factors are shown for the subtypes in Table 1. For both SCT dimensions, absolute values of skewness and kurtosis were below 1.5 for both subtypes.

Statistical Analysis

All statistical tests were two-tailed. Demographic and phenotypic characteristics of children in the subtype groups were compared using t-tests. Logistic regression analyses were conducted to examine whether baseline SCT Sluggish/Sleepy factor scores, baseline SCT Daydreamy factor scores, and ADHD subtype were associated with MPH responder status (being a MPH responder vs. a non-responder/placebo responder).

In modeling dose response effects, we tested both linear and quadratic terms across different dosages. Linear terms were found to have the best fit. Repeated measures analyses (SAS Proc GLM, SAS Version 9.2, SAS Institute, Cary, NC) included a linear dose term (mg/kg/day), our predictor (SCT factor or subtype) and predictor*dose interaction terms as independent variables. Dependent variables included inattentive, hyperactive-impulsive, and total symptom scores on placebo as well as on each MPH dose. We first examined the role of ADHD subtype as a primary predictor to determine if subtype moderated methylphenidate dose response in the absence of SCT consideration. Of note, since the ADHD-C group is expected to have higher baseline hyperactive-impulsive scores than the ADHD-I group, we expect the subtype*dose interaction to be significant for the hyperactive-impulsive ratings, and possibly for the total symptom scores as well, due to regression to the mean. Therefore, our primary outcome of interest for the predictor*dose models is inattentive symptom scores. We included covariates in the model that have been *variably* associated with ADHD medication response, including age,[29] IQ,[30] and mental health comorbidities,[30] such as disruptive behavior disorders (presence of DISC-diagnosed

oppositional defiant or conduct disorder) and anxiety disorders (presence of any of the following DISC-diagnosed disorders: social phobia, separation anxiety, panic, agoraphobia, generalized anxiety, obsessive compulsive, or post-traumatic stress disorder).

Models also included baseline parent and teacher ratings for each domain to account for any group differences in initial symptom severity, and to minimize false positive results associated with regression to the mean. In order to accommodate both parent and teacher weekly assessment ratings in the same model, a rater variable was included in the models to control and assess for effects of parent versus teacher ratings. Next, analyses examining SCT, dose, and the SCT*dose effects on methylphenidate response were conducted, adjusting for subtype and the full covariate panel. To determine if SCT differentially affected dose-response in children with ADHD-I versus ADHD-C, the SCT factor*dose interaction models were also conducted separately in ADHD-I only and ADHD-C only subsamples.

RESULTS

Comparison of participants with ADHD-I and ADHD-C

Table 1 shows study sample characteristics. ADHD-I and ADHD-C participants differed on mean age (ADHD-I were older), race/ethnicity (ADHD-I had a higher percentage of white participants and a lower percentage of black participants), presence of a disruptive behavior disorder (ADHD-I participants had a lower proportion of disruptive behavior disorders), and baseline hyperactive-impulsive and total symptom scores (ADHD-I group had lower average parent and teacher scores). As expected, children with ADHD-I also had higher Total SCT and Sluggish/Sleepy scores than children with ADHD-C (the subtypes did not differ on Daydreamy scores). Children with ADHD-I did not differ from children with ADHD-C in mean weight, sex, IQ, reading achievement scores, math achievement scores, presence of an anxiety disorder, presence of a mood disorder, or mean inattention scores.

SCT and ADHD symptoms/subtype in relation methylphenidate responder status

Higher baseline SCT Sluggish/Sleepy factor scores were associated with children having a lower likelihood of being a MPH responder (Wald=4.47, p=.04, OR=0.67 [95% CI: .46, .97). In contrast, neither baseline SCT Daydreamy factor scores nor ADHD subtype were associated with MPH responder status (Wald=0.96, p=.33, OR=0.81 [95% CI: .54, 1.23] and Wald=1.44, p=.23, OR=0.61 [95% CI: .27, 1.37] respectively).

