Brief, computerized inhibitory control training to leverage adolescent neural plasticity: A pilot effectiveness trial

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Abstract

Adolescence is a time of heightened neural plasticity. Many brain networks show protracted development through this period, such as those underlying inhibitory control (IC), a neurocognitive skill implicated in risk-taking and therefore relevant to public health. Although IC appears to be trainable in adults and young children, whether and how IC may be malleable during adolescence is not fully understood. In this pilot RCT, we tested the effects of a school-based IC training paradigm (versus active control) on IC performance and neural function in adolescents (N = 19) aged 15 to 17 recruited from a low-income school district. We also examined the extent to which training effects transferred to a non-trained IC task and real-world risk behavior, as well as potential moderation effects by early adversity exposure. Training altered brain function related to attention during IC preparation and implementation, though it did not alter IC performance in the training group compared to the control group. There was limited evidence of training transfer. Results have implications for translational neuroscience research in adolescents.

Adolescence is a period of heightened neural plasticity during which environmental input may be particularly able to shape brain development and behavior (Fuhrmann, Knoll, & Blakemore, 2015; Spear, 2013; Sisk & Zehr, 2005; Dahl, Allen, Wilbrecht, & Suleiman, 2018). Such periods of neural plasticity are often highlighted as key leverage points for intervention given the presumed increased sensitivity to environmental influence accompanying this plasticity. Indeed, some evidence suggests that late adolescence in particular may be a 'window of opportunity' for improving some cognitive skills (Knoll et al., 2016).

Inhibitory control (IC), or the ability to inhibit a habitual behavior in the service of a long-term goal, is one key cognitive and behavioral capacity that develops over the course of adolescence (Aron, Robbins, & Poldrack, 2014). Neural regions associated with IC also develop rapidly during this time. The prefrontal cortex, including the inferior frontal gyrus, a key region within the IC neural network, does not reach maturity until young adulthood. Alongside the developing IC neural network during adolescence, the dopaminergic reward system (e.g. ventral striatum) appears to be especially sensitive to environmental inputs and incentives, particularly those associated with peers (Casey, 2015). Deficits in IC have been associated with risk-taking (e.g. risky sexual behaviors, onset of heavy drinking) in adolescence (Wetherill, Squeglia, Yang, & Tapert, 2013; Goldenberg, Telzer, Lieberman, Fuligni, & Galvan, 2013). Notably, these risk-taking behaviors often occur in the presence of peers, a particularly salient context for adolescents. Thus, IC and its neural circuity have important public health implications given their relevance for risk-taking behavior.

Though increases in risk-taking are a hallmark of adolescence (Steinberg, 2004) and evidence suggests that this behavior is a means to achieve goals specific to this developmental stage (e.g., gaining autonomy), risk-taking can have negative consequences. Indeed, increases in

risk-taking parallel increases in morbidity and mortality rates during adolescence (Casey, 2015). A population particularly vulnerable to negative outcomes associated with risk-taking are adolescents who have experienced early life stress. Adolescents who have experienced poverty, community violence, and other adversity are more likely to engage in risky externalizing behaviors and substance use in adolescence and beyond (Doom, Vanzomeren-Dohm, & Simpson, 2016). Though limited work has examined the association between IC and risk-taking in adolescents exposed to early life stress specifically, evidence from younger children suggests that exposure to poverty and related stressors is associated with reduced IC (Brown, Ackerman, & Moore, 2013). Taken together, these findings point to adolescence as a potential window of opportunity for targeted intervention, especially for early life stress-exposed youth, to impact IC and its neural systems that underlie risk-taking behavior.

The emergence of computerized cognitive training paradigms represents a promising means to improve IC in a cost-effective, readily scalable manner. The use of well-validated tasks from cognitive neuroscience to train IC provides a way both to improve IC and to examine the neurocognitive pathways of training effects. Recent work in college students has demonstrated the efficacy of approximately 3 weeks of IC training administered in the laboratory that involved brief (~6 minute) sessions of a computerized task [Stop Signal Task (SST)] requiring participants to inhibit a repetitive motor response (Berkman, Kahn, & Merchant, 2014). This laboratory-based IC training appeared to improve IC behaviorally and, at the neural level, to engender a shift from reactive to proactive control, as evidenced by increases in right inferior frontal gyrus activation, in anticipation of the need for control (i.e., during the cue phase of the task). IC has also been trained with some success in the preschool context (Thorell, Lindqvist, Bergman Nutley, Bohlin, & Klingberg, 2009). A recent study using working memory training with

adolescents demonstrated increased working memory and reduced risk-taking in the presence of peers, but no transfer to cognitive control (Rosenbaum, Botdorf, Patrianakos, Steinberg, & Chein, 2017). However, the preschool-based study and the working memory training study lacked neuroimaging assessment, precluding examination of neural mechanisms of change. At present, it is not clear the extent to which IC training effects extend to adolescence or whether school-based training administrations may demonstrate similar neural effects as those seen in the laboratory.

Though the IC training literature in adolescents is nascent, evidence from the adult IC training literature suggests that leveraging the cue-learning aspects of a training task by pairing real-world cues that anticipate the need for control with IC engagement may increase the likelihood of training transfer to skills related to the training task (e.g. other forms of inhibitory control, emotion regulation; Beauchamp, Kahn, & Berkman, 2016). For adolescents, decision-making and IC appear to be particularly susceptible to peer influence. As social bonds and standing become increasingly important, adolescents become more likely to engage in risk behaviors when in the presence of peers (Chein, Albert, O'Brien, Uckert, & Steinberg, 2011). Reduction of risk-taking behavior in adolescents could, therefore, result from targeting IC in a manner that incorporates aspects of the highly salient and risk-relevant peer context.

The current pilot study sought to address these gaps in the literature by investigating the effectiveness of an IC training paradigm, currently validated in a sample of young adults, in a group of adolescents recruited from a low-income school district. As such, this study adopts a translational neuroscience approach by leveraging methods and insights from neuroscience about the function and malleability of core capacities such as IC to develop, refine, and test real-world interventions that might impact those capacities in individuals who most need them (Fisher &

Berkman, 2015). Based on previous research in adults demonstrating the critical importance of the cue phase of the IC training task, we modified a standard IC task to include images of adolescent faces to prime salient, real-world scenarios (i.e., peer contexts) when IC is likely necessary for adolescents. We used these same cues in a separate IC task administered to both groups pre- and post-intervention to assess 'near-transfer' to a related but untrained task. Additionally, to explore the feasibility and scalability of this intervention, we administered the IC training in a school context. We employed multiple behavioral and neural measures of IC that included the same adolescent face cues to allow for a detailed examination of potential training and transfer mechanisms.

Based on previous IC training work, we hypothesized that participants who received IC training (vs. active control) would show improved performance on behavioral measures of IC (over time and compared to the active control group) and show increased activation in IC-related regions (e.g., inferior frontal gyrus) during anticipation of IC (over time and compared to the active control group). Additionally, given the use of the same set of meaningful cues across both training and transfer tasks and overlapping neural circuitry recruited in the SST and Go/No-Go (Swick, Ashley, & Turken, 2011), we expected that the training would transfer to performance on an untrained IC task and potentially to real-world risk-taking behavior. Finally, in line with translational neuroscience goals to identify moderators of treatment effects, we conducted exploratory analyses using measures of early adversity as moderators of the effectiveness of IC training.

