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The Potential and Limitations of Using Digital Therapeutics to Address ADHD Symptoms

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Financial Disclosures

- NIMH
- NCATS
- NIH (Director’s office)

Outline

- ADHD facts
- Treatment needs
- Telemedicine
- Working memory training
- Virtual reality and beyond
- Conclusion
- Q & A

Key Symptoms

Inattention
- Not completing tasks
- Forgetting what needs to be done
- Daydreaming

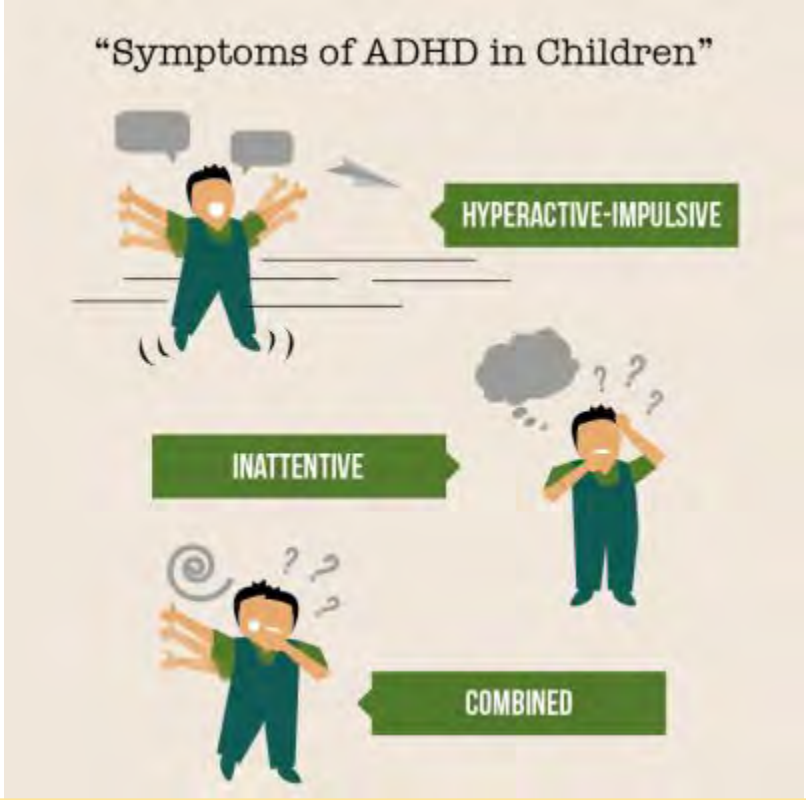
Impulsivity
- Doing things without thinking
- Interrupting others
- Stepping over boundaries

Hyperactivity
- Fidgeting
- Difficulty remaining seating
- High activity level

Behavioral Outcomes

- Not turn in homework
- Not finish assigned tasks
- Struggles with unstructured time
- Conflict in the home
- Difficulties with emotion regulation
- Stigmatizing
- Rejected by peers
- Greater rate of SUD
- Higher accident rates

Attention-deficit hyperactivity disorder



- About 10% of school age children
- About 4% of adults
- More prevalent in boys
- Neurodevelopmental disorder

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.). Arlington, VA: American Psychiatric Publishing.

Treatment for ADHD

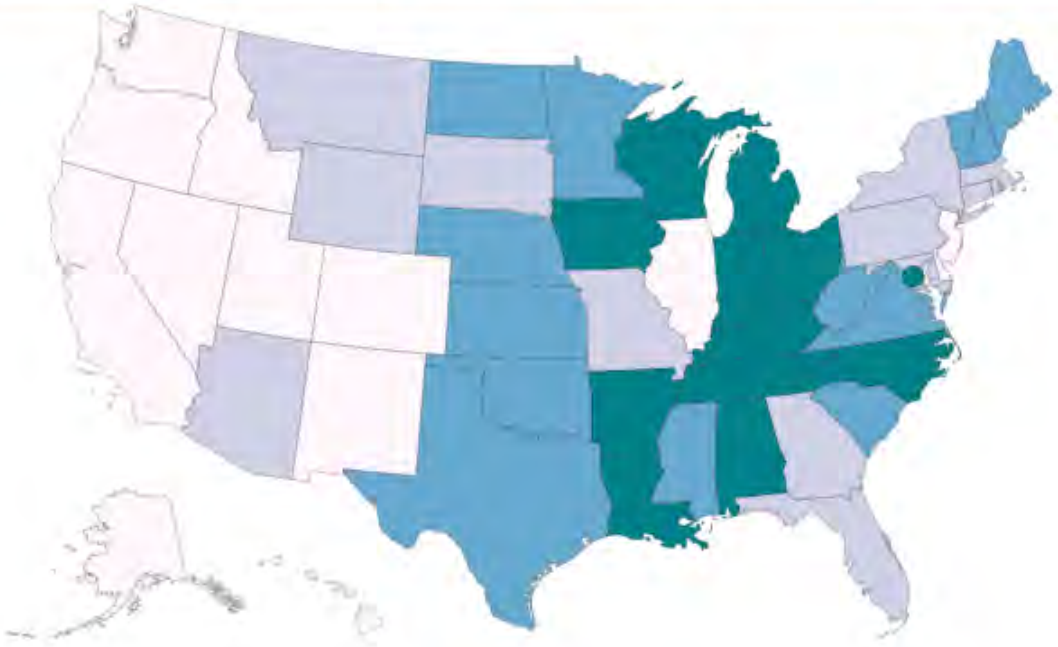
About 3 in 4 US children with current ADHD receive treatment

A national CDC parent survey from 2016 for children 2–17 years of age with current ADHD:

- 62% were taking ADHD medication
- 47% received behavioral treatment
- Altogether, 77% were receiving treatment. Of these children:
    - About 23% children with ADHD were receiving neither medication treatment nor behavioral treatment

Medication Treatment

Percent of children (aged 2–17 years) with ADHD currently taking medication treatment for ADHD



Prevalence Estimate for ADHD Medication

Parents reported whether a doctor or health professional ever told them that their child had ADHD, and then reported whether their child was currently taking medication for ADHD.

Select "Year reported" to view previous years.

- 2% - 5%
- 5.1% - 6.5%
- 6.5% - 7.5%
- 7.7% - 10.4%

Filters

Year reported

2011

Low rates of pharmacologic & behavioral tx for ADHD in Calif

Outcomes for ADHD worse than peers in 91% of variables including for those who had treatment (Molina et al. 2009)

Need for More Effective and Accepted Interventions

- Address unmet challenges
  - Effective, sustainable, fewer side effects
- More affordable
- Easier access
- More accepted (less stigma)
- Treatments that transfer across settings

Technology-Aided Interventions for ADHD

- Reach more people
- Lower stigma
- Reduce cost
- Children like the tools

Telemedicine and e-Health, Vol. 19, No. 3 | Original Research

A Study on the Effectiveness of Videoconferencing on Teaching Parent Training Skills to Parents of Children with ADHD

Yuhuan Xie, J. Faye Dixon, Ong Min Yee, Junshun Zhang, Y. Ann Chen, Sascha DeAngelo, Peter Yellowlees, Robert Hendren, and Julie B. Schweitzer

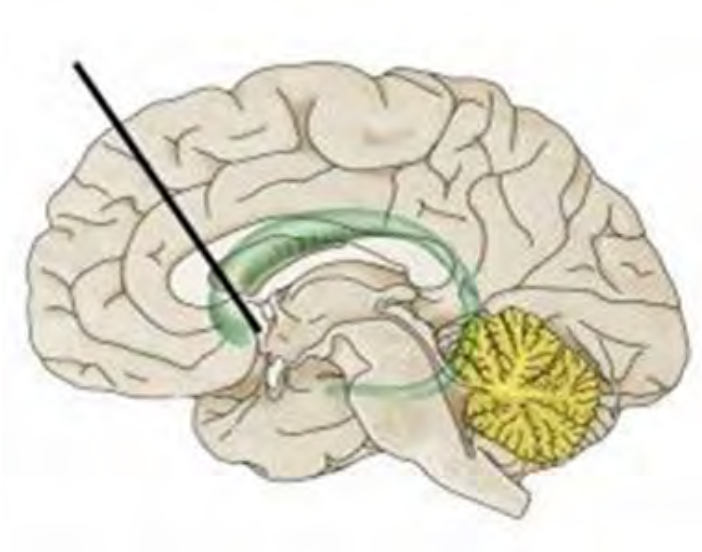
Published Online: 12 Mar 2013 | https://doi.org/10.1089/tmj.2012.0108

- RCT comparing face to face vs videoconferencing
- Group therapy model
- Improved parent disciplinary practices
- Improvement in ADHD
    - ODD and CD symptoms, more improvement in videoconferencing for hyperactivity measure (medium to large effects)
- Parent perceptions – liked both, with no significant differences between modalities

Game Playing is Highly Rewarding – Can it be Used for Good?

