Digital therapeutic engagement: moving beyond usage time to identify efficacious engagement

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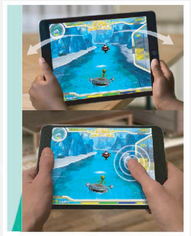
BACKGROUND

- Novel, targeted, and safe treatments are needed for patients with ADHD.
- AKL-T01 is an at-home digital therapeutic that uses a proprietary algorithm (SSME™) designed to improve attention and related cognitive control processes by training interference management at an adaptive and personalized high degree of difficulty. Interference is instantiated through a video game-like interface presenting two tasks that are to be done in parallel (multitasking). A perceptual discrimination targeting and a sensory motor navigation task. The goal is to successfully Steer their character through a course while avoiding bumping into obstacles, and to Tap the screen to collect targets when they appear.



- During the intervention period (days 1–28), participants are instructed to use AKL-T01 at home (iPad device) for ~25 min per day, 5 days per week, for 4 weeks.
- To date, we have studied AKL-T01 in over 600 children (8-15 years old) across 5 clinical studies (539 received AKL-T01), comprising Attention-Deficit/Hyperactivity Disorder, Autism Spectrum Disorder, Sensory Processing Disorder, and neurotypical participants.
- **Goal:** a meta-analysis of the impact of AKL-T01 on objective measures of attention and further evaluate how machine learning algorithms can help identify appropriate engagement with the intervention and its impact outcome measures.

META-ANALYTIC PHASE

TABLE 01 Summary of Study Demographic and Design

STUDY	AGE range	Population	N (TOTAL) Control	N (TOTAL) T01	API inclusion
ADHD-PoC [1]	8-12	ADHD + healthy	-	(80) 80	No
ADHD-STARS [2]	8-12	ADHD no meds	168	(348) 180	<1.8
ADHD-Adjunct [3]	8-14	ADHD on/off meds	-	(206) 206	No
ASD+ADHD [4]	9-15	ASD + ADHD	8	(19) 11	<0
SPD+ADHD [5]	8-13	SPD +SPD-IA + healthy	-	(62) 62	No

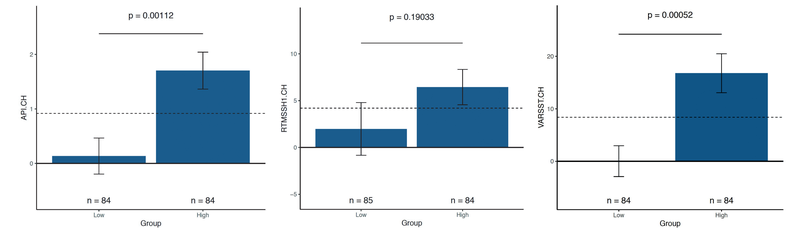
TABLE 02 Summary of Results on Attentional Metrics (participants on AKL-T01, n= 539)

TOVA METRIC	statistic / Population N	ADHD-POC 80	ADHD-STARS 180	ASD+ADHD 11	SPD+ADHD 62	ADHD-Adjunct 206	Total 539
API	Mean (SD) [Valid N]	0.91(3.38)[80]	0.92(3.16)[168]	1.86(3.66)[11]	0.97(1.88)[45]	-0.04(3.17)[200]	0.56(3.18)[504]
	p value	0.018	0.0002	0.12	0.0012	0.87	0.0001
	Cohen's D	0.27	0.29	0.51	0.51	-0.01	0.18
Sustained attention (RT Half1)	Mean (SD) [Valid N]	7.44(19.04)[80]	4.2(22.11)[169]	3.63(7.42)[11]	7.96(13.30)[45]	2.55(16.64)[200]	4.38(18.70)[505]
	t, p value	0.0008	0.015	0.14	0.0002	0.032	<0.0001
	Cohen's D	0.39	0.19	0.49	0.6	0.15	0.23
Reaction time variability (Total)	Mean (SD) [Valid N]	6.57(32.92)[80]	8.4(31.72)[168]	16.98(47.41)[11]	-	-1.74(28.76)[200]	3.87(31.45)[459]
	t, p value	0.08	0.0008	0.26		0.39	0.0087
	Cohen's D	0.20	0.26	0.36		-0.06	0.12
Derived Total Change [1]	Mean (SD) [Valid N]	6.16(21.34)[80]	5.83(20.15)[168]	10.79(22.58)[11]		0.06(19.22)[200]	3.49(20.20)[459]
	t, p value	0.01	0.0002	0.14		0.96	0.0002
	Cohen's D	0.29	0.29	0.48	-	0	0.17