ADHD subtype*dose effects on ADHD domain and total symptom scores

Significant subtype*dose joint effects were not observed for the inattentive or total symptom score outcomes (Table 2). However, as expected, significant ADHD subtype*dose interactions were observed for the hyperactive-impulsive domain such that children with ADHD-C had steeper reductions in hyperactive-impulsive symptoms with increasing MPH dose than those with ADHD-I (Table 2).

SCT*dose effects on ADHD domain and total symptom scores

SCT Daydreamy Factor*dose effects were not significant for any outcome (Table 2). However, SCT Sluggish/Sleepy Factor*dose joint effects were significant for the inattentive,

hyperactive-impulsive, and total symptom score outcomes, such that higher levels of Sluggish/Sleepy symptoms were related to a less robust dose-related reduction in symptom scores (Table 2). In order to illustrate the Sluggish/Sleepy by dose interaction for ease of interpretation, children were grouped by Sluggish/Sleepy factor score tertiles, and their MPH responses across doses were depicted for the inattentive, hyperactive-impulsive, and total symptom score outcomes (Figure 1).

To assess whether these SCT factor*dose effects were present to a comparable degree in both ADHD subtypes, the above analyses were performed again in subtype-stratified models. Sluggish/Sleepy*dose joint effects estimates were more striking in ADHD-C compared to ADHD-I models (B=1.99 vs. 1.03 for total symptom scores; B=1.19 vs. 0.74 for inattentive scores; B=0.79 vs. 0.29 for hyperactive-impulsive scores; see Figures 2 and 3). However, Sluggish/Sleepy*dose p-values were lower in ADHD-I models compared to ADHD-C models (p=0.04 vs. p=0.12, p=0.02 vs. p=0.06, and p=0.21 vs. p=0.26 for total, inattentive, and hyperactive-impulsive symptom scores respectively), likely due to having larger numbers of participants in the ADHD-I models. SCT Daydreamy*dose effects were not present for any outcome in either the ADHD-I or the ADHD-C subsamples (all ps>0.20).

DISCUSSION

Elevated levels of one aspect of SCT--the Sluggish/Sleepy factor– predicted a less robust response to methylphenidate in our sample of children with ADHD. Children with higher SCT Sluggish/Sleepy factor scores had less improvement in both inattentive and hyperactive-impulsive symptoms across methylphenidate doses, and were more likely to be methylphenidate non-responders or placebo responders, compared to children with lower Sluggish/Sleepy scores. This finding was observed in models that adjusted for ADHD subtype, and was consistent across outcomes. This is the first study to document a link between increased SCT levels and decreased responsiveness to methylphenidate, as significant findings did not emerge from the single prior study that investigated the association between SCT and methylphenidate response.[10] These contrasting results may be due to differences in study methodology, as the prior study did not evaluate the effects of the SCT Sluggish/Sleepy factor apart from the Daydreamy factor (which was not linked to methylphenidate response in our study). In addition, the prior study's sample was smaller than our own (N=88, likely leading to reduced statistical power), and included only children with ADHD-I, while our SCT*dose joint effects were more marked in children with ADHD-C versus ADHD-I. The finding that SCT's impact on methylphenidate response was more pronounced in ADHD-C versus ADHD-I is noteworthy since SCT and hyperactive-impulsive symptoms may at first glance appear to be mutually exclusive. Nevertheless, several studies have found elevated levels of SCT in a sizeable subset of children with the ADHD-C subtype (>25%).[7–9] Given that most SCT studies have focused on ADHD-I,[31–33] our findings point to a critical need to better understand SCT in ADHD-C.