Method

Participants

Twenty-four participants were recruited to participate in a self-control training study from local high schools in partnership with a local low-income school district. Recruitment strategies were developed in partnership with the school district collaborators to create a recruitment strategy that was implementable within each school context. Recruitment procedures involved special education teacher collaborators' identifying potentially eligible participants (i.e., children who they thought may benefit from self-control training), assessing child and parental interest, and obtaining permission for the research team to contact parents. The research team then contacted the parent of each eligible child to assess eligibility and, if eligible, scheduled the baseline assessment. In general, the training was made available to the entire class at the suggestion of teacher collaborators; however, only data from participants who were eligible for and completed the pre- and post-assessments are included here. Inclusion criteria included English as a first language, free of MRI contraindications, free of neurological, psychiatric, neurodevelopmental, and learning disorder diagnoses (besides ADHD), aged 15 to 17, and enrollment at high schools where study was conducted. Adolescents with ADHD diagnoses were not excluded from the study given that early life stress exposure is often associated with attention challenges, and our recruitment strategy focused on adolescents with difficulty with impulse control, a common symptom of ADHD.

Following phone screening with a parent, eligible participants were randomized into the training or active control condition. Of the 24 recruited participants, five participants' data were unusable due to structural brain abnormalities (n=1), failure to complete the endpoint session (n=1), technical problems with the training sessions (n=1), and inadequate behavioral performance (details about cutoffs are provided on pp. 16-17) at both baseline and endpoint assessments (n=2). The final sample for analyses included 19 participants (M_{age} = 16.2, SD_{age} =

.88; 11 training, 8 active control). Recruitment and data collection occurred from September 2014 to December 2015. The study protocol was approved by both the university Institutional Review Board and by the school district research council.

Study Overview

All participants completed an initial baseline assessment including task-based fMRI and questionnaires, 10-14 training or active control sessions (M = 11.84, SD = 1.12) at their high school over the course of 4-5 weeks ($M_{\text{days between assessments}}$ = 38.16, $SD_{\text{days between assessments}}$ = 8.07), and an endpoint assessment nearly identical to the baseline. Behavioral and neural measures from a modified version of an IC task (see below) were the primary dependent measure assessed at baseline and endpoint to determine training effectiveness, and this modified IC task served as the training or active control task (details below).

IC Training Task: Modified Stop Signal Task (SST)

The Stop Signal Task (SST) is a well-validated task designed to measure IC of a motor response (Verbruggen & Logan, 2008). The paradigm requires participants to inhibit a prepotent motor response to a go signal (i.e., an arrow pointing left or right) when the presentation of that go stimulus is followed by a stop signal (i.e., an auditory beep), which occurs on a minority of trials (i.e., 25%) at a variable latency following the go signal (i.e., the stop-signal delay; SSD). The SSD is dynamically adjusted based on participant performance through the use of a staircase function such that SSD is increased by 50ms following successful stops and decreased by 50ms following unsuccessful stops until 50% stop trial accuracy is achieved. The primary dependent measure of the SST is the Stop Signal Reaction Time (SSRT), which indexes the efficiency of the inhibitory control process and is calculated as the difference between the SSD and the speed

of the stop process. The integration method (Verbruggen, Chambers, & Logan, 2013) was used to estimate the speed of the stop process and SSRT.

For this pilot study, we modified the SST to include adolescent face stimuli in the cue phase of each trial (see Figure 1). This modification was motivated by previous research demonstrating increased rates of adolescent risk-taking behaviors in peer contexts (Chein et al., 2011) and increases in activation in key regions of the IC network (i.e., right inferior frontal gyrus) during the cue phase of the SST after training on the task (Berkman et al., 2014). By pairing an adolescent face with the cue phase of the SST, gains from training on the SST were hypothesized to be more likely to transfer to real-world peer contexts in which IC is especially needed during adolescence. The adolescent face stimuli were obtained from the NIMH Child Emotional Faces Picture Set (NIMH-ChEFS; Egger et al., 2011) and from a set of adolescent stimuli within the lab. The ethnic composition of the adolescent face stimuli (i.e. 93% white) generally corresponded with the majority white ethnic composition of the study sample (described in Table 1). Participants saw a different subset of these adolescent face stimuli at the baseline assessment, during training, and at the endpoint assessment.

A typical trial was comprised of an adolescent face cue that indicated the start of the trial (mean duration of 500ms; jittered following a gamma distribution), then the ‘go’ signal (i.e., an arrow pointing either right or left, with 1:1 relative frequency; duration of 1000ms), and an intertrial interval of variable duration (mean duration of 1400ms; jittered following a gamma distribution; Figure 1). The parameters of this modified SST are identical to those used in the previous IC training study using a similar task (Berkman et al., 2014) except for the jittered duration of the cue phase, an additional element included to reduce multicollinearity between this and other phases of the task, optimizing our ability to examine hypotheses about training-related

changes during the cue phase. Participants completed two runs at each of the baseline and endpoint assessments (192 go trials, 64 stop trials, ~13 mins). SSRT and Go reaction time (GoRT) were calculated individually for each run, and values were averaged across runs for baseline and endpoint assessments of IC and sustained attention during the SST, respectively.

Active Control Task: Modified Stop Signal Task without Sound

The active control task was identical to the training task as described above except without the auditory stop cue (i.e., no stop trials); as such, this task was essentially a forced choice reaction time task requiring sustained attention but no IC. In this way, the task provided a tight control by being identical visually and temporally to the training task while also providing no training on IC. The similarity between the two tasks also allowed made it difficult for participants to know if they were assigned to the training or active control group, thus reducing potential associated bias.

Training Sessions

Participants completed 10-14 training sessions consisting of one run of the training task (96 go trials, 32 stop trials, ~6.5 mins) or the active control task (128 go trials, 0 stop trials, ~6.5 mins). Adolescent faces used in the training and active control tasks were presented in a random order during each training session and were distinct from those used in both the baseline and endpoint assessments.

'Near' Transfer Measure: Modified Go/No-Go Task

A modified version of a standard Go/No-Go task served as a measure of 'near' transfer effects of IC training and was administered at the baseline and endpoint assessments in order to assess potential performance change over time. The Go/No-Go is a well-validated measure of response inhibition, the underlying neural circuitry of which both overlaps with and is distinct

from that of the SST (Swick et al., 2011). Participants are instructed to respond with a button press to a designated 'Go' stimulus and to withhold the button press to a designated 'No-go' stimulus. In our modified version of the Go/No-Go, the same adolescent face stimuli used in the cue phase of the modified SST were used as the Go and No-Go stimuli in the Go/No-Go task to maximize the similarity of cues used across tasks and increase the likelihood of transfer. Each run of the task consisted of 5 blocks of 50 trials per block. In each block, participants were instructed to press a button based on the gender of the adolescent face cue, with the gender used as the 'Go' stimulus versus the 'No-Go' stimulus alternating across blocks to avoid ceiling effects. Trial length was jittered such that the duration of the stimuli presentation followed by a cross-hair after participant response (when applicable) lasted for an average of 1333ms (range = 1167ms to 1500ms). Participants completed two runs at each of the baseline and endpoint assessments (202-203 Go trials, 47-48 No-Go trials, ~12 mins). Mean accuracy on NoGo trials and Go trials (i.e., number of correct trials / number of total trials) and go reaction time (GoRT) were calculated for each run and then averaged across runs for baseline and endpoint assessments of IC and sustained attention during the Go/No-Go, respectively.

