Supplement 1: Neurocognitive Test Battery

Tests for the Cognitive Battery were selected by our investigators based on criteria including: (a) relevance to the key constructs; (b) prior validation in the discrimination of attention-deficit/hyperactivity disorder (ADHD) samples from healthy volunteers; (c) psychometric properties (test-retest reliability, internal consistency, alternate forms reliability); (d) sensitivity to treatment effects; (e) breadth of prior use (comparability to literature); (f) appropriateness for use across a broad age range; and (g) feasibility of implementation (ease of administration, tolerability by participants). The following brief descriptions identify the versions of each task and the primary rationale for selection, along with the primary variables extracted from each task to serve as measures of our target constructs: Working Memory (WM), Inhibition, Reaction Time (RT), and Reaction Time Variability (RTV). These variable assignments are also summarized in the manuscript Table 1.

Stop Signal Task[1]: The computerized stop-signal task is a well-established measure of response inhibition. On each trial, participants perform a choice response time task in which they respond whether an arrow is pointing left or right with spatially compatible buttons on a box. They are instructed to respond as quickly as possible, except on trials where they hear an auditory beep, in which case they are to withhold their response. Stop signals are presented on 30% of trials; the delay at which the stop signal is presented is determined adaptively using a tracking paradigm, which ensures that (on average) participants will be successful at withholding their response on half of the stop trials. The tracking paradigm also allows the estimation of a stop-signal reaction time (SSRT), which is the amount of time needed to inhibit a response after presentation of the stop signal. This estimation is based on a well-established model that proposes a race between stop and go processes[2]. We used the mean SSRT for Inhibition and the standard deviation of

"go" response times for RTV.

Go-NoGo[3,4]: This computerized task involves continuous presentation of a high rate of "Go" trials (90%) and a lower rate of "NoGo" trials (10%) in order to bias the prepotent response towards responding and thus elicit higher rates of false positive errors of commission. There are 360 stimuli presented in 3 blocks of 120 trials; each trial includes stimulus presentation for 500ms and a 1s inter-stimulus interval during which participants respond, while a fixation cross is presented in the center of the display. This task has shown good discriminant validity and yields activation effects bilaterally in the ventrolateral prefrontal cortex; these activations correlated with clinical persistence of ADHD and false positive response rates. We used the response time for valid "hit" trials (for RT) and the standard deviation of RT to hit trials (for RTV).

Spatial Working Memory[5]: This computerized spatial version of the Sternberg item recognition task[6,7] requires maintenance of a set of spatial locations over a delay. Participants see a target array of 1, 3, or 5 circles positioned around a central fixation. After a fixed delay, participants are shown a single circle and required to indicate whether that circle was in the same position as one of the targets. Trial events include a 2s target-array presentation, a 3s delay period, and a 3s fixed response interval. A central fixation was visible throughout each of the 36 trials (12 per memory set size). We used measures of mean accuracy (for WM), mean response time (RT) on correct trials (for RT), and standard deviation of correct trial RT (for RTV).

WISC-IV Letter Number Sequencing[8]: This task from the Wechsler Intelligence Scale for Children–Fourth Edition (WISC-IV) is one of the two tests with scores loading on the Working Memory Index. It requires participants to listen to mixed series of letters and numbers and then repeat them back in numeric and alphabetic order. This is among the best standardized tests of

working memory available, with documented true score and test-retest reliability across the age span from 6 to 16 based on results from a nationwide standardization study. We used the total raw score (for WM).

WISC-IV Digit Span[8]: This task from the WISC-IV also loads on the Working Memory Index. It requires participants to listen to numbers read aloud and then repeat them back forward, backwards, or in ascending numeric order. This is among the best standardized tests of working memory available, with documented true score and test-retest reliability across the age span from 6 to 16 based on results from a nationwide standardization study. We used the total raw scores from forward and backward conditions (for WM).

WISC-IV Spatial Span[8]: This task from the WISC-IV is a supplementary process score that assesses working memory using nonverbal visuospatial material. It requires participants to observe the examiner tap a spatially distributed sequence of blocks that are affixed to a board, and then imitate the sequence of taps forward and backwards. We used the total raw scores from forward and backward conditions (for WM).

