Study Protocol Approved by UCSF Ethics Committee

Project Summary

Inattention negatively impacts all aspects of a child's life including home, school, and community function. Cognitive and physical interventions are two promising non-pharmaceutical approaches used to remediate inattention challenges, with combined approaches being marketed to teachers, therapists, and parents often without research validation. Here, we assessed the feasibility of incorporating an integrated, cognitive-physical, closed-loop video game (pediatric body-brain trainer or 'pediBBT') into an after-school program, and also evaluated if there were attention benefits following its use. Unlike other cognitive-physical interventions, pediBBT uses both real-time heart rate data and cognitive performance data to titrate the physical and cognitive demands of game play via adaptive algorithms. 22 children (7-12 years of age) were recruited with a range of inattention issues to participate in this single-arm, longitudinal study (24 sessions over 8 weeks, ~30min/day), with follow-up assessments administered 1 year after the intervention. Outcome measures interrogated attention abilities through a parent survey of their child's behaviors, as well as objective performance-based and neural measures of attention. In addition to near perfect compliance by our participants, we observed significant improvements on the parent-based reports of ADHD symptoms, as well as on cognitive tests and neural measures of attention following the intervention (also on some secondary measures of cognitive control and physical fitness). Parent report and objective measures continued to show signs of positive effects 1-year later, suggesting sustainability of intervention-based benefits. These findings support future research involving a large-scale, randomized controlled trial to replicate and extend these findings.

Rationale & background information

Cognitive control functions (e.g. attention, working memory, goal-management) dictate our ability to learn and accomplish selected behavioral goals, with deficiencies in these processes found in a range of mental illnesses including ADHD (among others). Cognitive training interventions and physical fitness training are two approaches that have been successfully used to enhance deficient cognitive control abilities across a variety of populations, including children with issues of inattention. Given that each approach has led to improvements in untrained cognitive abilities, the possibility exists that a 'synergistic' effect on these abilities may be attainable through the combination of each training approach. Developing such a training tool may realize these synergistic effects in humans while simultaneously providing mechanistic evidence regarding how the process of learning can be augmented using the same approach. For the main study, we propose to utilize a novel video game-based intervention ("Pediatric Body-Brain Trainer", or pediBBT) that incorporates i) adaptive algorithms critical for cognitive training, ii) physiological measures such as heart rate into the core game mechanics, and iii) motion capture technology to incorporate whole-body kinematics into game play to leverage principles of embodied cognition.

General Information:

What is the protocol title and clinical trial number and registration date?

Does body-brain training improve measures of attention in children?
ISRCTN59416198;
Registration date: 24/05/2021

Who could participate?

Children between the ages of 7 and 12 years with school or community-based diagnosis of ADHD or parental concerns for inattention attending Neil Cummings Elementary School, where the intervention took place as an after-school program were eligible for participation.

What does the study involve?

All participants will play a game called 'pediBBT'. Participants are asked to participate in this study 4 days a week for 6-weeks, with each day consisting of 9, 3-minute sessions, with training occurring at Neil Cummings Elementary School as opposed to a clinic or laboratory. A research assistant will monitor participation and provide support and feedback to the parents and children during training. Prior to and after the intervention, children have their attention assessed and parents complete a questionnaire about their child's inattention. Certain measures will be repeated 1 year after the intervention as well.

What were the possible benefits and risks of participating?

There are no direct benefits or risks associated with participating in this study.

Where was the study run from?

Neuroscape, University of California, San Francisco (USA)

When was the study and how long did it run for?

January 2018 to December 2020

Who funded the study?

University of California San Francisco Academic Senate Resource Allocation Program, Neuroscape (USA)

Who was the main contact?