Procedure

At the baseline assessment, participants' parents provided informed consent for their adolescent to participate, and the adolescent provided assent to participate. Participants then completed practice versions of all tasks within a mock MRI scanner. Prior to entering the scanner, participants were checked for MRI safety by a qualified MRI technician. The scan session included acquisition of a high-resolution structural scan, a field map, and two functional runs each of four tasks (the modified SST, the modified Go/No-Go, and two other tasks not reported here). The order of the modified SST, the modified Go/No-Go, and one of the other

tasks was counter-balanced across participants, while the fourth task was always presented last. After the scan session, participants completed a set of computer-based questionnaires. At the end of the baseline session, the participants were randomly assigned to either the training group or the active control group. Over the course of the next 4 to 5 weeks, participants completed 10-14 sessions of either the training or active control task at school during scheduled break times on laptops provided by the research team. After completing at least 10 training sessions, participants returned for an endpoint assessment identical to the baseline assessment except for the omission of the mock scanner session.

Questionnaires

Questionnaires measuring trait moderators, which were not expected to change as a result of the IC training, were administered once (e.g., sociodemographic risk, early adversity experiences), whereas those measuring constructs hypothesized to be impacted by the IC training as a result of 'far' transfer effects were measured at both sessions (e.g., risk-taking behavior). To maximize use of available data, total scores were calculated and proportionally weighted based on the number of total items on which a participant had data.

Early life stress – Adverse Childhood Experiences Survey. To assess experiences of early adversity often associated with negative outcomes, the Adverse Childhood Experiences Study Family Health History Questionnaire (ACES; Felitti et al., 1998) was administered. The ACES questionnaire measures a range of adverse childhood experiences including parental separation, parental substance use, neglect, and abuse. ACES coding was performed consistent with practices in the literature (Dube et al., 2003). Three participants did not complete the ACES questionnaire. These participants were included in analyses investigating overall training effectiveness and excluded from moderator analyses.

Early life stress – Cumulative risk. Consistent with commonly used cumulative risk approaches to assess early life stress and sociodemographic risk (Evans, Li, & Whipple, 2013), a cumulative risk variable was calculated from four available sociodemographic risk variables: maternal education, household density, perceived financial stress, and household instability. Each of these four individual risk variables was dichotomized (0 = no risk, 1 = risk) based on typical cut-offs and conceptualizations of risk (i.e., completed some high school or less, more household inhabitants than rooms, just enough or not enough money to get by, and three or more lifetime moves, respectively).

Risk-taking behavior. The Youth Risk Behavior Survey (YRBS; Centers for Disease Control and Prevention, 2014) and the Risk Behavior and Deviant Peer Association Scale (PAL-2; Stormshak et al., 2011) were used to measure risk-taking behaviors across domains. To investigate potential 'far' transfer effects of IC training on risk-taking behavior, variables across the two questionnaires specifically assessing risk-taking behaviors across the last 30 days were combined into baseline and endpoint composite risk variables (e.g., carried a weapon, used alcohol, cut class, attended a party, lied to parents, etc.). One participant did not complete the YRBS at baseline; three participants did not complete the PAL-2 at baseline. These participants were included for overall training effectiveness analyses but excluded from far transfer analyses. A composite measure of deviant peer association was also calculated for baseline and endpoint based on relevant questions from the PAL-2 (e.g., hanging out with friends who got into fights, stole, smoked, used alcohol or drugs, were suspended from or dropped out of school, etc.).

fMRI data collection

fMRI data were acquired using a 3T Siemens Skyra scanner. Functional scans were acquired using a multi-band accelerated EPI sequence (CMRR, University of Minnesota;

repetition time [TR] = 2000 ms, echo time [TE] = 27ms, flip angle = 90, matrix size = 100 x 100, 72 slices, field of view = 200 mm, slice thickness = 2mm). A high-resolution structural T1-weighted MP-RAGE pulse sequence (TR = 2500ms, TE = 3.41ms, inversion time = 1100ms, flip angle = 7, matrix size = 256 x 256, 176 slices, voxel size = 1 mm^3, field of view = 256 mm, slice thickness = 1 mm) was acquired for each participant to be used for coregistration and construction of a study-specific template for normalization. A double-echo gradient echo sequence (TR = 639ms, TE1 = 4.37, TE2 = 6.83, flip angle = 60, matrix size = 100 x 100, field of view = 200 mm, 72 slices, slice thickness = 2mm) was also acquired for each participant to be used to correct for magnetic field inhomogeneities present during the scan session.

fMRI preprocessing and analysis

Neuroimaging data were preprocessed using a combination of FSL and SPM12. All DICOMs were converted to NifTi format using MRIConvert. Structural scans were coregistered iteratively to the MNI template using 7 diminishing sampling distances, segmented for grey matter, white matter, and cerebrospinal fluid, and skull stripped using FSL's Brain Extraction Tool (BET). A study-specific template was constructed from the tissue probability maps obtained through segmentation using DARTEL. Baseline structural scans were used for the construction of the DARTEL template for all but one participant whose baseline structural scan evidenced motion; this participant's endpoint structural scan was used in DARTEL template construction. Field map phase and magnitude images were constructed from the double-echo gradient sequence using FSL. Two participants were missing a fieldmap for one scan session; an averaged fieldmap from all participants was created for each timepoint to be used with those participants who were missing a fieldmap at a given session. Functional images were realigned with one another, unwarped using the constructed fieldmaps to correct for field inhomogeneities,

skull-stripped using BET, coregistered to each participant's own structural, and normalized and smoothed using the study-specific template and a 4 mm^3 FWHM Gaussian kernel.

Following preprocessing, statistical analyses were conducted in SPM12. For each participant, the general linear model was used to estimate event-related condition effects using a canonical hemodynamic response function, a 128s high-pass filter, and a first-order autoregressive error structure. At the single-subject level, a fixed effects analysis was used to model BOLD signal with separate regressors corresponding to each condition of interest (i.e., for the SST: Correct Go trials, Correct Stop trials, Failed Stop trials, Cue phase; for the Go/No-Go: Correct Go trials, Correct No-Go trials, Failed No-Go trials, Instructions). To correct for motion, additional regressors of no interest were added at the single-subject level for Euclidian composite scores of X, Y, Z translation and pitch, roll, yaw rotation, and the first derivative of each derived from the output of the realignment process for each run. An additional motion regressor of no interest was added to indicate volumes in which significant motion was detected based on differences in mean global intensity and standard deviation from volume to volume (for SST runs: range of 0 to 41 volumes per run; range of 0 to 25.75 average volumes per subject across runs; for Go/No-Go runs: range of 0 to 31 volumes per run; range of 0 to 13.25 average volumes per subject across runs). Linear contrasts were created for each comparison of interest (i.e., for the SST: Correct Stop > Correct Go, Failed Stop > Correct Go, Cue > Rest; for the Go/No-Go: Correct NoGo > Correct Go, Failed NoGo > Correct Go), and these contrasts were imported to group-level random effects analyses for inference to the population. Age was entered as a covariate in all group-level models, and ACES and cumulative risk were entered as centered potential moderators when appropriate. MarsBaR was used to extract parameter estimates for significant clusters present in group-level models.