Color-Word Interference Test[9] is a computerized test that measures several aspects of executive function. The participant will be asked to read words that are colors when they are printed in neutral (i.e., black), congruent (i.e., same color as the word), and incongruent (i.e., different color as the printed word) ink colors. This "interference effect" when the incongruent stimuli are presented represents the person's ability to cope with incompatible stimuli and process complex input. We selected the version from the Delis-Kaplan Executive Function System (D-KEFS) because this has stronger psychometric and normative data from a nationally representative sample and was co-normed with other executive function measures enabling stronger cross-test comparisons. We used the Inhibition raw score and the Inhibition/Switching raw score

controlling for Color Naming and Word Reading scores (for Inhibition).

Attention Network Test (ANT)[10,11]: This computerized test is a combination of a cued reaction time[12] and flanker task[13]. The ANT requires participants to determine whether a central arrow points left or right. This task is varied by several conditions, including flankers on both sides that are congruent (pointed in the same direction as the central arrow), incongruent, or neutral (no arrows, just lines). In addition, cues are given to alert the participant of timing and position of the arrows. The participant's reaction time to the alerting cues, spatial cues and flankers are the primary dependent variables. Our version eliminated the orienting cues. We used the total error scores (for Inhibition), the mean response time (for RT), and the standard deviation of RT (for RTV).

Trail Making Test[9]: The Trail Making Test (TMT) from the Delis-Kaplan Executive Function System (D-KEFS) is a test of complex visual search, mental flexibility, and motor function. In addition, attention, working memory, and the ability to mentally maintain two simultaneous sequences contribute to strong performance on this test. During this task, participants are asked to draw a line connecting numbers (Part A) or letters and numbers (Part B) in consecutive order. Dependent measures are time to complete the task and number of errors. As for the Stroop procedure, we selected the D-KEFS version of this task for CIDAR assessments. We used the Number-Letter Switching raw score, controlling for Visual Scanning and Number Sequencing scores (for Inhibition).

Time Discrimination Task[14,15]: This is a computerized time perception measure that determines the idiosyncratic threshold at which intervals differing by several milliseconds can be perceived as different. This computerized task is presented with a green circle on the left side of the screen, followed by a red circle on the right side of the screen. One of the circles has a fixed

duration of 1000 milliseconds (msecs), while the other (comparison) circle is shown for varied amounts of time. After the presentation of the circles, a question appears on the screen, asking which circle lasted longer. Participants respond by pressing a key that corresponds with the color (red or green) of the circle they thought lasted longer. We used the median correct response time (for RT), and the standard deviation of valid response time (for RTV).

References

1. Logan GD, Cowan WB, Davis KA. On the ability to inhibit simple and choice reaction time responses: a model and a method. *J Exp Psychol Hum Percept.Perform.* 1984;10:276-291.

2. Band GP, van der Molen MW, Logan GD. Horse-race model simulations of the stop-signal procedure. *Acta Psychol (Amst).* 2003;112:105-142.

3. Schulz KP, Newcorn JH, Fan J, Tang CY, Halperin JM. Brain activation gradients in ventrolateral prefrontal cortex related to persistence of ADHD in adolescent boys. *J Am Acad Child Adolesc Psychiatry.* 2005;44:47-54.

4. Conners CK. *Conners' CPT II for windows.* North Tonawanda, NY: Multi-Health Systems; 2002.

5. Glahn DC, Therman S, Manninen M, et al. Spatial working memory as an endophenotype for schizophrenia. *Biological psychiatry.* 2003;53:624-626.

6. Sternberg S. Memory-scanning: mental processes revealed by reaction- time experiments. *American Scientist.* 1969;57:421-457.

7. Jonides J, Smith EE, Koeppe RA, Awh E, Minoshima S, Mintun MA. Spatial working memory in humans as revealed by PET. *Nature.* 1993;363:623-625.

8. Wechsler D. *Wechsler Intelligence Scale for Children–Fourth Edition (WISC-IV).* San Antonio, TX: Psychological Corporation; 2003.

9. Delis DC, Kaplan E, Kramer JH. *D-KEFS executive function system.* San Antonio, TX: The Psychological Corporation; 2001.

10. Fan J, Fossella J, Sommer T, Wu Y, Posner MI. Mapping the genetic variation of executive attention onto brain activity. *Proc Natl Acad Sci USA.* 2003;100:7406-7411.