Further study is also needed to understand the pathophysiology of SCT compared to ADHD inattentive symptoms, as well as the reasons why increased Sluggish/Sleepy symptoms may portend poorer methylphenidate response. A recent fMRI study found an association

between SCT symptoms and hypoactivity in the superior parietal lobe, while ADHD inattentive symptoms were linked to hypoactivity in the thalamus as well as greater activity in the supplementary motor area.[34] The authors concluded that the SCT neural signature of decreased superior parietal lobe activity may reflect impaired reorientation or shifting of attention.[34] Of note, a SPECT study by Cho et al comparing methylphenidate responders and non-responders found an association between non-response and lower cerebral blood flow in the superior parietal lobe,[35] suggesting that SCT-related dysfunction in this brain region may underlie the blunted methylphenidate effects observed in the present study.

Our study has several strengths, including a large sample of stimulant naïve youth. We also systematically evaluated 3 methylphenidate dose levels and placebo using both parent and teacher ratings, and thus can comment on response across a range of dose conditions evaluated in a double blind fashion while incorporating both home and school perspectives. The consideration of both ADHD subtype and anxiety in our SCT Sluggish/Sleepy*dose models is also a significant strength. Some but not all prior studies have suggested that children with the inattentive subtype and those with comorbid ADHD and anxiety may show a less robust response to methylphenidate.[30, 36–42] Although SCT symptoms, ADHD inattentive symptoms, and anxiety symptoms load on separate factors,[43–45] these symptoms domains are correlated, which may prompt concern that the observed Sluggish/Sleepy*dose effects could be confounded by subtype or anxiety effects. Demonstration of Sluggish/Sleepy*dose effects in models adjusting for subtype and anxiety, as well in ADHD-C only models, allays these concerns.

Our study limitations include its short-term nature, so we are unable to comment on the longer-term persistence of the documented methylphenidate response patterns. In addition, in accordance with usual clinical practice, we depended on parent and teacher ADHD symptom ratings to determine methylphenidate response, rather than using direct behavioral observations or neuropsychological measures. We are also limited in our SCT measurement in that we collected teacher but not parent ratings of SCT. Furthermore, the preponderance of children with ADHD-I in our sample may be viewed as a potential limitation when considering the generalizability of our SCT-related findings. However, our sample contained a generous number of children with ADHD-C (n=45), and sub-analyses looking at SCT*dose effects solely in ADHD-C documented Sluggish/Sleepy by dose joint effects on methylphenidate response.

CONCLUSION

The present study has several important implications. First, our findings highlight the need to investigate specific SCT dimensions in future studies, rather than approaching SCT as a unitary construct. Furthermore, our study results, should they stand the test of replication, may impact clinical care in their suggestion that having high levels of Sluggish/Sleepy symptoms may portend reduced responsiveness to methylphenidate. Hence, future studies should re-evaluate effects of baseline Sluggish/Sleepy and Daydreamy symptomatology on methylphenidate response, and seek to determine if there is a threshold of severity at which SCT symptoms affect methylphenidate response. In addition, there is a need to determine

whether these SCT factors predict response to alternative ADHD treatments, including other medication as well as non-medication modalities.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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CLINICAL POINTS

1. No factors have been identified that consistently predict methylphenidate response in children with ADHD.
2. There is growing interest in a new ADHD-related phenotype called sluggish cognitive temp (SCT), and the relationship between SCT symptomatology and medication response.
3. Higher levels of specific SCT symptoms related to being sleepy and slow-moving were linked to a diminished methylphenidate response in this study.