Joaquin A. Anguera, Joaquin.anguera@ucsf.edu

Study goals and objectives:

Our study goal was to gauge the feasibility of using this intervention for a subsequent large-scale intervention trial, with potential efficacy effects a secondary goal. Our objectives were to assess 3 primary outcome measures for improvement that we have used/assessed in previous trials:

1. Parent report of inattention using the Vanderbilt at baseline and post-intervention (6 weeks later)
2. Objective measure of attention using the Continuous Performance Task (CPT) at baseline and post-intervention (6 weeks later)
3. Objective measure of attention using EEG during the Continuous Performance Task (CPT) at baseline and post-intervention (6 weeks later)

Study design: This study was designed to be an **intervention based study, using a non-randomized, single-arm longitudinal** design to directly gauge the feasibility of using this intervention for a subsequent large-scale intervention trial,

Recruitment Criteria Overview

1. Males and Females, aged 7-12
2. Inclusion criteria
    a. Children between the ages of 7 and 12 years
    b. School or community-based diagnosis of ADHD or parental concerns for inattention
    c. No concerns of ADHD or inattention but were simply interested in participating
3. Exclusion criteria
    a. Concern for Autism Spectrum Disorder (Social Communication Questionnaire score <15)
    b. Prematurity (gestational age <32 weeks)
    c. Seizures requiring current medication management, psychosis or mood disorder (as assessed

by Behavior Assessment System for Children, Second Edition)

Detailed methodology:

Children attending Neil Cummins Elementary School in Corte Madera California between the ages of 7 and 12 years (20 males; 10.5 years +/- 1.2) were recruited for participation through school postings, newsletters, and word of mouth describing a study for children struggling with attention. Participating children had either i) parental concerns of inattention, ii) a school or community-based diagnosis of ADHD, or iii) neither and were simply interested in participating. Children engaged in 24 sessions of pediBBT training over 8 weeks (each session being approximately 30min of training + breaks), with a research assistant present for each session to monitor participation and provide support and feedback to the parents and children during training.

The Wechsler Intelligence Scale for Children Fifth Edition (WISC-V) was administered to all participants at the pre-training visit, with inclusion of children with Verbal Comprehension Index (VCI) ≥ 70. The processing speed index (PSI) from the WISC-V was also administered at the 1-year follow-up visit. Children were excluded if there was a concern for prematurity (gestational age < 32 weeks), seizures requiring current medication management, or concern for Autism Spectrum Disorder as measured using the Social Communication Questionnaire (score >15).

Steps for data collection

1. Screening for general inclusion/exclusion criteria
2. Consenting
3. Baseline outcome data collection
4. Cognitive control training intervention period
5. Return visit for post-intervention outcome data collection
6. Return visit for 1-year outcome data collection

Measures administered

1. Continuous Performance Task (CPT)
2. Vanderbilt measure of inattention (Parent Report)
3. Working Memory Task (AID)
4. EEG recording during CPT task
5. NeuroRacer Multitasking Assessment
6. Basic Response Time (BRT)
7. Measures of physical fitness
8. Surveys of general health

Time commitment

- Consenting: 30 minutes based on individual reading speed and comprehension level
- Outcome assessments at baseline, 6 week, and 1 year time points: 2 hours
- Intervention training: 25-35 minutes 4x/week for 6weeks

Safety Considerations

A screening for general inclusion/exclusion and detailed explanation during consenting was performed to ensure that both parents and participants were aware of the requirements of the present study. During the study, a study coordinator was present at all times to ensure that the participant was aware of their requested actions. A checklist was used during each outcome testing session with a notes section to record any potential adverse event that would be relayed immediately to the principle investigator and all other parties involved (parents, UCSF IRB, etc.). After every training run, participants were asked the level of intensity ("How hard was that?") to ensure that any given training run did not reach a level of exertion that would be concerning for

all parties involved. Participants were given the ability to end study participation at any time, reinforcing that no consequences would emerge if they chose to elect this course of action at any time.

PediBBT intervention: PediBBT (**Figure 1a**) integrates full body motion capture technology with cardiac and cognitive adaptive algorithms into a high-level (art, music, story) 3D video game targeting cognitive and physical fitness goals. There are three pediBBT modules, with each targeting a different aspect of cognitive control: a visual search task for attention (with increasing distraction), a spatial span task for working memory, and a task-switching paradigm targeting cognitive flexibility abilities[27] (see **Figure 1b**). The visual search task challenges individuals to search the screen for a designated target amongst an adaptively changing number of distracting elements, with success or failure on a given trial adaptively changing the amount of time allowed to respond. The task switch module involves memorizing an exemplar object presented, and then responding to the target object that is most like the exemplar presented, with the target object changing in its discriminability in an adaptive fashion on a trial-by-trial basis based on one's performance. Finally, the working memory task involves memorizing the location or sequence of target objects on screen, followed by a 5-7 second delay period, and participants having to correctly identify said order or location, with correct trials leading to a greater number of items for memorization on the next trial. There are also three levels of ascending difficulty within each module, with participants advancing to a subsequent level after seven sessions.