One participant (active control) did not have sufficient Correct Stop trials to model at the single-subject level across the two runs of the endpoint scan; this participant was excluded for repeated measures analyses of the Correct Stop > Correct Go contrast. One additional participant did not have any Correct Stop trials on the first run at each timepoint. Thus, these runs were not included in the neuroimaging or behavioral analyses. For the Go/No-Go, one participant (training) did not have usable behavioral data for the two runs of the baseline scan and was thus not included in the Go/No-Go behavioral or neuroimaging analyses.

Analysis plan

Behavioral and questionnaire data processing. Behavioral and questionnaire data were analyzed in SPSS and examined for normality and the presence of outliers. Data points above or below 2.5 times the median absolute deviation were classified as outliers (Leys, Ley, Klein, Bernard, & Licata, 2013) and winsorized to the next highest value within range, preserving rank order. For IVs not hypothesized to be impacted by the IC training (i.e., ACES, cumulative risk), outliers were winsorized based on the whole sample. For DVs hypothesized to be impacted by the training (i.e., behavioral measures of SST and Go/No-Go, risk-taking), outliers were winsorized within experimental group.

SST runs were excluded for inadequate performance if more than 33% of trials in a given run were invalid (i.e., failure to respond on a go trial), if fewer than 66% of go trial responses were correct, if SSRT was less than 50 ms, if Go RT was less than 100 ms or greater than 2000 ms, or if the percentage of correct inhibition trials was less than 12.5 (Schachar, Levin, Max, Purvis, & Chen, 2004). A total of 8 runs were excluded due to inadequate accuracy (n=2) or inhibition performance (n=6). Five outliers [n=1 (training) for SSRT at baseline, n=1 (training)

for SSRT at endpoint, n=1 GoRT (control) at baseline, n=2 GoRT (training, control) at endpoint] were winsorized.

Go/No-Go runs were excluded for inadequate performance if participants had < 50% Go trial accuracy (Lock, Garrett, Beenhakker, & Reiss, 2011). One participant (training) had inadequate accuracy on both baseline runs necessitating exclusion. Ten outliers [n=4 (2 training, 2 control) for Go Accuracy at baseline, n=3 (1 training, 2 control) for Go Accuracy at endpoint, n=1 (control) for NoGo Accuracy at baseline, n=1 (training) for Go RT at baseline, and n=1 (control) for Go RT at endpoint] were winsorized.

One outlier (training) within the ACES variable and two outliers (1 training, 1 control) across the risk-taking variables were winsorized.

Behavioral data analysis. Repeated measures analyses using the GLM were conducted to predict training-related changes in SSRT and GoRT over time, training-related changes in NoGo Accuracy, Go Accuracy, and GoRT on the Go/No-Go task over time, and training-related changes in self-reported risk-taking behavior and deviant peer association over time. ACES and cumulative risk (mean-centered) were investigated as moderators of training-related changes in SSRT (i.e., SSRT percent change) using the PROCESS macro in SPSS.

fMRI data analysis. Group-level models were constructed to examine the group × time interaction on neural activation during successful IC (Correct Stop > Correct Go contrast), failed IC (Failed Stop > Correct Go), and IC preparation (Cue > Rest) and on neural activation during successful IC (Correct NoGo > Correct Go) and failed IC (Failed NoGo > Correct Go) on the Go/No-Go task. ACES and cumulative risk were examined as moderators of training-related changes in brain activation during the Correct Stop > Correct Go, Failed Stop > Correct Go, and the Cue > Rest contrasts.

We utilized the Analysis of Functional NeuroImages (AFNI) 3dClustSim function with the –acf (spatial autocorrelation function) option to determine appropriate cluster-extent thresholds that maintained a family-wise error rate of alpha < .05 with a voxel-wise threshold of $p < .005$, separate for each statistical model. Values of intrinsic smoothness required by 3dClustSim were calculated using individual subject residuals derived from each group-level model. This 3dClustSim procedure yielded minimum cluster extents ranging from 81 to 119 voxels (each 2x2x2mm in volume) for the SST and from 94 to 104 voxels (each 2x2x2mm in volume) for the Go/No-Go. All clusters surviving correction are displayed on an averaged image of all participants' smoothed, normalized structural images.

Results

Preliminary Analyses

Descriptive statistics for demographics, early life stress, task behavioral performance, and risk-taking variables across the entire sample and split by group are presented in Table 1. There were no significant baseline differences on gender, ACES, cumulative risk, SST performance, or total number of risk-taking behavior categories endorsed. Significant baseline group differences did exist in terms of age, $t(17) = -2.8$, $p = .012$ and NoGo Accuracy on the Go/No-Go, $t(17) = -2.21$, $p = .041$, with the training group being significantly older and demonstrating significantly greater NoGo Accuracy at baseline compared to the active control group. Given this significant difference in age between the training and active control groups, age was used as a covariate in all subsequent analyses unless otherwise noted.

Effectiveness of IC training

Behavioral effects of IC training. The group × time interaction on SSRT was our primary measure of the behavioral effectiveness of IC training. This interaction was not

significant, $F(1,15) = .977$, $p = .339$, $\eta_p^2 = .061$, though it was in the expected direction (Figure 2d). Simple effects revealed that the training group improved significantly over time on SSRT, $F(1,15) = 10.489$, $p = .006$, $\eta_p^2 = .41$, while the active control group did not, $F(1,15) = 1.487$, $p = .241$, $\eta_p^2 = .09$. Age was not significantly related to SSRT at baseline ($r(18) = -.321$, $p = .194$), SSRT at endpoint ($r(18) = -.389$, $p = .111$), or SSRT % change ($r(18) = -.197$, $p = .434$), so we also examined the group × time interaction without age as a covariate and found a similar pattern of results.

The group × time interaction on GoRT, $F(1,15) = .848$, $p = .372$, $\eta_p^2 = .053$, was not significant. Simple effects revealed that GoRT significantly decreased from baseline to endpoint within the training group, $F(1,15) = 5.909$, $p = .028$, $\eta_p^2 = .28$ while the decrease over time in GoRT in the active control group was not significant, $F(1,15) = .442$, $p = .516$, $\eta_p^2 = .03$.

Given the significant age difference between groups at baseline, we also conducted exploratory post-hoc analyses investigating the main effect of age and the presence of an age × condition interaction on SSRT and GoRT at endpoint. Neither a main effect of age nor an age × condition interaction emerged for SSRT or GoRT at endpoint (all ps > .49).

Neural effects of IC training over time on IC implementation. In the Correct Stop > Correct Go contrast, the training group demonstrated increased activation across time compared to the active control group in left occipitotemporal cortex ($k = 259$, [-46 -76 -6]), a region typically associated with visual attention (Figure 2a; Table 2). Examination of simple effects within each group demonstrated no significant changes in activation across time within the training group, and decreases in activation over time in a number of temporal, occipital, and cerebellar regions in the control group, suggesting that the group × time effect was largely driven by these activation decreases in the control group.

Given the high variability in performance in this sample compared to previous work with adults, we also examined the Failed Stop > Correct Go contrast (Figure 2b, Table 2). The group × time interaction in this contrast revealed significant clusters in the left (k=320, [-34 50 18]) and right (k = 136, [36 44 24]) lateral prefrontal cortex spanning the middle and superior frontal gyri that increased in the training group relative to the active control group from baseline to endpoint (Figure 2b). Simple effects revealed that this interaction was largely driven by increases in the left (k=300, [-34 52 22]) and right (k=153, [32 48 28]) middle and superior frontal gyri in the training group over time.