Self-injection of addicting drugs affects the "reward system" and dopamine release

Gaming increases dopamine; dopamine is deficient in ADHD
Stimulant medication increases dopamine



ADHD the most significant psychiatric predictor of Internet and videogame addiction in adolescents (n = 2000)
Ko et al., 2009

ADHD and Neurodevelopment

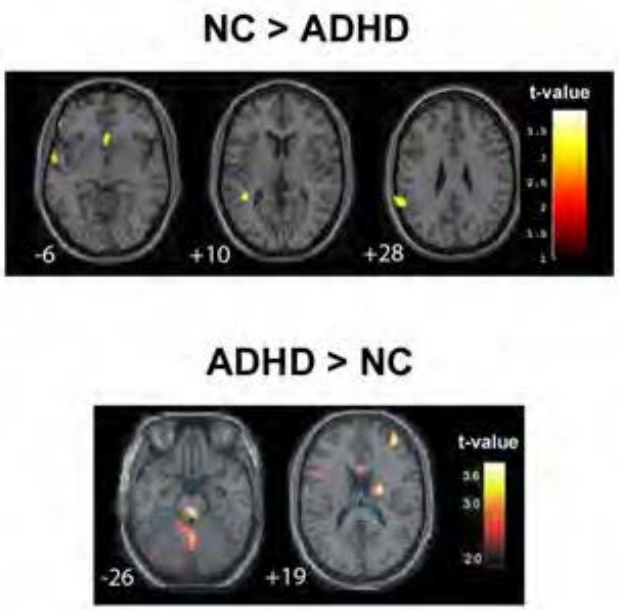
ADHD is associated with abnormalities in brain anatomy, connectivity and neurotransmitter function

- Delay in cortical maturation most prominent in prefrontal, also in frontal, striatal, parietal, and cerebellar cortices
- Advanced maturation in motor area
- Decreased volumes and thickness in cortical regions

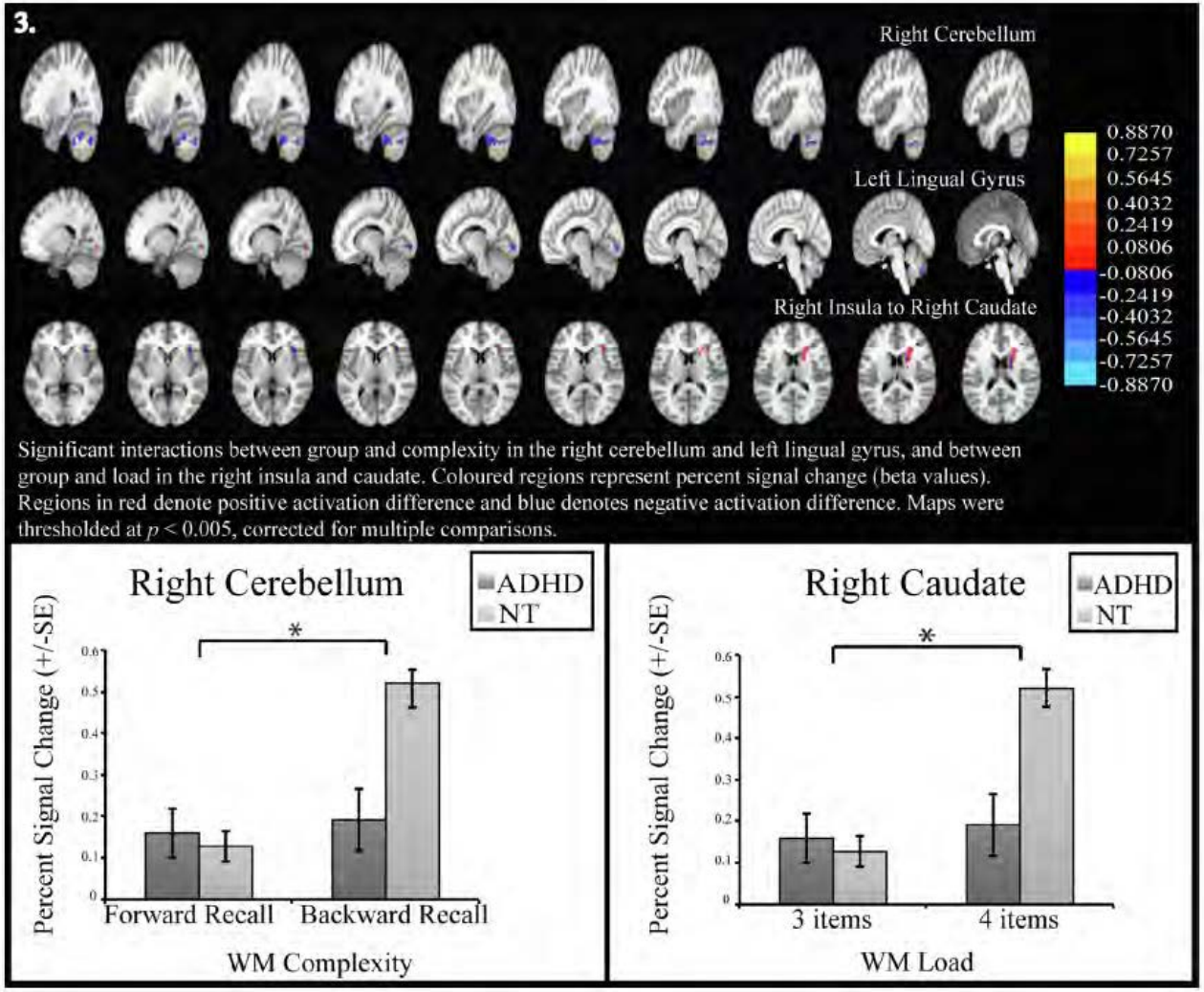
Diminution of symptoms over development may be associated with normalization of cortical regions, but not necessarily brain connectivity

Cognitive training and digital therapeutics typically based on brain-related alterations in ADHD – unlike behavior therapies

Working Memory-related Brain Alterations in ADHD



Schweitzer et al., 2004



Mukherjee et al., 2021

Can Working Memory Training Improve ADHD Symptoms?

Pilot RCT Testing Cogmed in ADHD

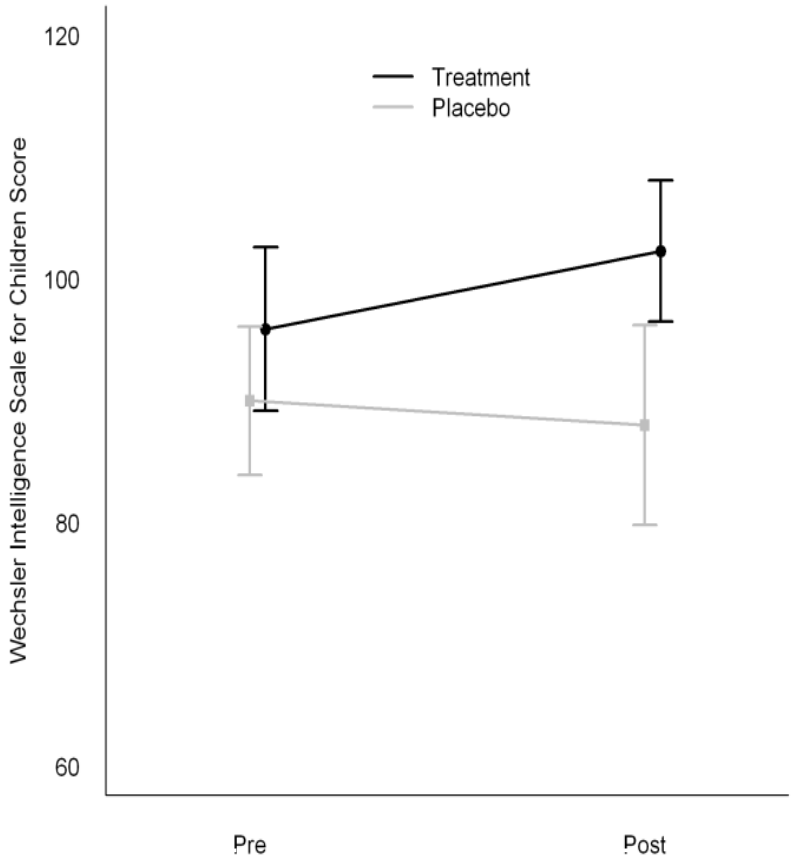
n = 14 placebo
n = 12 training
Average age 9.7 years