Participants respond with their hands and feet to the aforementioned cognitive tasks by engaging three physical domains (aerobic, balance, and flexibility). PediBBT uses an off-the-shelf Microsoft Xbox Kinect 2™ to collect movement-based kinematics in response to game-based challenges presented[28], and also involves the use of an Apple Watch™ to capture heart rate data which is incorporated in real time during game play to adjust the physical demands of the intervention. As an example, if a participant's heart rate is below a pre-determined threshold on a given trial, the distance required to respond on the next trial is increased, causing the participant to move a greater amplitude (often lunging, jumping, or even sprinting to one's side) and then quickly returning to a starting position in anticipation of the next trial. Similarly, if an individual was training at a heart rate greater than this pre-determined threshold, then the distances required to respond would decrease to lessen one's movement amplitudes on a given trial. This algorithmic approach modulated a participant's heart rate to try and ensure that their training was predominantly performed at their ideal physical training window. Participants receive physiological and cognitive feedback on a continual basis by incorporating real-time heart rate data and cognitive performance metrics into the software's adaptive algorithms to titrate the demands and rewards of game play. This ensures that each participant is appropriately challenged and engaged during their training experience. Thus, the cognitive and physical tasks do not compete for cognitive resources—they work in concert towards a common task-based goal, overcoming a problem in previous studies where cognitive and physical fitness training were combined[29–37].

Feasibility and Outcome Assessment Measures

To assess feasibility, we probed the following questions: i) how practical was setting up the pediBBT platform outside of the laboratory, ii) how many participants who began training withdrew from the study, and iii) what was the percentile of assigned training sessions completed. To assess attention-related improvements in this pilot study, we collected a number of different outcome measures: a parent report, objective performance-based laboratory measures, and electroencephalography (EEG) recordings. Here we focused on measures of attention that have previously been used by our group to quantify improvements following a digital intervention in children with issues of inattention[33,9] (designated as 'primary' outcome measures). The use of these same measure also facilitates comparisons between the current study and this prior work to provide context for any improvements observed (**Figure 1c).** All other outcome measures collected were subsequently designated 'secondary' measures of interest, including measures of physical fitness that were assessed given the nature of the training. These designations are stipulated in our trial registration as well (ISRCTN registry [59416198]).

Follow-up: Assessment data was collected following training as well as 1-year later. At the 1-year mark only the primary outcome measures were collected, as well the Neuroracer assessment.