Neural effects of IC training over time on IC preparation. During the cue phase, the training group showed increased activation compared to the active control group over time in the cerebellum (k=108, [0 -60 -38]) and hippocampus extending into parahippocampal gyrus (k=97, [16 -26 -18]; Figure 2c; Table 3). Simple effects revealed that this interaction was driven by increases in activation in the cerebellum (k=91, [4 -54 -10]) in the training group over time.

Training Transfer Effects

Behavioral 'near' transfer effects of IC training over time. The group × time interaction on NoGo Accuracy was not significant, $F(1,16) = .389$, $p = .373$, $\eta_p^2 = .05$, and was also in the opposite direction of our predictions (i.e., the training group appeared to have greater decrements in NoGo Accuracy over time compared to the active control group; Figure 3c). Simple effects revealed that NoGo Accuracy declined significantly in the training group, $F(1,16) = 7.316$, $p = .016$, $\eta_p^2 = .31$, but not in the active control group, $F(1,16) = 1.024$, $p = .327$, $\eta_p^2 = .06$. These results should be interpreted in light of the significant baseline group difference in NoGo Accuracy and may indicate regression to the mean.

The group × time interaction on Go Accuracy was not significant, $F(1,16) = .7$, $p = .415$, $\eta_p^2 = .042$. Simple effects revealed a significant decrease in Go Accuracy over time in both the training group, $F(1,16) = 17.824$, $p = .001$, $\eta_p^2 = .53$, and the active control group, $F(1,16) = 5.916$, $p = .027$, $\eta_p^2 = .27$, (Figure 3d), with both groups maintaining at least 94% Go Accuracy at endpoint.

For GoRT during the Go/No-Go task, the group × time interaction was not significant, $F(1,16) = .033$, $p = .859$, $\eta_p^2 = .002$. The simple effects of time within the training group, $F(1,16) = .432$, $p = .52$, $\eta_p^2 = .03$, and within the active control group, $F(1,16) = .094$, $p = .763$, $\eta_p^2 = .01$, on GoRT were also non-significant.

To further examine the extent to which changes in Go/No-Go task performance may be associated with training, partial correlations were examined between percent change in SSRT and percent change in NoGo Accuracy, Go Accuracy, and Go RT, controlling for age. SSRT percent change was not significantly correlated with any of the Go/No-Go task performance indices (all rs < .15, all ps > .6).

Neural 'near' transfer effects of IC training over time. During successful IC implementation in the Go/No-Go task (Correct NoGo > Correct Go), the training group demonstrated significantly greater activation in right cuneus (k=425, [16, -70, 42]) and angular gyrus (k=154, [40, -74, 42]) compared to the active control group across time (Figure 3a; Table 4). Simple effects within each group suggested that these group × time interaction effects were driven by both increases in right cuneus (k=138, [16, -70, 42]) in the training group over time, as well as decreases in the precuneus (k=196, [-2, -58, 42]) in the active control group over time. To further examine the extent to which these changes in neural activation during the Go/No-Go may be related to neural changes in the training group during the trained SST task, the association

between parameter estimates from the cuneus and angular gyrus clusters from the group × time interaction during Go/No-Go successful IC and those from the left occipitotemporal cluster from the group × time interaction during SST successful IC were examined, controlling for age. The left occipitotemporal cluster was significantly positively correlated with both the cuneus, $r(15) = .678$, $p = .003$, and the angular gyrus, $r(15) = .6$, $p = .011$, clusters.

Neural activation during failed IC implementation (i.e., Failed No Go > Correct Go contrast) was also examined for potential transfer effects (Figure 3b; Table 4). The training group showed significantly greater activation in left angular gyrus (k=145, [-40, -64, 42]), a region increasingly recognized for its role in the integration of multisensory information to influence attentional processes (Seghier, 2013), from baseline to endpoint compared to the active control group. Examination of simple effects revealed that these differences were largely driven by decreases in activation in the active control group over time in the left angular gyrus (k=145, [-40, -64, 42]), as well as a number of frontal regions including right superior frontal gyrus, (k=255, [8, 48, 42]) and left superior (k=146, [-18, 36, 36]), and middle (k=143, [-38, 12, 44]) frontal gyri. To further investigate the extent to which neural changes over time during failed IC in the Go/No-Go task may relate to those in the trained SST, partial correlations between parameter estimates of the middle frontal gyrus cluster from the group × time interaction during failed IC on the SST and those of the left angular gyrus cluster found for the group × time interaction during failed IC on the Go/No-Go were examined. Changes in activation in the training compared to the control group related to failed IC during the Go/No-Go task in the left angular gyrus cluster demonstrated a marginally significant positive association with those in the SST-related middle frontal gyrus cluster, $r(16) = .41$, $p = .091$.

Behavioral 'far' transfer effects of IC training over time on risk-taking behavior. The group × time interaction on change in the total number of risk-taking behaviors was not significant, $F(1,14) = .472$, $p = .503$, $\eta_p^2 = .033$, and the direction of observed effects was in fact opposite of what we had hypothesized (i.e., the training group appeared to show an increase in risk-taking behaviors over time compared to the control group). Simple effects analyses demonstrated that the effect of time was not significant in either the training group, $F(1,14) = .986$, $p = .337$, $\eta_p^2 = .07$, or the control group, $F(1,14) = .014$, $p = .907$, $\eta_p^2 = .001$.

Given the incorporation of adolescent face cues in our IC training to attempt to associate IC with peer contexts, we also examined the group × time interaction effects on the change in number of deviant peer associations participants endorsed. This group × time interaction was significant, $F(1,12) = 5.261$, $p = .041$, $\eta_p^2 = .305$, and, similar to the non-significant effects on total risk behaviors reported above, the direction of observed effects was opposite of what we had hypothesized (i.e., the training group showed an increase in risk-taking behaviors over time, while the control group showed a decrease). Simple effects analyses demonstrated that the increase in deviant peer associations over time in the training group was not significant, $F(1,12) = 2.34$, $p = .152$, $\eta_p^2 = .16$, and the decrease in deviant associations over time in the control group was marginally significant, $F(1,12) = 4.038$, $p = .068$, $\eta_p^2 = .25$.

Moderation of IC Training Effectiveness by Early Life Stress

Behaviorally, both ACES and cumulative risk were examined as potential moderators of IC training effectiveness in a moderation model predicting SSRT percent change from group membership (training vs. control), controlling for age, with more negative SSRT percent change indicating a greater improvement in IC over time. In this model, neither training group membership, $\beta = -9.671$, $SE = 8.17$, $t(11) = -1.18$, $p = .262$, nor ACES, $\beta = -4.318$, $t(11) = -.899$,

p = .388, or the interaction of ACES and group, β = 9.932, $t(11) = 1.29$, p = .223, were significant predictors, indicating that ACES did not moderate the training effect. For cumulative risk, no predictors in the model were significant (all ts < 1.5).

Neurally, potential moderation of training effects was investigated by incorporating ACES and cumulative risk as covariates in the group × time models of IC implementation and preparation. For models of successful IC implementation and failed IC implementation, no clusters survived correction for either the models incorporating ACES or those incorporating cumulative risk. For models of IC preparation, the control group demonstrated significant associations between ACES and changes in brain activation over time in a number of occipital and parietal regions as well as cerebellum (Figure 4; Table 5). To decompose this moderation effect, parameter estimates were extracted from the occipital cortex cluster and plotted with ACES by group, demonstrating a stronger association between changes in occipital cortex activation during the Cue phase and ACES in the control group compared to the training group (Figure 4). The control group also showed a stronger association between cumulative risk and changes in activation in the left superior parietal lobule (k=96, [-22, -44, 68]) over time compared to the training group.