11. Fan J, McCandliss BD, Sommer T, Raz A, Posner MI. Testing the efficiency and independence of attentional networks. *J Cogn Neurosci.* 2002;14:340-347.

12. Posner MI. Orienting of attention. *Q J Exp Psychol.* 1980;32:3-25.

13. Eriksen BA, Eriksen CW. Effects of noise letters upon the identification of a target letter in a nonsearch task. *Percept Psychophys.* 1974;16:143-149.

14. Smith A, Taylor E, Lidzba K, Rubia K. A right hemispheric frontocerebellar network for time discrimination of several hundreds of milliseconds. *Neuroimage.* 2003;20:344-350.

15. Smith A, Taylor E, Rogers JW, Newman S, Rubia K. Evidence for a pure time perception deficit in children with ADHD. *J Child Psychol Psychiatry.* 2002;43:529-542.

Figure S1: Structural equation model for cognitive variables loading on four latent constructs. Note: Rectangles represent observed variables; ovals represent latent variables. ANT = Attention Networks Test, total errors (reversed sign); ANTRT = Attention Networks Test, mean reaction time (RT); ANTSD = Attention Networks Test, standard deviation (SD) of valid RT; CWI = Delis-Kaplan Executive Function System (D-KEFS) Color-Word Interference Test (CWIT), Inhibition raw score; CWIS = D-KEFS CWIT Inhibition/Switching raw score (controlling for Color Naming and Word Reading scores); DSB = Wechsler Intelligence Scale for Children, 4th Edition (WISC-IV) Digit Span Backward – total raw score; DSF = WISC-IV Digit Span Forward – total raw score; GNGRT = Go-NoGo Test, mean RT for valid hits; GNGSD = Go-NoGo Test, SD of valid RT; INH = inhibition; LNS = WISC-IV Letter Number Sequencing – total raw score; RTV = reaction time variability; SSB = WISC-IV Spatial Span Backward – total raw score; SSF = WISC-IV Spatial Span Forward– total raw score; SSRT = Stop Signal Test – mean Stop Signal Reaction Time; SSTSD = Stop Signal Test, SD of "Go" RT; SWMA = Spatial Working Memory – mean accuracy; SWMRT = Spatial Working Memory, mean RT correct trials; SWMSD = spatial working memory, SD of RT correct trials; TDTRT = Time Discrimination Test, median correct RT; TDTSD = Time Discrimination Test, SD of valid RT; TMTS = D-KEFS Trail Making Test Number-Letter Switching raw score (controlling for Visual Scanning and Number Sequencing scores); WM = working memory.

Table S2. Confirmatory Factor Analysis (CFA) Parameter Estimates

Observed Variable	Latent Construct	β	*B*	SE
SWMA	WM	0.77	1.08	.08
DSF	WM	0.60	0.83	.08
SSF	WM	0.69	0.96	.08
DSB	WM	0.67	0.94	.08
SSB	WM	0.79	1.12	.08
LNS	WM	0.70	1[a]	0[a]
SSRT	Inhibition	0.67	1[a]	0[a]
CWI	Inhibition	0.39	0.89	.08
CWIS	Inhibition	0.22	1.92	.81
TMTS	Inhibition	0.69	0.58	.08
ANT	Inhibition	0.62	0.32	.08
TDTRT	RT	0.09	0.31	.18
ANTRT	RT	0.66	2.34	.44
GNGRT	RT	0.89	3.12	.56
SWMRT	RT	0.28	1[a]	0[a]
TDTSD	RTV	0.32	1[a]	0[a]
ANTSD	RTV	0.52	1.75	.29
SSTSD	RTV	0.50	1.58	.27
GNGSD	RTV	0.99	3.17	.47
SWMSD	RTV	0.92	3.00	.44