- Cogmed: Computerized Training Program
  - 90 trials of WM games each day ~40 minutes
  - Tasks require storage and manipulation of sequences:
    - Verbal: e.g., repeating back a sequence of digits in reverse order
    - Visuo-spatial: e.g., recalling the location of objects on different portions of the computer screen
  - Adaptive Training, so the child is always working at level closely matches WM capability
  - Placebo group did same number of sessions, but not adaptive
  - Coach monitors progress, providing feedback to encourage completion

Green et al., 2012

Cogmed: JM – Children Play Several WM Games

Working Memory Training on Cogmed Significantly Improves WMI Scores Compared to Placebo in ADHD

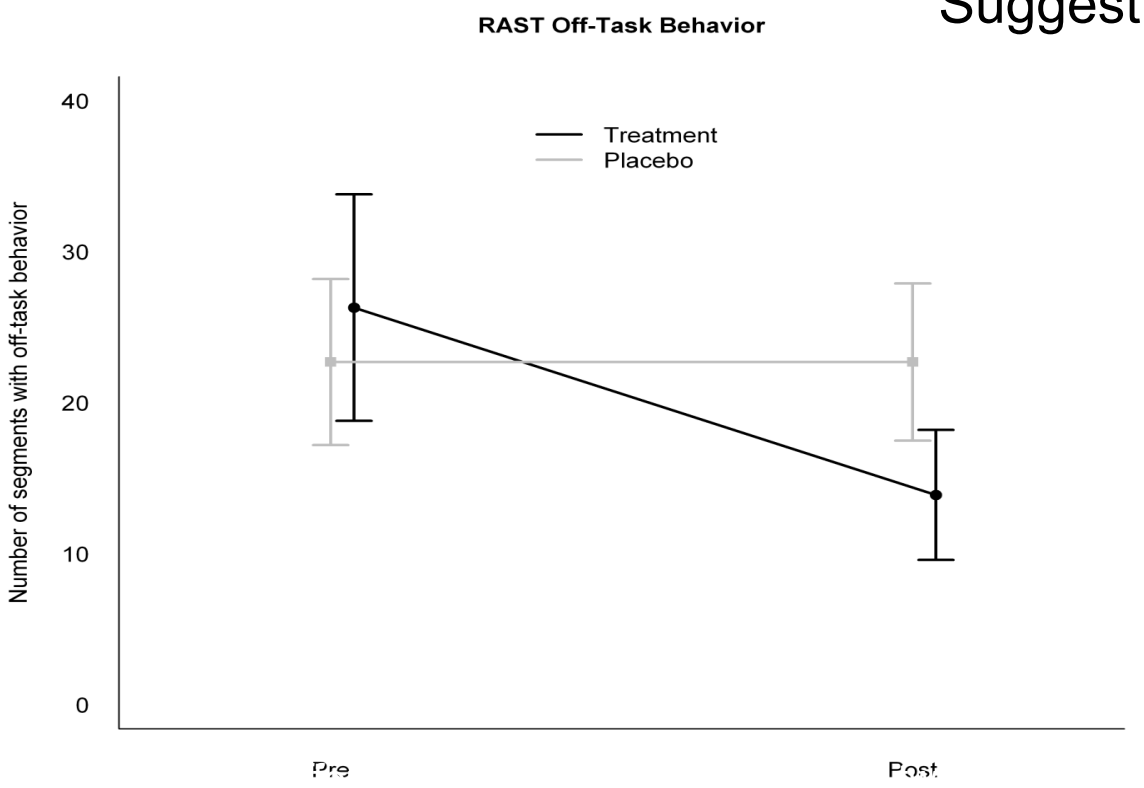


d = .81

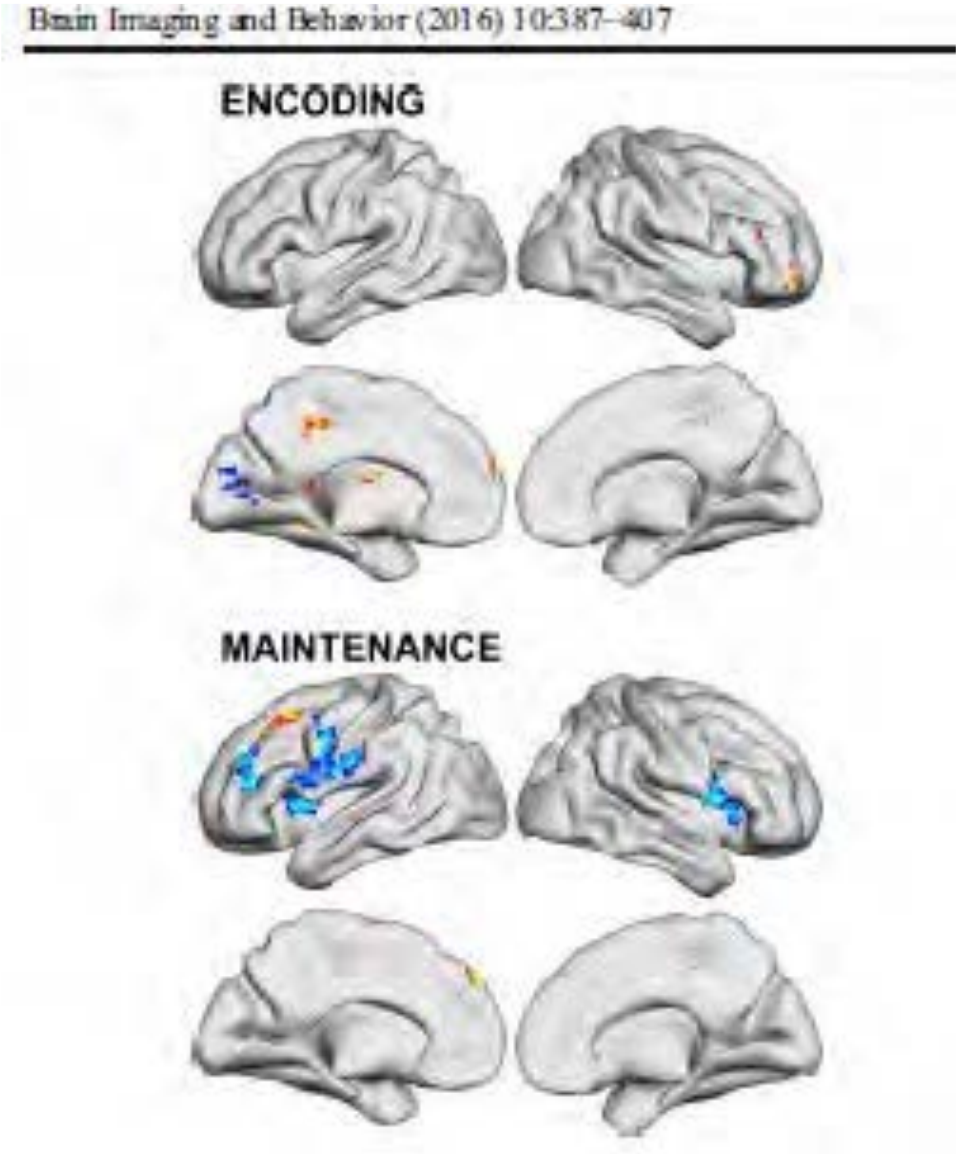
Green et al., 2012

RAST Off-task Behavior During Academic Task Decreases with Working Memory Training and Not Placebo in ADHD –

Suggestion of generalization



Green et al., 2012



WM training increased:

- WM performance
- ADHD clinical functioning
- WM-related ADHD brain activity in frontal, parietal, temporal lobe regions