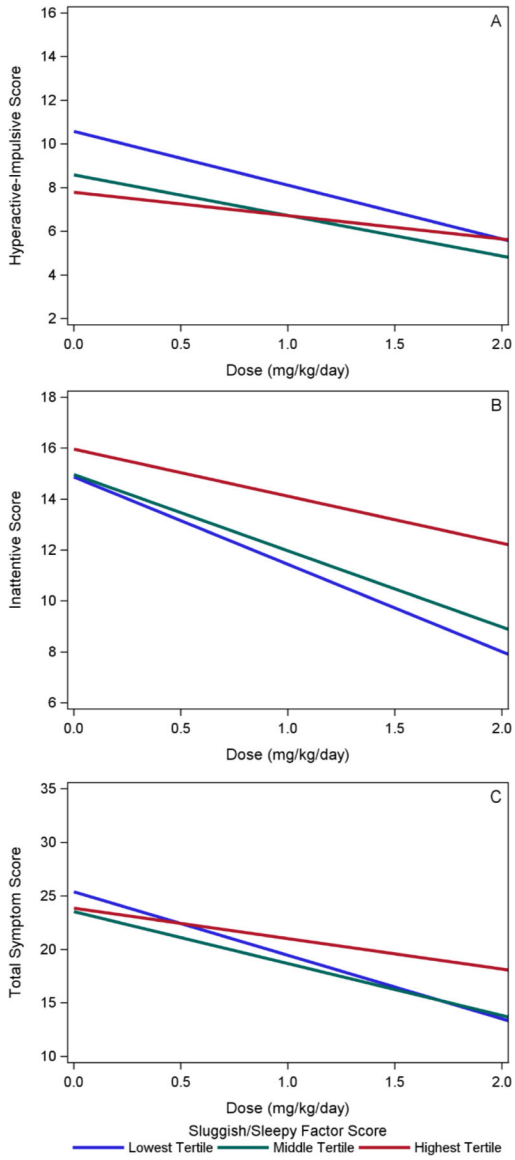

Figure 1.

Sluggish/SleepyFactor*Dose Effects on Parent- and Teacher-Rated Hyperactive-Impulsive (A), Inattentive (B), and ADHD Total Symptom Scores (C) for Tertiles of Sluggish/SleepyFactor in ADHD-Inattentive Type and ADHD-Combined Type Participants (N=158)[a]

[a]Models adjusted for baseline scores, DSM-based subtype, age, IQ, disruptive behavior disorders, anxiety disorders, rater.

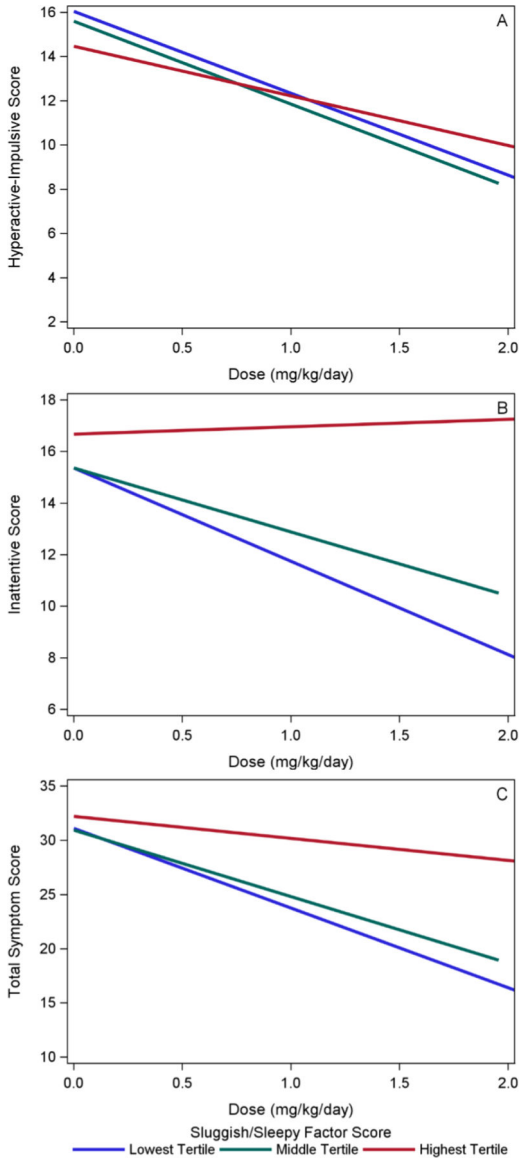

Figure 2.