Discussion

This pilot study examined the effectiveness of a brief, computerized IC training intervention delivered in the classroom to a group of adolescents recruited from a low-income school district. This study represents a step toward the translational neuroscience goal of identifying cost-effective, potentially scalable interventions grounded in neuroscientific evidence that target key neurocognitive skills such as IC (Fisher & Berkman, 2015). Previous research in adults found behavioral improvement in IC with training, and we expected that adolescents

might show even greater change given the increasingly recognized neural plasticity characterizing this developmental stage (Fuhrmann et al., 2015; Spear, 2013; Sisk & Zehr, 2005; Dahl et al., 2018) and the adolescent-relevant cues incorporated in our IC training task. Surprisingly, adolescents who received the IC training did not show significant behavioral improvement in IC ability compared to those in the active control group. However, the effect was in the expected direction, and simple effects tests suggest that IC ability was impacted in the training group, but not in the active control group, in this small sample. In contrast to the behavioral results, neuroimaging analyses revealed significant changes in task-related neural activation over time between the two groups during both IC implementation and IC preparation. This divergence between behavioral and neural results highlights the utility of employing both neuroimaging and behavioral measures in intervention studies to allow for examination of neural mechanisms that may account for the lack of behavioral differences and identify strategies (e.g., increase in dosage, different intervention targets) to increase intervention effectiveness. For example, as described in more detail below, the pattern of neural results associated with this IC training suggest targeting attention directly may be an impactful intervention strategy.

The IC training altered task-related neural activation during both IC implementation and preparation. Neural changes associated with IC training during successful IC implementation in occipital and temporal regions often implicated in visual attention were driven by decreases in activation across time in the control group. This pattern suggests that the training group may have maintained attention on the task over time more so than the active control group. Given the relatively non-demanding nature of the active control task, it is also possible that the control group did not find the task to be sufficiently engaging and failed to attend to the task consistently, thus making the active control condition less of an ‘active’ control. The changes in

activation during IC implementation here differ from those found in previous work in adults, in which training-related changes were found only during IC preparation (Berkman et al., 2014). The present result suggests that IC training in adolescents may have a direct impact on neural activity during IC implementation, potentially due to the high salience of the adolescent face cues utilized in this study. During failed IC implementation, the training group showed increases over time compared to the active control group in bilateral middle frontal gyrus. These changes are consistent with the idea that changes in attention drove the observed training effects: training resulted in greater engagement of the attention network (e.g., superior and middle frontal gyri) specifically in response to IC errors.

Interestingly, training increased activation during IC preparation in cerebellum and hippocampus, associated with motor control and memory, in the training group and decreased activation in temporal and occipital regions, often associated with visual attention, in the control group. This pattern of results contrasts with previous work in adults that found increases in IC network region activation during IC preparation (Berkman et al., 2014). These results were unexpected so we interpret them with caution, but they may suggest changes related to sustained attention as a potential critical mechanism of IC training effects in adolescents.

The lack of strong behavioral effects of IC training in this sample may be due to multiple factors. The pilot sample size may preclude identification of small to moderate effects of IC training, and there was substantial variability in task performance compared to adult samples. Despite randomization and a relatively tight recruitment age range, there was also a significant baseline difference in age between the groups. Given evidence that older adolescents may be particularly sensitive to cognitive training (Knoll, Fuhrman, Sakhardande, Stamp, Speekenbrink, & Blakemore, 2016), we tested, though did not confirm, the presence of an age × condition

interaction on IC measures at endpoint. Interestingly, age was not significantly associated with any measures of change in IC over time, somewhat mitigating concern about the baseline group age difference. It is possible that the classroom setting reduced the signal-to-noise ratio of training effects given the distractions of this environment compared to the laboratory. Also, the importance of motivational factors in cognitive training has recently been noted (Beauchamp et al., 2016; Berkman, 2016). Although we sought to increase the salience of the IC training task through the incorporation of adolescent face cues, our task may not have been sufficiently engaging to motivate the adolescents.

Alternatively, these weak effects of training could suggest that the training is simply not effective. Though this training was theoretically informed and based on a previous version shown to be effective in an undergraduate sample, it is possible that effects do not generalize beyond the initial sample tested in a laboratory setting. This training could be ineffective in adolescents, populations with higher levels of risk, and/or when administered in less-controlled environments. Given the design employed in the present study, it is difficult to determine which of these factors individually or in combination could have contributed to the weak effects. Future work in larger adolescent samples with a range of risk exposure is needed to determine the extent to which this training may or may not be effective.

In terms of transfer effects, we hypothesized that the IC training would transfer to an untrained IC task (a modified Go/No-Go) because of the overlapping neural circuitry recruited by the IC tasks and because the same adolescent face cues were used across the tasks. Given that the IC training did not demonstrate significant increases in IC ability in the training compared to the control group over time in this sample, we did not expect to see robust transfer effects. Indeed, the training group did not demonstrate significant changes in performance on the Go/No-

Go compared to controls over time. In fact, simple effects revealed that the training group exhibited significantly worse NoGo performance on the Go/No-Go over time, and both groups showed significantly worse Go performance over time. Interestingly, percent change in SSRT, an indicator of training effectiveness, was not related to percent change in any of the Go/No-Go performance indices, suggesting that Go/No-Go effects may be better accounted for by another factor (e.g., regression to the mean) rather than by effects of the IC training.

Neural 'near' transfer analyses revealed a set of regions showing increases in activation over time in the training group compared to the control group for the Go/No-Go during successful and failed IC implementation that was distinct from those seen during the SST. Specifically, the training group showed increases in activation in the cuneus during successful IC implementation over time compared to the active control group, which appeared to be driven by increases in this region in the training group over time, and decreases in activation in the left angular gyrus during failed IC implementation, driven by decreases in the control group over time. The cuneus is often implicated in visual processing; maintained activation in this region in the training group is consistent with increases in sustained attention and task engagement associated with training. Maintained activation in the angular gyrus over time in the training group compared to control is also consistent with this account given that this region has been associated with multisensory integration in attention processing (Seghier, 2013). Interestingly, activation in these regions was significantly correlated with the activation in left occipitotemporal cortex found during IC implementation in the SST, providing some support for shared mechanisms of IC implementation across these tasks, specifically in the training group compared to the control across time. Though we interpret these neural effects with caution given the weak training effects and lack of behavioral differences in Go/No-Go performance across

groups, these findings appear to be broadly consistent with an attention-based account of training effects in this group of adolescents.

We also examined the potential for 'far' transfer effects from the IC training to real-world risk-taking behavior. Again, given the lack of strong evidence for training effectiveness in this sample, we did not expect to find evidence for training 'far' transfer. Consistent with this expectation, there were no group differences in trajectories of risk-taking behaviors. However, deviant peer associations significantly decreased over time in the control group compared to the training group, contrary to hypotheses. These results should be interpreted in light of the marginally significant group difference at baseline in deviant peer associations with the control group reporting more. Of note, though deviant peer association was assessed, the extent to which adolescents engaged in the risk-taking behaviors specifically with peers was not; future iterations of this peer-oriented IC training should incorporate measurements of risk-taking with peers specifically.