Stevens et al., 2016

Testing Cogmed WM Training in ASD and FXS with Intellectual Disability

- Assessed feasibility of Cogmed in ASD with ID
  - ASD and FXS both have WM difficulties and elevated ADHD symptoms
    - FXS – known genetic alteration vs unknown for ASD
  - Long term question: could improvements in attention improve response to ASD Tx?
  - Non RCT
  - Study 1: Feasibility and satisfaction;
  - Study 2: Improvement in performance, predicting treatment response by ADHD symptoms and genetic vs idiopathic ASD

Parents Satisfied with Treatment - Motivation, Enjoyment for Treatment is Mixed

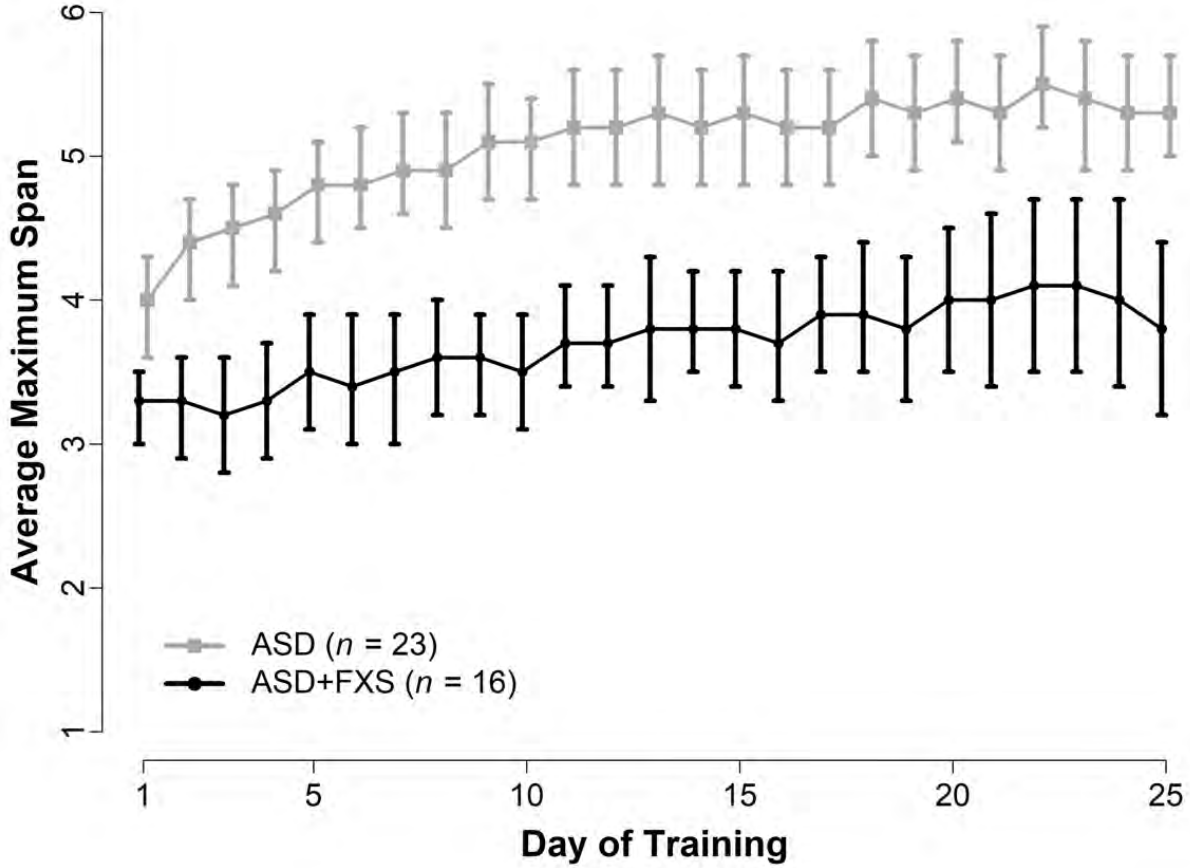
	Mean (1-5)	Agree	Neutral	Disagree
Satisfaction				
Staff show interest and concern	4.52 (.59)	24 (96)	1 (4)	0 (0)
Staff are skilled	4.56 (.58)	24 (96)	1 (4)	0 (0)
Treatment is of high quality	4.24 (.93)	22 (88)	2 (8)	1 (4)
Motivation				
Child enjoyed training	3.76 (.78)	18 (72)	5 (20)	2 (8)
Easy to keep child motivated	3.44 (1.08)	14 (56)	4 (16)	7 (28)
Training as enjoyable as commercial games	2.64 (.95)	4 (16)	6 (24)	15 (60)
Child's motivation improved by end of training	2.88 (1.01)	8 (32)	6 (24)	11 (44)

	ASD (n = 26)			ASD+FXS (n = 18)			Post- vs. Pre-Difference	
							Estimate (95%CI)	P-value
	Pre-Mean (SD)	Post-Mean (SD)	Effect Size[b]	Pre-Mean (SD)	Post-Mean (SD)	Effect Size[b]		
Near Transfer (WM) Measures								
Stanford Binet 5 Block Span	11.5 (6.3)	14.6 (5.8)	0.50	7.6 (4.6)	9.7 (4.9)	0.48	2.40 (1.45, 3.36)	<0.001
Leiter-Revised Spatial Memory[c]	21.9 (16.4)	26.1 (20.2)	0.26	14.9 (8.3)	18.1 (9.9)	0.37	3.34 (0.69, 5.98)	0.01
WISC IV[d] Digits Backward	3.5 (2.8)	4.1 (2.7)	0.20	2.1 (2.0)	2.4 (2.1)	0.17	0.38 (0.09, 0.68)	0.01
Far Transfer(non-WM) Measures								
PDDBI Score								
REPRIT[e]	72.6 (34.2)	62.5 (33.8)	-0.30	42.4 (19.2)	46.0 (22.1)	0.19	-10.1 (-16.5, -3.7)	0.003
EXSCA[f]	140.1 (36.3)	145.1 (37.1)	0.14	155.1 (32.6)	140.6 (28.6)	-0.44	1.51 (-5.19, 8.22)	0.65
RAST[g]								
Percent Intervals Off-Task	35.9 (32.1)	25.6 (32.7)	-0.32	43.4 (37.3)	35.7 (34.1)	-0.20	-0.44 (-0.77, -0.10)	0.01
Percent Intervals Fidgeting	14.6 (22.1)	19.7 (28.7)	0.23	39.4 (16.2)	37.0 (28.0)	-0.15	0.03 (-0.42, 0.47)	0.91
Percent Intervals Vocalizing	38.8 (29.6)	43.8 (36.3)	0.17	41.2 (30.4)	39.0 (37.3)	-0.07	0.01 (-0.26, 0.27)	0.96
Percent Intervals Play Object	19.1 (30.3)	17.1 (28.5)	-0.07	17.4 (33.4)	24.2 (35.5)	0.20	0.00 (-0.59, 0.59)	1.00
Percent Intervals Out of Seat	7.0 (13.7)	1.1 (3.0)	-0.43	13.2 (26.5)	2.8 (8.3)	-0.39	-1.66 (-2.72, -0.59)	0.003

WM Tng Improves Near Transfer & Selected Far Transfer Behaviors in ASD and ID

Calub et al., in press, AJIDD

ASD Group Demonstrates Greater Improvement than FXS Group on Actual WM Training



Calub et al., in press, AJIDD

Cognitive Training for Fragile X Syndrome: Results of a Double Blind Controlled Trial of Cogmed

David Hessl, Ph.D.
Director, Translational Psychophysiology and Assessment Laboratory (T-PAL)