Sluggish/SleepyFactor*Dose Effects on Parent- and Teacher-Rated Hyperactive-Impulsive (A), Inattentive (B), and ADHD Total Symptom Scores (C) for Tertiles of Sluggish/SleepyFactor in ADHD-Combined Type Participants Only (N=42)[a]

[a]Models adjusted for baseline scores, age, IQ, disruptive behavior disorders, anxiety disorders, rater.

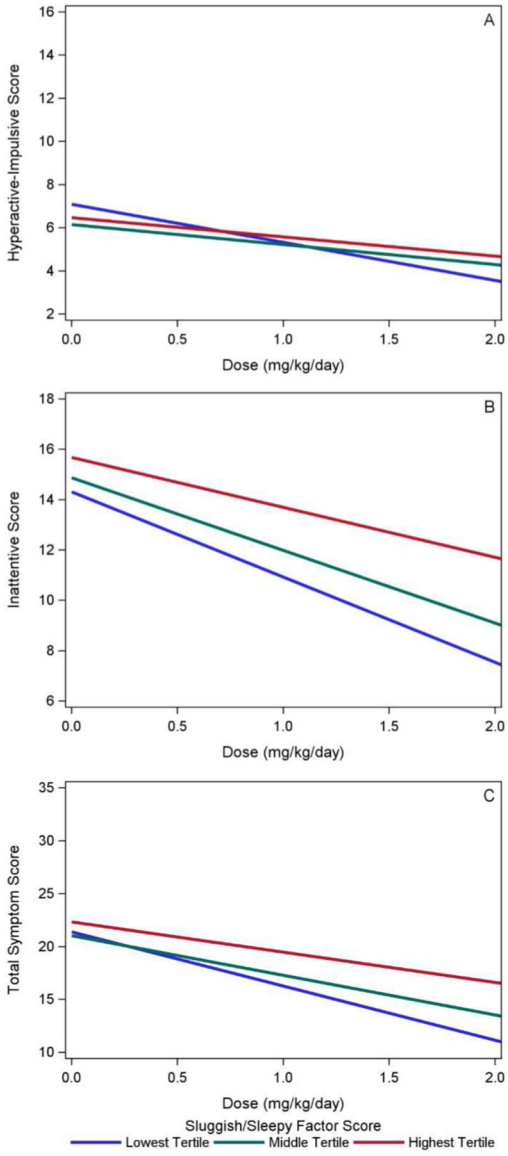

Figure 3.

Sluggish/SleepyFactor*Dose Effects on Parent- and Teacher-Rated Hyperactive-Impulsive (A), Inattentive (B), and ADHD Total Symptom Scores (C) for Tertiles of Sluggish/SleepyFactor in ADHD-Inattentive Type Participants Only (N=116)[a]

[a]Models adjusted for baseline scores, age, IQ, disruptive behavior disorders, anxiety disorders, rater.

Table 1.

Study Sample Characteristics

Variable	ADHD Inattentive Type (N=126)	ADHD Combined Type (N=45)	*p*-value for Group Comparisons
Age, year, mean (SD)	8.6 (1.3)	7.9 (1.0)	<0.001
Weight, kilograms, mean (SD)	34.4 (9.8)	31.9 (7.1)	0.13
Female, no. (%)	40 (32%)	9 (20%)	0.18
Race/ethnicity[a], no. (%)			
White	109 (89%)	30 (67%)	<0.01
Black	6 (5%)	15 (33%)	
Hispanic/Latino	4 (3%)	0 (0%)	
Other	3 (3%)	0 (0%)	
Abbreviated IQ, mean (SD)	107.8 (13.3)	105.6 (12.0)	0.35
WIAT word reading score, mean (SD)	102.8 (10.5)	100.7 (12.7)	0.29
WIAT math calculation score, mean (SD)	101.4 (14.4)	96.6 (13.2)	0.05
Anxiety Disorder[b], no. (%)			
No	112 (89%)	38 (84%)	0.44
Yes	14 (11%)	7 (16%)	
Mood Disorder[c], no. (%)			
No	125 (99%)	44 (98%)	0.46
Yes	1 (1%)	1 (2%)	
Disruptive Behavior Disorder[d], no. (%)			
No	100 (79%)	26 (58%)	0.01
Yes	26 (21%)	19 (42%)	
Parent Vanderbilt Scores, mean (SD)			
Hyperactive Symptom Score	9.8 (6.1)	20.0 (5.3)	<.001