Note: ANT = Attention Networks Test, total errors (reversed sign); ANTRT = Attention Networks Test, mean reaction time (RT); ANTSD = Attention Networks Test, standard deviation (SD) of valid RT; CWI = Delis-Kaplan Executive Function System (D-KEFS) Color-Word Interference Test (CWIT), Inhibition raw score; CWIS = D-KEFS CWIT Inhibition/Switching raw score (controlling for Color Naming and Word Reading scores); DSB = Wechsler Intelligence Scale for Children, 4th Edition (WISC-IV) Digit Span Backward – total raw score; DSF = WISC-IV Digit Span Forward – total raw score; GNGRT = Go-NoGo Test, mean RT for valid hits; GNGSD = Go-NoGo Test, SD of valid RT; INH = inhibition; LNS = WISC-IV Letter Number Sequencing – total raw score; RTV = reaction time variability; SSB = WISC-IV Spatial Span Backward – total raw score; SSF = WISC-IV Spatial Span Forward– total raw score; SSRT = Stop Signal Test – mean Stop Signal Reaction Time; SSTSD = Stop Signal Test, SD of "Go" RT; SWMA = Spatial Working Memory – mean accuracy; SWMRT = Spatial Working Memory, mean RT correct trials; SWMSD = spatial working memory, SD of RT correct trials; TDTRT = Time Discrimination Test, median correct RT; TDTSD = Time Discrimination Test, SD of valid RT; TMTS = D-KEFS Trail Making Test Number-Letter Switching raw score (controlling for Visual Scanning and Number Sequencing scores); WM = working memory.

Table S3. Comparisons of Non-Clinical Comparison Group to Patients With Attention-Deficit/Hyperactivity Disorder (ADHD) on Cognitive Measures at Baseline

	Non-Clinical Comparison Group		Patients With ADHD		F	*p*
	Mean	SD	Mean	SD		
SWMA	75.3	14.7	67.1	14.1	22.1	<.01
DSF	8.9	2.4	8.0	2.2	10.9	<.01
SSF	7.1	2.4	6.4	2.0	9.5	<.01
DSB	7.1	2.2	6.3	1.9	12.3	<.01
SSB	6.5	2.1	5.4	2.2	16.4	<.01
LNS	16.7	4.5	14.9	4.6	10.3	<.01
SSRT	232.5	1034.1	387.2	136.8	8.2	<.01
CWI	83.4	26.0	93.1	31.2	7.1	<.01
CWIS	-2.7	17.1	0.6	20.3	2.1	.2
TMTS	-3.8	39.9	0.9	49.3	0.7	.4
ANT	0.9	0.1	0.8	0.3	8.3	<.01
TDTRT	711.2	173.5	7.3	162.7	0.7	.41
ANTRT	806.8	171.4	857.2	149.0	6.1	.01
GNGRT	443.7	102.0	473.2	126.3	4.2	.04
SWMRT	1347.1	420.5	1379.5	271.5	0.8	.40
TDTSD	356.8	83.4	374.6	92.6	2.1	.15
ANTSD	198.5	60.8	232.2	54.9	19.4	<.01
SSTSD	179.6	59.6	210.7	82.2	11.3	<.01
GNGSD	231.3	157.2	290.7	157.9	10.0	<.01
SWMSD	233.1	158.9	273.9	158.1	4.4	.04

Note: ANT = Attention Networks Test, total errors (reversed sign); ANTRT = Attention Networks Test, mean reaction time (RT); ANTSD = Attention Networks Test, standard deviation (SD) of valid RT; CWI = Delis-Kaplan Executive Function System (D-KEFS) Color-Word Interference Test (CWIT), Inhibition raw score; CWIS = D-KEFS CWIT Inhibition/Switching raw score (controlling for Color Naming and Word Reading scores); DSB = Wechsler Intelligence Scale for Children, 4th Edition (WISC-IV) Digit Span Backward – total raw score; DSF = WISC-IV Digit Span Forward – total raw score; GNGRT = Go-NoGo Test, mean RT for valid hits; GNGSD = Go-NoGo Test, SD of valid RT; INH = inhibition; LNS = WISC-IV Letter Number Sequencing – total raw score; RTV = reaction time variability; SSB = WISC-IV Spatial Span Backward – total raw score; SSF = WISC-IV Spatial Span Forward– total raw score; SSRT = Stop Signal Test – mean Stop Signal Reaction Time; SSTSD = Stop Signal Test, SD of "Go" RT; SWMA = Spatial Working Memory – mean accuracy; SWMRT = Spatial Working Memory, mean RT correct trials; SWMSD = spatial working memory, SD of RT correct trials; TDTRT = Time Discrimination Test, median correct RT; TDTSD = Time Discrimination Test, SD of valid RT; TMTS = D-KEFS Trail Making Test Number-Letter Switching raw score (controlling for Visual Scanning and Number Sequencing scores); WM = working memory.