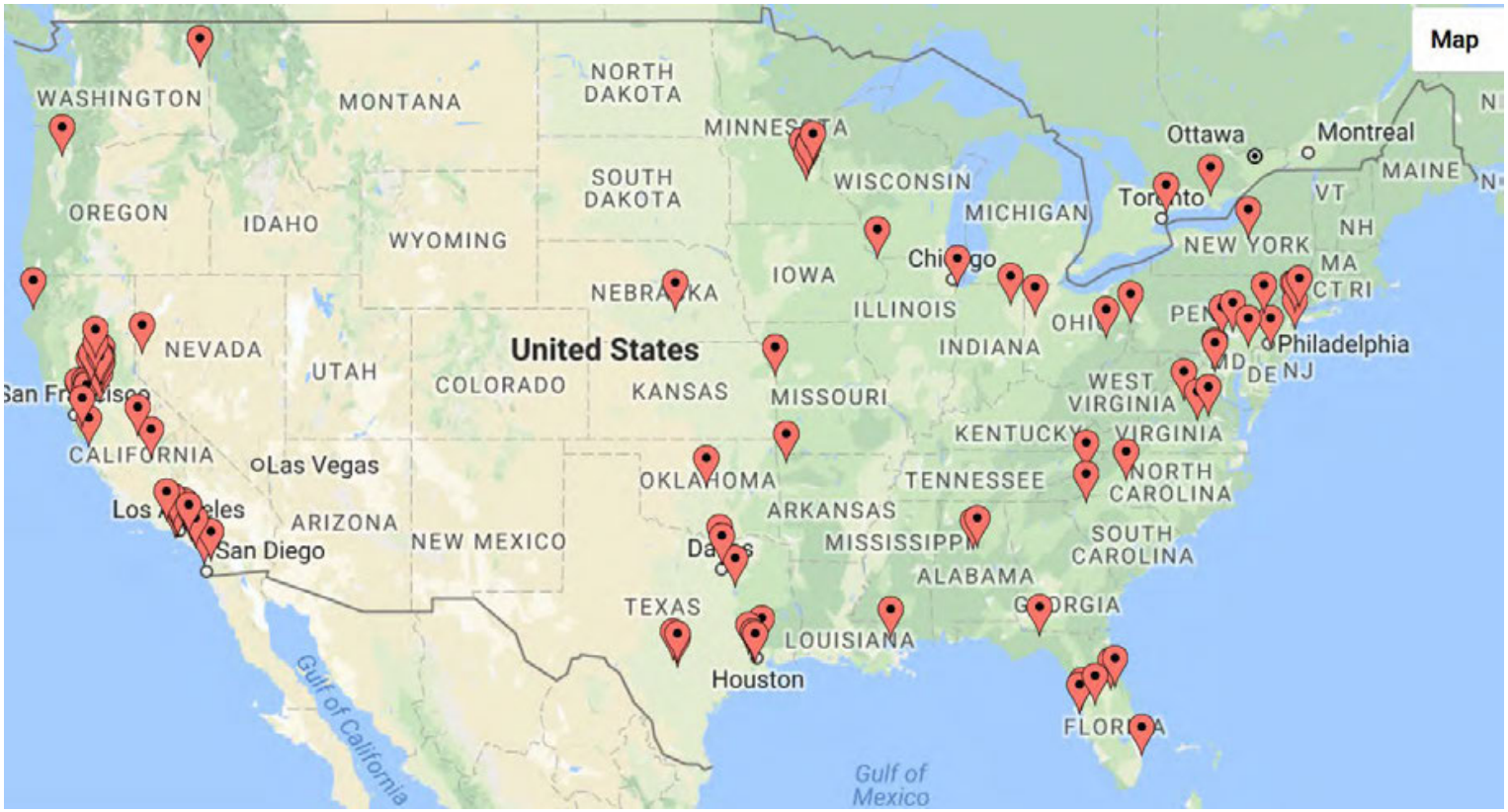
Julie Schweitzer, PhD.
Director, AIR Laboratory, MIND Institute

The John Merck Fund

COGMED
Working Memory Training

Hessl et al., 2019, JND;
Scott et al., 2020, Brain Sciences

Family Home Visits (X3 each)

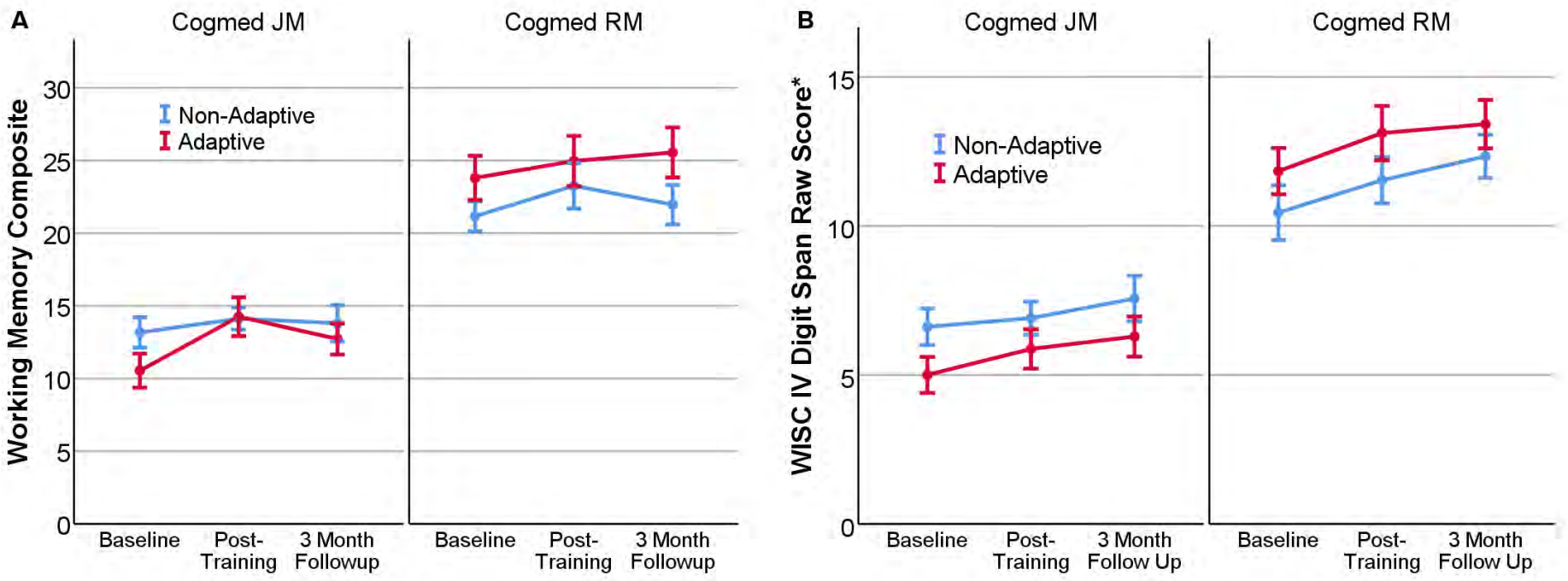


Demographics

Age – 12. 5 years
IQ – 64
Mental age – 7 years

WM Composite Reveals Improvement in Adaptive and Non-Adaptive Groups

Non-Adaptive N = 50
Adaptive N = 50



Factors That Mediate Training Efficacy in ID (Scott et al., 2020)

- Baseline level of functioning
  - Higher IQ & Mental Age led to greater improvement (differs from TD literature)
- Training quality
  - Greater advancement in training on the tasks related to greater improvements
  - Faster and less variable response time on training, associated with improvements (i.e., better attention during training associated with more improvement)
- Effects of medication or other treatment combined with WMT? – unknown

Cognitive Training

- Verdict not in yet, studies demonstrate good near transfer effects and some far transfer effects in ADHD, ASD
- Most experimental designs are inadequate
- Training needs to be highly rewarding to work
  - Less able to compete with computer games for time and attention now
- Can trainings be developed to be more targeted to individual differences?
- Future trainings developed to transfer to real world

Generalization of Training Games/Apps to Real World Setting

VRAM- Virtual Attention Reality Management

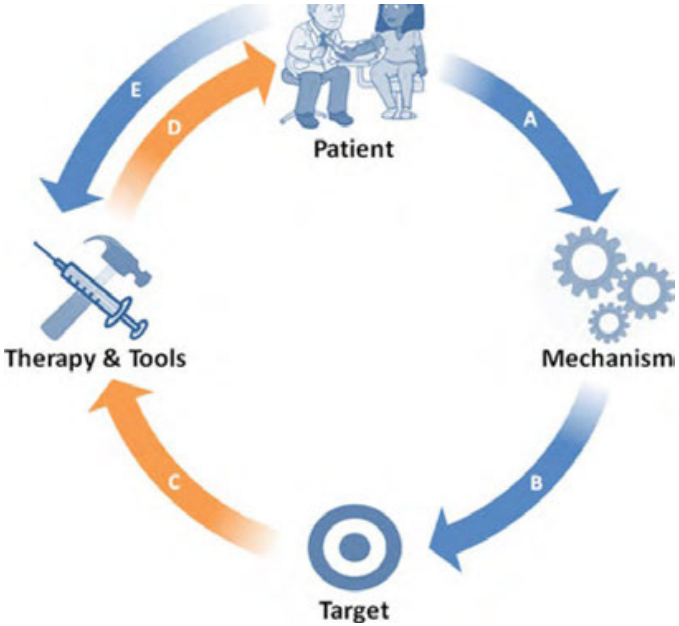
Reducing Distractibility in Children with ADHD using Habituation Training via Virtual Reality Technology

Joy Geng, Ph.D.