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Variable	ADHD Inattentive Type (N=126)	ADHD Combined Type (N=45)	*p*-value for Group Comparisons
Inattention Symptom Score	20.5 (4.2)	21.1 (5.0)	0.53
Total Symptom Score	30.3 (8.1)	41.1 (9.6)	<.001
Teacher Vanderbilt Scores, mean (SD)			
Hyperactive Symptom Score	7.4 (5.7)	20.3 (4.4)	<.001
Inattention Symptom Score	19.6 (5.3)	21.0 (4.8)	0.13
Total Symptom Score	26.9 (9.0)	41.1 (7.4)	<.001
Sluggish Cognitive Tempo Scores (SCT), mean (SD)			
Total SCT Score	17.4 (8.8)	13.4 (8.3)	<0.01
Daydreamy Score	11.8 (5.2)	10.0 (5.5)	0.06
Sleepy/Sluggish Score	5.6 (4.4)	3.4 (3.9)	<0.01

SD = Standard Deviations; ADHD=Attention Deficit/Hyperactivity Disorder; IQ=Intelligence Quotient; WIAT=Wechsler Individual Achievement Test

[a]Reported by a parent/caregiver;

[b]Social phobia, separation anxiety, panic agoraphobia, generalized anxiety disorder, obsessive compulsive disorder, and/or post-traumatic stress disorder;

[c]Major depressive episode/dysthymia,

[d]Oppositional defiant or conduct disorder.

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Table 2.

Predictor, Predictor*Dose, and Dose Effects[a]

Predictor	Hyperactive-Impulsive Symptoms		Inattentive Symptoms		Total Symptoms	
	Unstandardized Estimate (β)	p-value	Unstandardized Estimate (β)	p-value	Unstandardized Estimate (β)	p-value
Model 1: Predictor of interest = DSM-based Subtypes (N=163); reference group=ADHD-I[b]						
Subtype	2.61 (0.16)	<0.0001	0.35 (0.09)	0.59	2.86 (0.13)	0.01
Dose	−1.38 (−0.13)	<0.0001	−2.83 (−0.26)	<0.0001	−4.21 (−0.22)	<0.0001
Subtype*Dose	−1.94 (−0.18)	0.0002	0.29 (0.03)	0.64	−1.65 (−0.09)	0.11
Model 2: Predictor of interest = SCT Sluggish/SleepyFactor (N=158)[c]						
Sluggish/SleepyFactor	−0.39 (0.01)	0.19	0.21 (0.13)	0.46	−0.21 (0.08)	0.66
Dose	−2.01 (−0.08)	<0.0001	−2.81 (−0.26)	<0.0001	−4.82 (−0.25)	<0.0001
Sluggish/SleepyFactor*Dose	0.59 (0.05)	<0.001	0.81 (0.07)	0.004	1.40 (0.07)	0.002
Model 3: Predictor of interest = SCT Daydreamy Factor (N=158)[c]						
Daydreamy Factor	−0.15 (0.01)	0.002	0.80 (0.14)	0.08	0.57 (0.08)	0.24
Dose	−1.99 (−0.18)	<0.0001	−2.81 (−0.26)	<0.0001	−4.80 (−0.25)	<0.0001
Daydreamy Factor* Dose	0.32 (0.03)	0.18	0.22 (0.02)	0.44	0.55 (0.03)	0.25

[a] ADHD.

[b] Models are adjusted for baseline scores, age, IQ, disruptive behavior disorders, anxiety disorders, and rater.

[c] Models are adjusted for baseline scores, DSM-based subtype, age, IQ, disruptive behavior disorders, anxiety disorders, and rater.

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