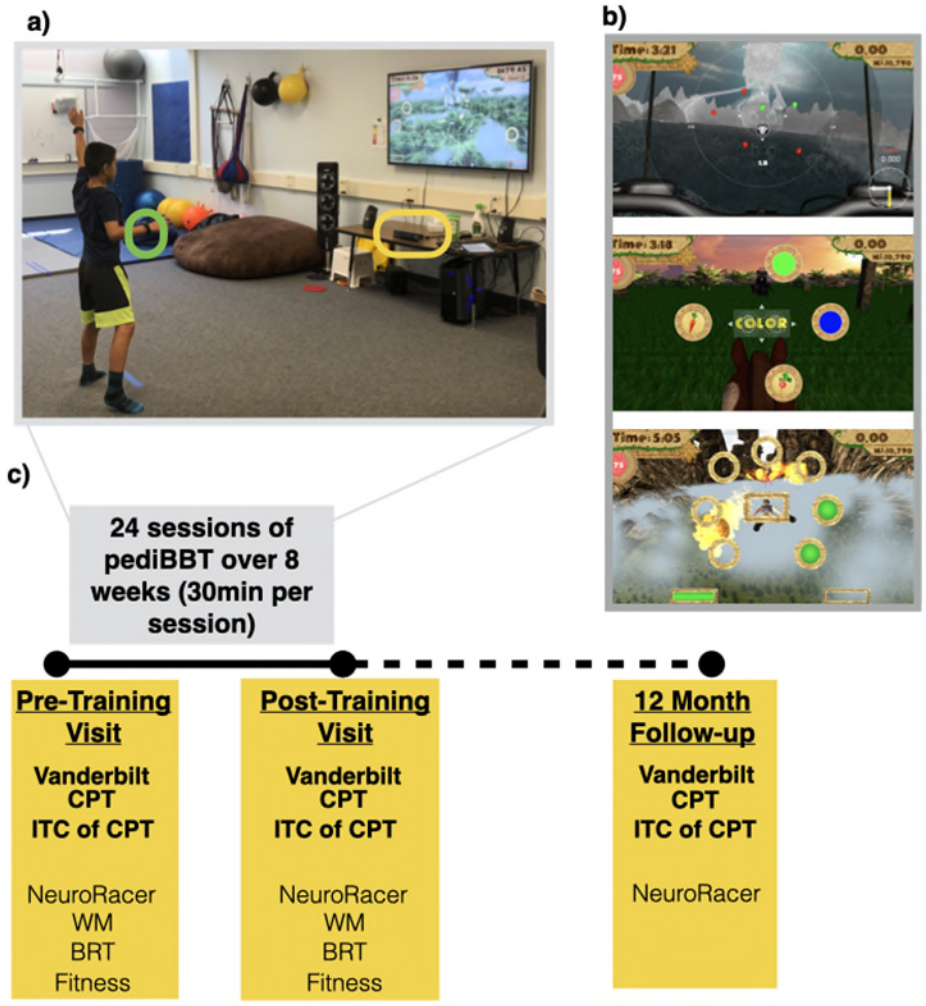

Figure 1. pediBBT schematic

1) Primary Outcome Measures: Attention

Vanderbilt: The Vanderbilt Attention Deficit/Hyperactivity Disorder Parent Rating Scale (VADPRS), which utilizes information based on the *Diagnostic and Statistical Manual of Mental Disorders, 4th Ed.* (DSM-IV), was administered to assess ADHD symptoms as well as changes in parental perception of inattention[9]. This measure was collected from the participants' primary caregiver prior to, immediately following the intervention, and at the 1-year follow-up. Inattention concerns were assessed using the 1st 9 questions on the Vanderbilt, where participants parents rated questions of inattention on a scale from 0-3, with 0 representing never having a concern, 1 having occasional concerns, 2 often having concerns, and 3 representing very often having concerns. Note that participants scoring a 2 or a 3 on at least 6 of these 9 questions in conjunction with a score of 4 or 5 on any of the performance questions (questions 48–55) are characterized as having the inattentive subtype of ADHD.

***Continuous Performance Task (CPT)*:** Our measure of sustained attention was a modified version of a well-validated continuous performance task (CPT), the Test of Variables of Attention (TOVA)[39,40], which provides an index of sustained attention and impulsivity. We have used this task as an outcome measure in previous intervention studies from Neuroscape[41–44]. The experiment was programmed in Presentation (http://neurobs.com) and the stimuli were presented on a CRT monitor. For the present study, we adapted the task for use with EEG recordings, which requires many trials with a motoric response. In this task, participants maintain fixation on a central crosshairs and grey squares are shown on a black background at the top or bottom of the field of view. During the sustained condition, target stimuli were presented infrequently at the top of the screen as a 1:4 ratio of targets to nontargets and participants are instructed to only respond to these

target stimuli. During the impulsivity condition, target stimuli were presented frequently at the top of the screen as a 4:1 ratio of targets to nontargets and participants are instructed to only respond to these target stimuli. Participants completed 2 blocks of 125 trials for each condition. Our primary variable of interest on this assessment was response time variability (RTV), as this particular metric has been shown to be sensitive to changes following a digital intervention [18,41,42,45]. This outcome measure was collected at baseline, training completion, and the 1-year follow-up. For completeness, we also describe other measures typically reported from this task, including response time (RT), d-Prime, and ex-gaussian tau (a metric related to RTV that quantifies attentional lapses by examining the distribution of long RTs[46,47]).

EEG Data Collection and Analysis: While participants performed the CPT task, EEG activity was recorded with Active Two head cap (Cortech-Solutions) with a BioSemi ActiveTwo 64-channel EEG acquisition system in conjunction with BioSemi ActiView software (Cortech-Solutions). Signals were amplified and digitized at 1024 Hz with a 16-bit resolution. Anti-aliasing filters were used and data were band-pass filtered between 0.01–100 Hz during data acquisition. Data was preprocessed using Analyzer software (Brain Vision, LLC), with blinks and eye-movement artifacts removed through an independent components analysis, as were epochs with excessive peak-to-peak deflections (±100mV). All EEG data underwent the same processing methodology as previously established by our lab[48,49] to reveal specific neural signatures to guide subsequent interpretations[50–53].