Jared Stokes, Ph.D.

Skip Rizzo, Ph.D.

Translation: the process of turning observations in the laboratory, clinic, and community into interventions that improve the health of individuals and the public—ranging from therapeutics and diagnostics to medical procedures and behavioral medicine



Reverse Translation: Bedside to Bench to Community

Parent asking for method to teach her son to ignore distractors in classroom setting

Wagner, J.A. Patient-centered reverse translation. *Clin. Pharmacol. Ther*. 2017

Using Virtual Reality to Reduce Distractibility

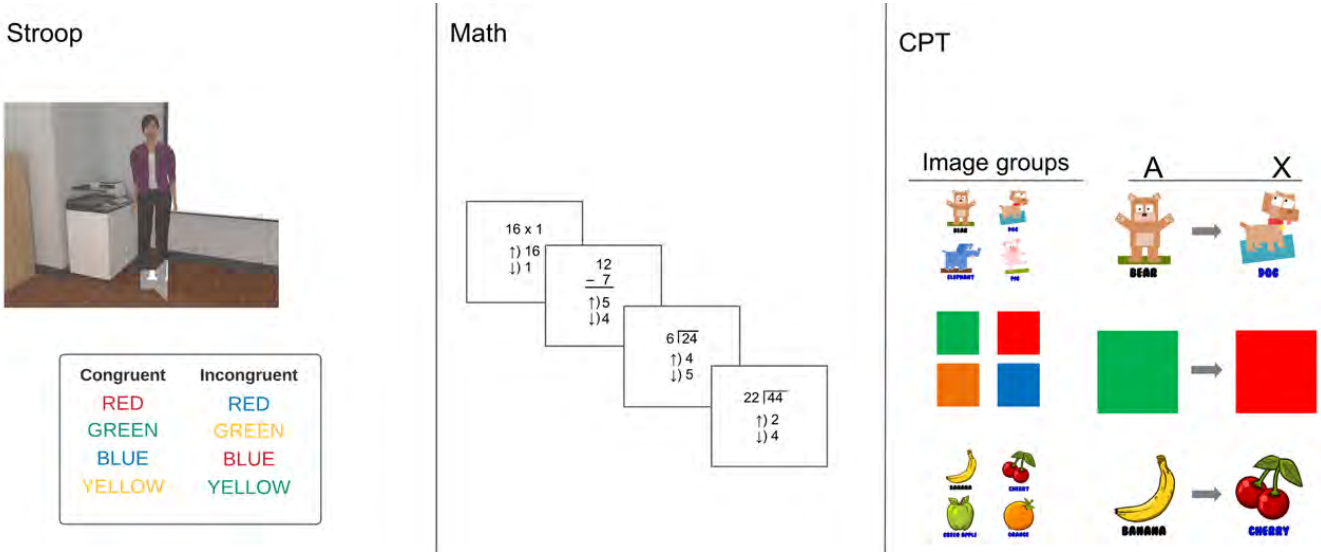
- Well-recognized, common ADHD issue across life span
  - Impairs academic, occupational, social functioning
  - Public health issue
    - Higher accident rates
    - Distracted driving accidents costs $40 billion per year
- Need - lack of targeted treatments specifically for distractibility
- Habituation
  - Bottom up learning process rather than top down – PFC mediated
  - Relatively simple learning process, long hx of basic science literature
  - VR permits repeated exposure to distractors