API (Attention Performance Index): is a composite score of the sum of three z-scores from the Response Time in Half 1, d' in Half 2, and Reaction Time Variability (total)

MACHINE LEARNING RESULTS

FIGURE 03 Attentional Metrics Change Scores by Median Splits by level of TRI (STARS-ADHD)



Dotted line refers to mean change scores from STARS-ADHD study

TABLE 03 Summary of Effect Sizes on Attentional Metrics (STARS-ADHD)

TOVA METRIC	Cohen's D ADHD-STARS	Cohen's D ADHD-STARS + TRI
API	0.29	0.51
Sustained attention (RT Half1)	0.19	0.20
Reaction time variability (Total)	0.26	0.55

METHODS

FIGURE 01 EXAMPLE OF CLINICAL STUDY DESIGN

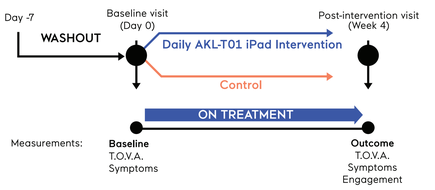


FIGURE 02 TOVA® - TEST CONSTRUCTION

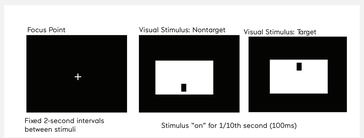
There are two subtests:

First half (the "Infrequent" or vigilance test), the target-to-nontarget ratio is 1:3.5. The subject is required to pay close attention.

✓ Individuals with "low CNS arousal" tend to do poorly on this form—a measure of inattention

Second half (the "Frequent" or high-response test), the target-to-nontarget ratio is 3.5:1. Subjects are expected to inhibit the tendency to respond.

✓ Individuals with "high CNS arousal" can become overstimulated, and individuals with "low CNS arousal" can "wake up"—a measure of impulsivity



MACHINE LEARNING PHASE

- In a sensitivity analysis of our largest clinical trial (STARS-ADHD, n=168; mean effect sizes 0.29), number of sessions played (usage time) was not highly correlated with efficacy.
- While aspects such as the frequency and total duration of use may play a role in treatment efficacy, the quality of interaction, ie. whether users engage and play as intended, is likely another important factor in treatment efficacy.
- We identified key features of engagement (Task-Responsive Interaction; TRI) and subject matter experts manually labeled 600 representative treatment sessions.
- We then trained a machine learning algorithm (random forest classifier) to categorize the remaining sessions. Model accuracy was assessed using a holdout set. Results showed high accuracy in predicting engagement labels provided by the subject matter experts.
- Subjects were divided into high/low TRI based on a median split of their average TRI label across all sessions.

CONCLUSIONS

- ✓ Results from a meta-analysis on pediatric populations following 1-month intervention with AKL-T01 showed an overall small (0.17 effect size) but significant improvement in objective measures of attention (Cohen's D ranged between 0.12-0.23 across measures).
- ✓ The task-responsive interaction (TRI) classifier is able to distinguish between different levels of participant engagement with AKL-T01.
- ✓ Unlike usage time, participants with higher engagement (High TRI) across all sessions showed a greater improvement in objective attentional measures.
- ✓ This approach provides a better predictor of efficacious engagement than traditional methods.

REFERENCES

1. Davis, et al., 2018, PloS ONE
2. Kollins, et al., 2020, Lancet Digital Health
3. Data on file, NCT=03649074 (manuscript in progress)
4. Yesrys et al, 2019, Journal of Autism and Developmental Disorders
5. Anguera et al, 2017, PLoS ONE

DISCLOSURES

EC, DD, AJ: Employed by Akili Interactive Labs and may own stock options

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