Based on our previous work[41], we chose to examine inter-trial coherence (ITC) for the neural correlates associated with performance during each condition of the CPT task. ITC assesses the electrophysiological response consistency of activity at a given region, and reflects the extent to which synchronization occurs from trial to trial in EEG at a particular frequency and latency. ITC has been shown to be correlated with RTV[4154] and has been shown to be sensitive to intervention-based changes. ITC has been implicated in sustained attention abilities[5556,57], including correlating with RTV across the lifespan[58]. ITC is quantified by the unit "phase locking value" (PLV), which ranges between 0 and 1, with a value of 0 indicating that the phase synchrony is completely random, and a value of 1 indicating that the phase-locking is perfectly synchronized across trials. ITC is defined as: $ITC(f,t) = 1n\sum k = 1nF_k(f,t)|F_k(f,t)|$. The ITC time series was created by resolving 4-40 Hz activity using a fast Fourier transform (FFT) in EEGLAB. After the time series was resolved, 50 msec bins following the onset of the stimuli were created from 0-600msec. We selected a cluster of frontal electrodes (Fz, FPz, AF3, AF4, and AFz) based on previous literature that has used this same electrode cluster for similar analyses[9,41,42]. In each case, PLVs were controlled for individual state differences at each session by baseline correcting each individual's PLVs using their -200 to 0 period (thus, relative PLV). Note that this outcome measure was also collected at the 1-year follow-up.

2) Secondary Measures

***NeuroRacer Multitasking Assessment*:** We assessed multitasking abilities derived from a test used in our previous work[56] by comparing performance during a perceptual discrimination task under dual- vs. single-tasking conditions. Participants responded to a designated stimulus presented on a computer monitor (green circles) while ignoring all other color/shape combinations. Participants were exposed to 3 blocks of 36 target stimuli and 36 non-target stimuli, with each stimulus appearing on the screen for 400msec and an inter-trial interval of 2000-3000msec (with 500msec jitter). A fixation cross was present on the screen at all times above the car and below the color/shape signs. Participants were instructed and reminded after each run to maintain focus on the fixation cross. The fixation cross provided performance feedback on each task: it turned green for 50msec when the correct sign was selected within the time window or an irrelevant sign was ignored. When either of the aforementioned conditions were not met, it would turn red for 50msec. For the NeuroRacer multitasking assessment, cognitive performance was evaluated using the signal detection metric of discriminability (d-Prime, or d') in the form of a cost index. This index calculated the percentage change in d' from when a participant performed a perceptual discrimination task by itself ('single tasking') versus when they performed this same task while concurrently performing a visuomotor tracking task ('multitasking'). Thus, the equation for this index is as follows: (multitasking d' – single-tasking d'/ single-tasking d'). Visuomotor tracking performance was measured by the amount of time that the participant was able to keep the car at the center of the road. Note that this behavioral outcome measure was also collected at the 1-year follow-up.

Delayed Recognition Working Memory: We administered a delayed recognition task designed to measure changes in participants' ability to maintain an accurate mental representation of items in working memory either in presence or absence of distracting or interfering information. We have used this task in numerous previous studies[53,59]. Here we examined performance on the Ignore Distractor (ID) condition of this task, where participants were instructed to ignore a distracting stimuli while performing this task. More specifically, each trial began with the presentation of a face displayed for 800 msec, followed by a delay period (3 sec), the presentation of a face stimulus as a distractor (800 msec), a second delay period (3 sec), and the presentation of a face probe (1 sec). The participants were instructed to make a match/nonmatch button press response at the probe as quickly as possible, without sacrificing accuracy. This was followed by a self-paced inter-trial interval (ITI). Our primary variables of interest on this assessment were accuracy and RT, as each has been used in previous studies using this task[56,60,61,62]. The experiment was programmed in E-Prime (https://pstnet.com/products/e-prime/) and the stimuli were presented on a CRT monitor. Due to time restrictions, this measure was not collected at the 1-year follow-up.