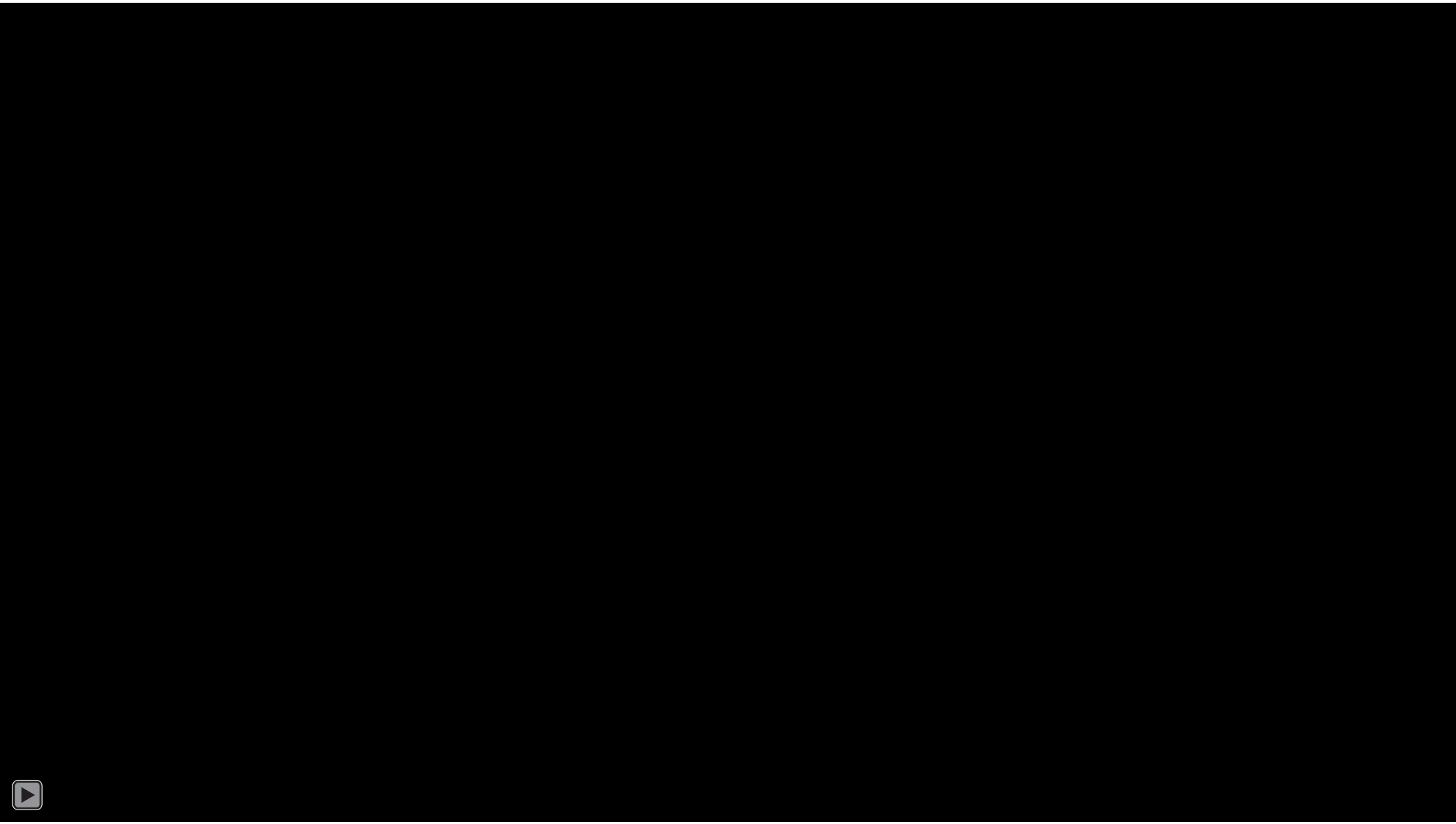
VRAM Classroom and Tasks

Stokes, et al., submitted

Classroom and distractors

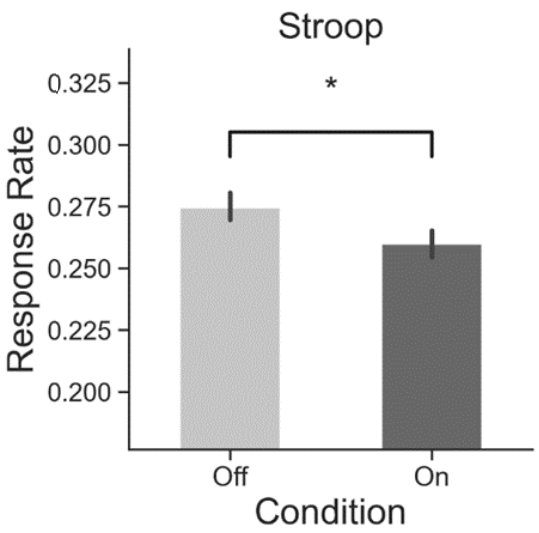
Classroom tasks

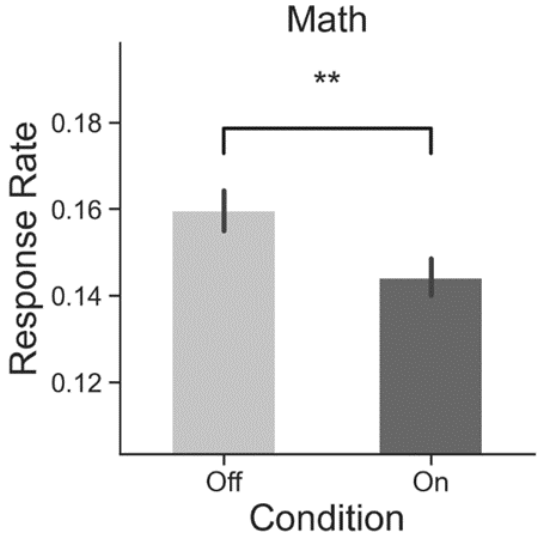


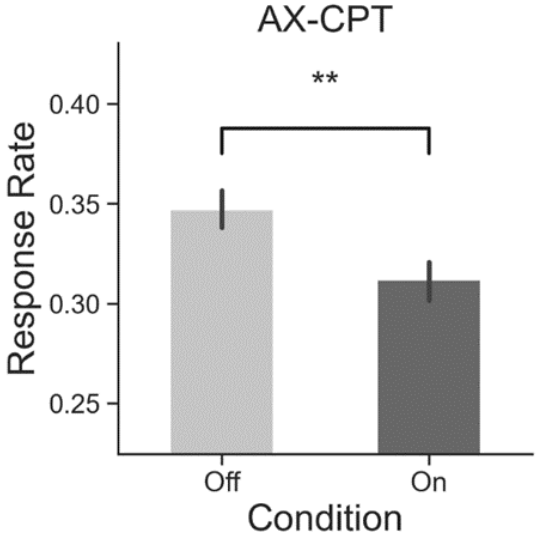


Distractors Reduce Rate of Problems Completed Regardless of Task

N = 20



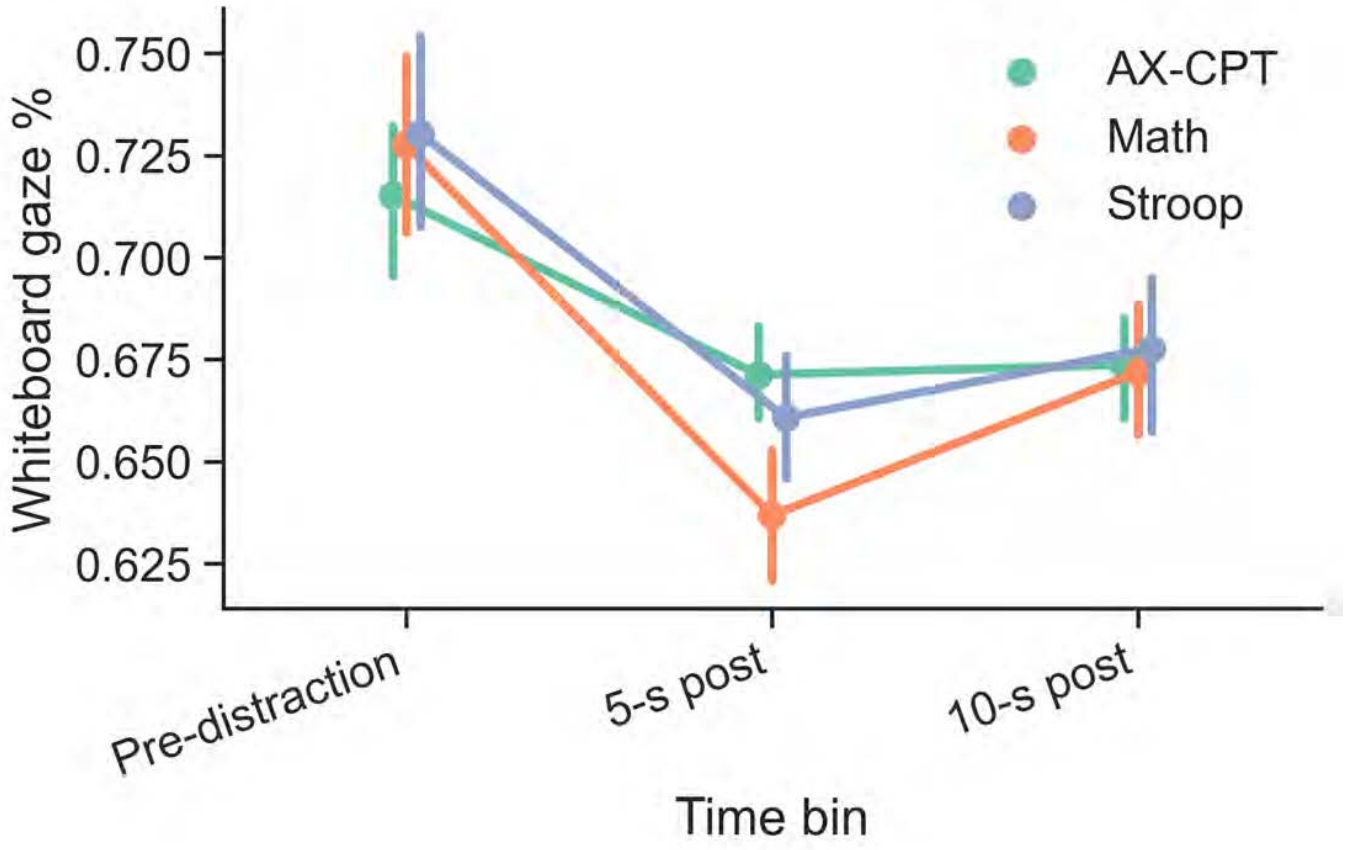




Stokes, et al., submitted

Distractors Produce Sustained Reductions in Looking at Classroom Whiteboard – Simulating Inattention