We found no evidence for moderation of IC training effects in terms of SSRT; however, significant neural effects did emerge such that increases in activation across time in the occipital cortex during IC preparation were more strongly associated with ACES in the control group compared to the training group. Though these results are difficult to interpret given the absence of training related changes in this region, they highlight the additional information afforded by neuroimaging methodology that may be able to be incorporated into more nuanced accounts of IC training effects for specific sets of individuals, particularly in future implementations of this IC training with larger sample sizes.

These results suggest exciting future directions for the continued refinement of this IC training approach. Future iterations of this IC training task could attempt to further increase the

salience of the adolescent face cues by using images of actual peers, personalized for each individual, to more directly investigate this potential mechanism of training effectiveness. From a motivational perspective, increasing adolescent buy-in to engage in the task could be another pathway to increase compliance with the training sessions and effectiveness of the training itself. Given the high salience of the social environment, a more socially-oriented implementation of the training in which adolescents compete with one another over the course of the training could increase engagement and potentially prime the social context during IC training in a more readily scalable way. Future work can also consider the extent to which the effectiveness of this computerized IC training may be increased by combining it with other non-computerized interventions that incorporate a broader set of intervention targets. For instance, combining this IC training with school curricula that embed training of executive functions like IC within activities that also incorporate the development of social-emotional skills (Diamond & Lee, 2011) or with parenting interventions such as Triple P (Sanders, 2008) and Parent Management Training – Oregon (Forgatch & Kjøbli, 2016) that have been shown to impact externalizing behaviors may be a promising strategy to increase its impact.

This pilot study was limited by its small sample size. However, this limitation is offset somewhat by the repeated measures design, which allows for greater statistical power to test IC training effects within the context of the group × time interaction compared to strictly between-groups comparisons. The decision to allow special education teachers to nominate potential participants based on teachers' perceptions of the students' impulse control abilities reflected our intention to provide the IC training to those students who might most benefit. Future research would benefit from quantifying this selection criterion to include a measure of impulse control. Since impulse control more broadly, as opposed to ADHD specifically, was the focus of our

study, we chose to not gather ADHD diagnostic information in order to protect the privacy of our participants' mental health status. Future work could characterize the extent to which ADHD status may moderate intervention effects. As noted, administering IC training in the classroom resulted in a high level of variability and potential for distraction during training sessions. This limitation is inherent in the tradeoff between ecological validity and experimental control. Delivering the intervention in a school setting is far more ecologically valid and scalable than lab-based interventions. As such, this study is an initial step towards the translational neuroscience goal of identifying cost-effective interventions that target key neurocognitive skills like IC and are deliverable at scale.

In conclusion, we found a divergence between behavioral and neural measures of IC training-related change in adolescents. There was limited evidence for behavioral change in IC following training, but there were changes in functional neural activation in both training and control groups over time. In contrast with previous IC training work in adults, the neural results reported here suggest that IC training may impact the adolescent brain through an attention mechanism. Future work can identify ways to increase the effectiveness of this IC training to change adolescent IC behavior, such as increasing the motivational salience of the training task and optimizing the training administration environment. The current work provides an important first step in examining the effects of an ecologically-valid IC training on adolescent brain activity and implies next steps for leveraging that plasticity for positive change.

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Table 1.

Descriptive statistics and baseline group comparisons for demographic, early life stress, behavioral performance, and risk-taking data across time for entire sample and by group

	Entire Sample	N	Training Group	N	Control Group	N	Diff
Demographics							
Age (years)	16.20 (.88)	19	16.62 (.85)	11	15.64 (.59)	8	$p = .012$
Gender (% male)	52.6%	19	63.6%	11	37.5%	8	ns
Ethnicity (% white)	60%	19	55%	11	75%	8	ns
Adverse Childhood Experiences (ACEs)	1.86 (1.06)	17	1.95 (.81)	9	1.75 (1.33)	8	ns
Cumulative Risk	1.56 (1.30)	19	1.82 (1.47)	11	1.21 (.99)	8	ns
SST Performance							
SSRT (ms)							
Baseline	283.30 (85.66)	18	258.27 (45.11)	11	322.65 (120.18)	7	ns
Endpoint	243.92 (81.60)	18	210 (35.76)	11	297.23 (106.35)	7	-
GoRT (ms)							
Baseline	590.64 (85.38)	18	583.78 (74.35)	11	601.43 (105.91)	7	ns
Endpoint	539.18 (53.00)	18	529.18 (60.73)	11	554.89 (36.61)	7	-
GNG Performance							
No Go Accuracy (%)							
Baseline	72.34 (.10)	19	75.81 (.08)	11	67.56 (.07)	8	$p = .041$
Endpoint	63.12 (.13)	19	63.06 (.13)	11	63.19 (.14)	8	-
Go Accuracy (%)							
Baseline	98.31 (.01)	19	98.27 (.01)	11	98.36 (.01)	8	ns
Endpoint	95.25 (.03)	19	95.26 (.03)	11	95.24 (.03)	8	-
GoRT (ms)							
Baseline	511.41 (47.48)	19	507.97 (29.28)	11	513.55 (57.49)	8	ns
Endpoint	521.71 (56.43)	19	527.05 (36.78)	11	513.57 (54.23)	8	-
Risk-taking Behavior							
Total risk-taking							
Baseline	2.49 (2.35)	17	1.59 (1.06)	10	3.27 (3.26)	7	ns
Endpoint	2.59 (2.07)	19	2.11 (1.65)	11	3.13 (2.53)	8	-
Deviant Peer Association							
Baseline	3.09 (3.44)	16	1.67 (1.99)	10	5.5 (4.42)	6	$p = .086$
Endpoint	2.81 (2.92)	18	2.15 (2.04)	10	3.5 (3.74)	8	-

Table 2.

MNI coordinates, k values, and statistics for significant clusters in IC implementation models

	Anatomical region	*k*	*t*	*x*	*y*	*z*
Correct Stop > Correct Go						
Training > Control, Endpoint > Baseline	L occipototemporal cortex	259	5.629	-46	-78	-6
			4.754	-48	-48	-16
Control > Training, Endpoint > Baseline	-	-	-	-	-	-
Training, Endpoint > Baseline	-	-	-	-	-	-
Training, Baseline > Endpoint	-	-	-	-	-	-
Control, Endpoint > Baseline	-	-	-	-	-	-
Control, Baseline > Endpoint	R cerebellum	287	5.866	8	-52	0
			5.469	10	-76	-8
			3.324	28	-58	0
	L fusiform gyrus	245	5.311	-38	-78	-10
			3.715	-20	-64	-8
	L precuneus	236	5.454	12	-76	20
			3.550	0	-62	28
	L middle occipital gyrus	182	5.991	-30	-86	18
	L superior medial gyrus	125	4.550	2	58	32
	R middle temporal gyrus	110	5.603	58	-38	-6
Failed Stop > Correct Go						
Training > Control, Endpoint > Baseline	L middle frontal gyrus	320	5.829	-34	50	18
	R middle frontal gyrus	166	4.729	36	44	24
			3.544	22	58	18
Control > Training, Endpoint > Baseline	-	-	-	-	-	-
Training, Endpoint > Baseline	L middle frontal gyrus	300	6.896	-34	52	22
	R middle frontal gyrus	153	6.028	32	48	28
Training, Baseline > Endpoint	-	-	-	-	-	-
Control, Endpoint > Baseline	-	-	-	-	-	-
Control, Baseline > Endpoint	-	-	-	-	-	-

Note: Corrected using 3dClustSim with acf; voxelwise threshold of $p > .005$, cluster size k > 107 for Correct Stop > Correct Go contrast and k > 114 for Failed Stop > Correct Go contrast

Table 3.