Physical Outcome Measures: The physical outcome measures performed before and after training include elements from the FitnessGram[63–69], a field-test battery for youths used by the Presidential Youth Fitness Program that has established standards for ages 5-17 years. Participants performed a Curl-Up, 90 degree Push Up, Trunk Lift, and the PACER run to assess changes in fitness and strength. These measures were not collected at the 1-year follow-up.

Basic Response Time (BRT) Task: We administered a measure of basic response time to ensure that any differences we see between groups are not due to differences in motoric quickness. Thus, this task acts as a control measure, where we would expect no changes in performance, compared to other outcomes where we hypothesize there will be significant improvements over time. In this task, participants respond to a target stimulus (40 trials) with a button press. Here we assessed RT and RTV in line with our previous work[53,70].

Data Management and Statistical Analysis

Both assessment and training data were collected locally on desktop computers, and backed up to external hard drives. Data were then back up to a UCSF IT approved and validated cloud server. Data were imported at the single subject level in a wide format to a spreadsheet for data collected at each assessment period, as well as for each date training occurred.

Changes in cognitive control and survey measures were assessed with paired samples t-tests comparing (1) pre- to post-training performance, (2) post-training to 1-year follow-up performance, and (3) pre-training to 1-year follow-up. This approach was taken (as opposed to a repeated measures ANOVA with all three timepoints) due to the small number of participants who completed all assessments at each timepoint. The goal of the 1-year follow-up comparisons to both the post- and pre-training time points was to reveal those measures that had comparable performance 1-year later (post-training versus 1-year), as well as those whose improvements at the 1-year mark surpassed performance initially evaluated at baseline (pre-training versus 1-year). For the EEG ITC analyses, we conducted repeated measures ANOVAs with within-subjects factors of time window (0-600msec via 50 msec bins) and session (pre and post), separately for each CPT task condition (impulsive and sustained), as this analysis allowed us to evidence training-related changes at specific time windows following stimulus onset as in our previous work[13]. Where a session by time window interaction was present, follow-up paired samples t-tests tests were conducted to identify which 50msec time window (from 0-600msec) showed a significant change between sessions. Statistical tests comparing post-training to 1-year follow-up for the EEG data were conducted using nonparametric Wilcoxon Signed Rank tests due to the small number of participants with available data (less than 10 in these cases). The change in peak neural ITC (or change in ITC averaged across all time windows if no interaction was present) was entered into correlational analyses with our other primary metrics of interest. All correlations conducted reflect a Pearson product-moment correlation. While we present the results of all correlations here without any correction for multiple comparisons given the pilot nature of this work, we also mention which of these results would survive a false discovery rate (FDR) correction. Further, effect sizes for changes in our metrics of interest were calculated using Cohen's d. All statistical analyses were conducted using SPSS 22.0 (SPSS Inc.), with a p-value of .05 set as the threshold for significance.

Quality Assurance

This study and all study protocols were approved by the UCSF Institutional Review Board. Any adverse incidents observed by the research staff were to be reported immediately to the principle investigator, recorded in detail, discussed amongst the PI and co-investigators to understand the seriousness of the incident and the appropriate response, and subsequently submitted to the UCSF IRB if the incident was determined to be more than minimal.

Expected outcomes of the study

This study will contribute to advancement of knowledge particularly for future work using these technologies. The results will be utilized as the foundation for future studies with a larger sample size as well as appropriately determined control groups.

Project duration of the project

January 2018 to December 2020, with data collection beginning in Feburary of 2018 and the final 1-year follow-up occurring in December of 2020.

Problems anticipated

None as reported or anticipated.

Project management

J.A.A., A.G., E.M. designed the experiments; J.A.A., R.A.S., and A.G. developed the BBT software; J.V., M.E., and B.J. collected the data; J.A.A., M.A.R., M.E., B.J., J.V., A.S., and C.G. analyzed the data; and J.A.A., M.A.R., J.V., A.S., C.G., A.G., and E.M. wrote the paper. All authors discussed the results.

Ethics

Informed consent was collected from the parents of each participant, with each participant given an informed assent. A research associate from the research team discussed 1-on-1 with each parent and potential participant the overall time required for participation in each phase of the study, potential risks/benefits associated with participating, and the (lack of) repercussions for withdrawing from the study at anytime.

Consent form

A copy of the consent form can be found at:

https://www.isrctn.com/editorial/retrieveFile/319a3aa0-4a52-4217-bbf5-83153c7025e0/39914