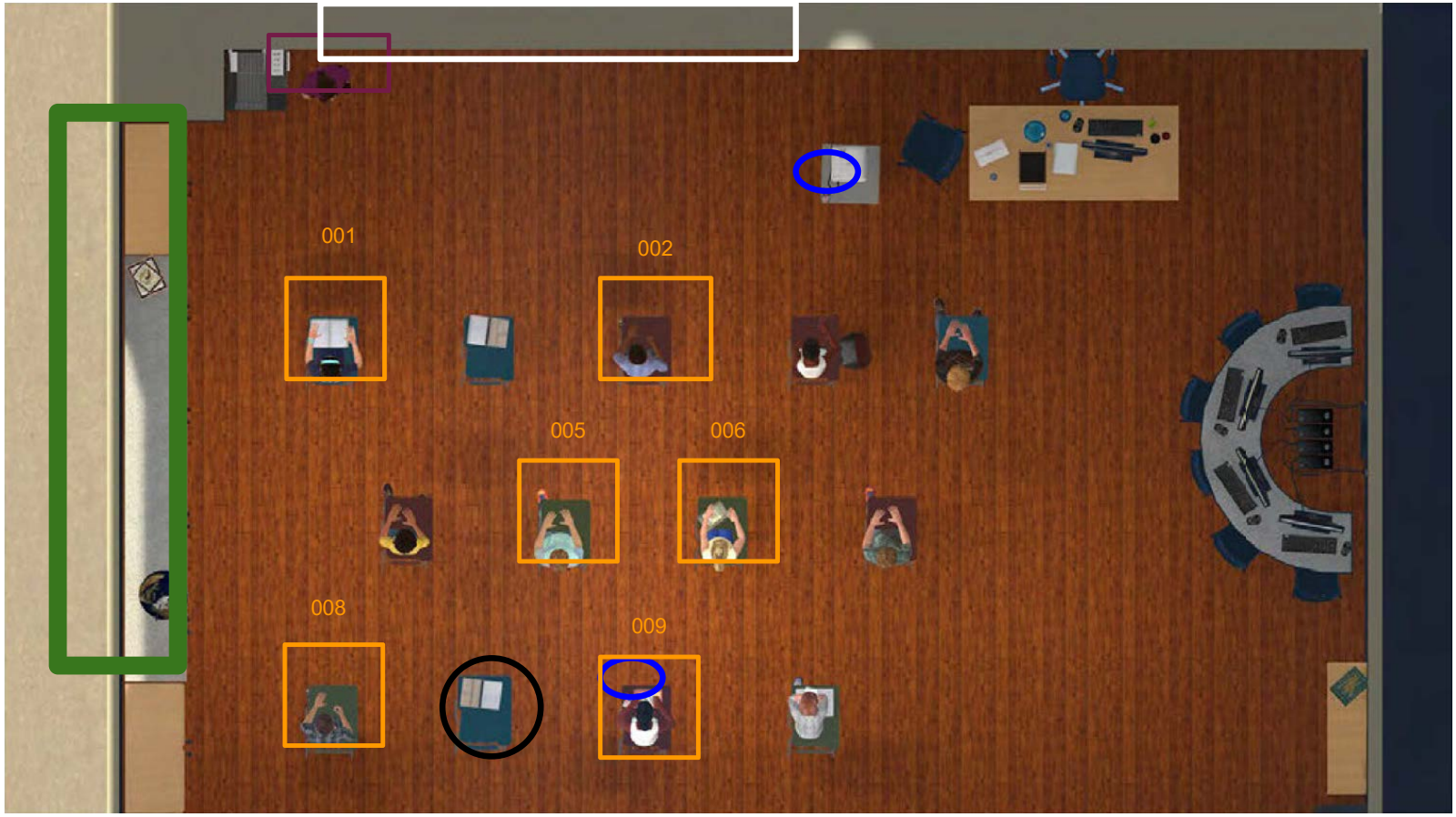
N = 20



Stokes, et al., submitted

What is Distracting? Understanding distraction will lead to better treatments

Ability to Measure Multiple Objects and Distance

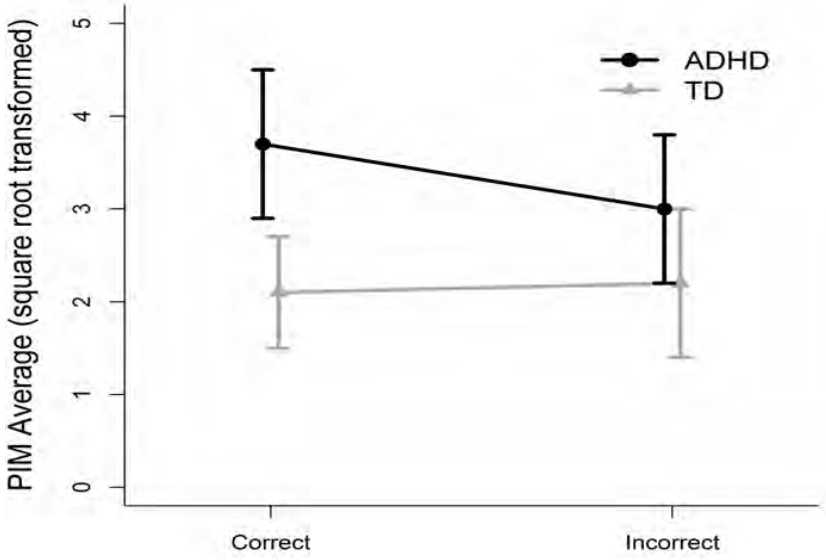


Green : window; Orange : Students with distractors; White: whiteboard; Blue : phone; Black : subject desk;

Data on treatment effects of VR therapy to follow

Can Fidgeting be helpful for ADHD?

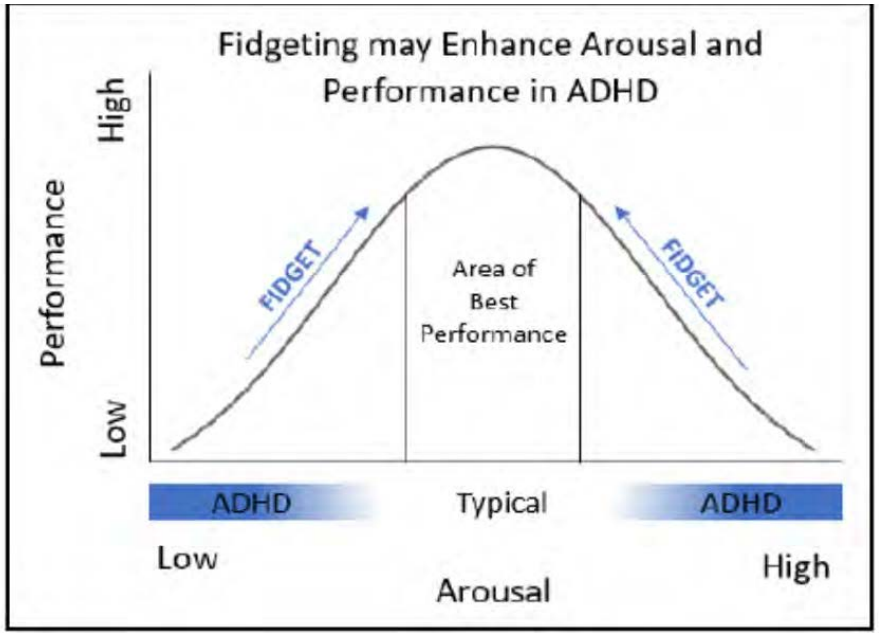
ADHD Group Demonstrate Better Attention with More Intense Movement

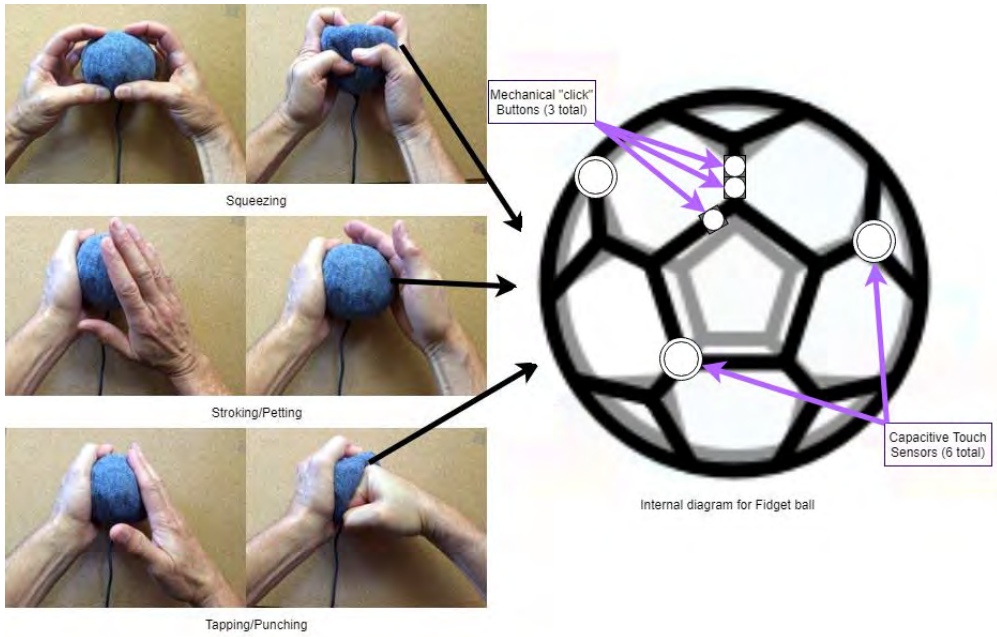


Correlations between flanker on trial-by-trial accuracy and intensity & frequency of movement

Hartanto et al., 2015

Can Intrinsic and Extrinsic Fidgeting Enhance Attentional and Emotional Regulation in ADHD?





Collaborators: Katherine Isbister, Ph.D., Daniel Shapiro, Ph.D.

Current State of Digital Therapeutics for ADHD

- WMT – Cognitive Tx can improve near transfer performance
- WMT may improve selected areas of performance for far transfer effects
- Literature mixed
- Need to engage children – otherwise transfer to real world behaviors won't work
- Need better measures of real world behaviors
- Training currently not developed for generalization – developed with idea to target brain regions that would lead to generalization
- Great potential for digital therapeutics, but newer ones needed
- Digital applications for organization, time management, memory, cues, feedback, turning in assignments

UC Davis MIND AIR Laboratory

Understanding & Treating Attention, Impulsivity & Regulation (AIR) Challenges

Questions?