MNI coordinates, k values, and statistics for significant clusters for IC preparation model

	Anatomical region	*k*	*t*	*x*	*y*	*z*
Cue > Rest						
Training > Control, Endpoint > Baseline	Cerebellum	108	5.636	0	-60	-38
	Hippocampus	97	5.132	16	-26	-18
Control > Training, Endpoint > Baseline	-	-	-	-	-	-
Training, Endpoint > Baseline	Cerebellum	91	6.268	4	-54	-10
Training, Baseline > Endpoint	-	-	-	-	-	-
Control, Endpoint > Baseline	-	-	-	-	-	-
Control, Baseline > Endpoint	-	-	-	-	-	-

Note: Corrected using 3dClustSim with acf; voxelwise threshold of $p < .005$, cluster size $k > 88$ for Cue > Rest contrast

Table 4.

MNI coordinates, k values, and statistics for significant clusters in near transfer IC implementation models of the Go/No-Go task

	Anatomical region	*k*	*t*	*x*	*y*	*z*
Correct NoGo > Correct Go						
Training > Control, Endpoint > Baseline	R cuneus	425	5.610	16	-70	42
			4.347	-4	-70	44
			3.951	6	-52	42
	R angular gyrus	154	5.038	40	-74	42
			4.560	38	-54	40
	L calcarine gyrus	94	3.928	-8	-84	10
Control > Training, Endpoint > Baseline	-	-	-	-	-	-
Training, Endpoint > Baseline	R cuneus	138	4.591	16	-70	42
		138	4.368	4	-56	30
Training, Baseline > Endpoint	-	-	-	-	-	-
Control, Endpoint > Baseline	-	-	-	-	-	-
Control, Baseline > Endpoint	Precuneus	196	5.073	-2	-58	42
Failed NoGo > Correct Go						
Training > Control, Endpoint > Baseline	L angular gyrus	145	4.882	-40	-64	42
Control > Training, Endpoint > Baseline	-	-	-	-	-	-
Training, Endpoint > Baseline	-	-	-	-	-	-
Training, Baseline > Endpoint	-	-	-	-	-	-
Control, Endpoint > Baseline	-	-	-	-	-	-
Control, Baseline > Endpoint	L angular gyrus	427	6.025	-40	-64	42
			3.420	-58	-56	32
	R superior frontal gyrus/cingulate	255	5.870	8	48	42
			4.822	28	44	38
			3.176	26	26	48
	L superior frontal gyrus	146	5.399	-18	36	36
			4.252	-26	16	58
	Anterior cingulate cortex	166	5.222	-2	52	10
	L middle frontal gyrus	143	4.708	-38	12	44
	R angular gyrus	160	4.702	50	-64	38

Note: Corrected using 3dClustSim with acf; voxelwise threshold of $p > .005$, cluster size k > 94 for Correct NoGo > Correct Go contrast and k > 104 for Failed NoGo > Correct Go contrast

Table 5.

MNI coordinates, k values, and statistics for significant clusters in models of ACES and CR moderation of changes in IC preparation over time

	Anatomical region	*k*	*t*	*x*	*y*	*z*
ACES pos. correlated with change in Correct Stop > Correct Go over time						
Training > Control	-	-	-	-	-	-
Control > Training	-	-	-	-	-	-
Training	-	-	-	-	-	-
Control	Occipital cortex	236	7.327	26	-82	20
	Cerebellum	196	7.129	-20	-76	-10
	Cuneus	116	5.863	-16	-88	20
	Posterior cingulate	123	5.332	-4	-38	34
	Lingual gyrus	90	5.126	12	-80	-6
	Precuneus	87	4.480	-18	-56	52
Cumulative risk pos. correlated with change in Correct Stop > Correct Go over time						
Training > Control	-	-	-	-	-	-
Control > Training	L superior parietal lobule	96	5.030	-22	-44	68
Training	-	-	-	-	-	-
Control	-	-	-	-	-	-

Note: Corrected using 3dClustSim with acf; voxelwise threshold of $p > .005$, cluster size k > 81 for Cue > Rest w/ACES contrast and k > 91 for Cue > Rest w/Cumulative risk contrast

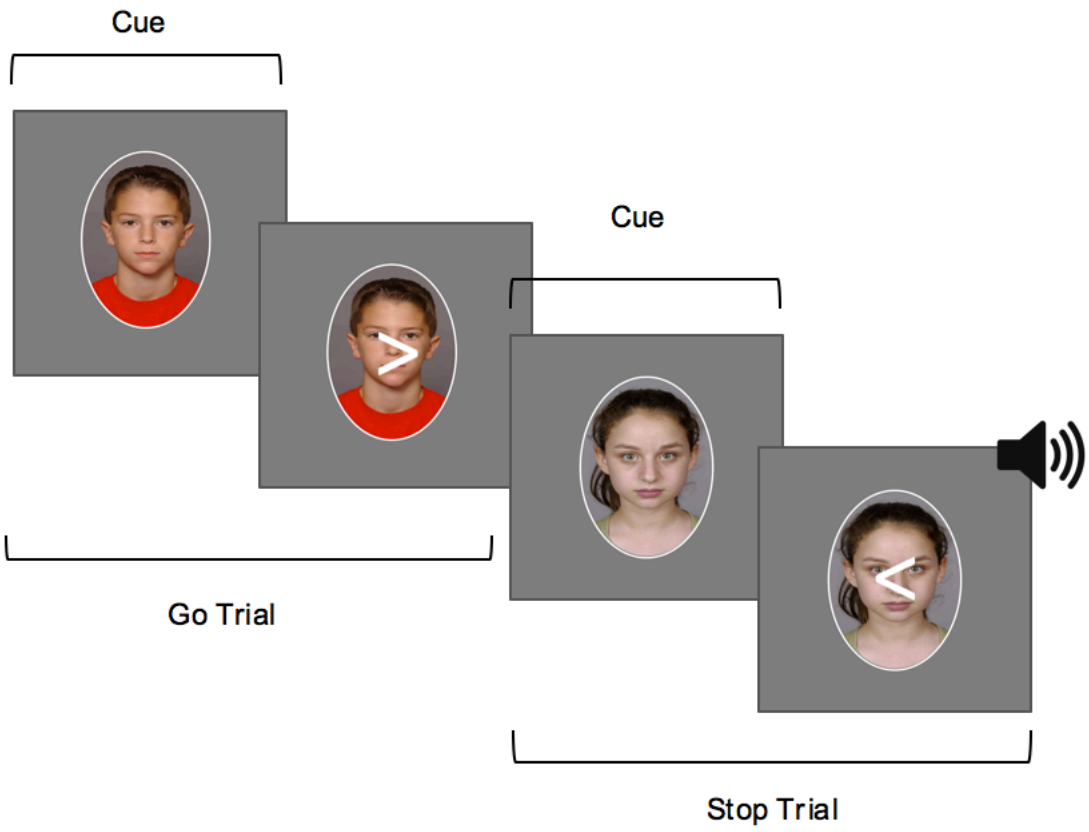

Figure 1. *Sample Go and Stop trials of modified Stop Signal Task.*

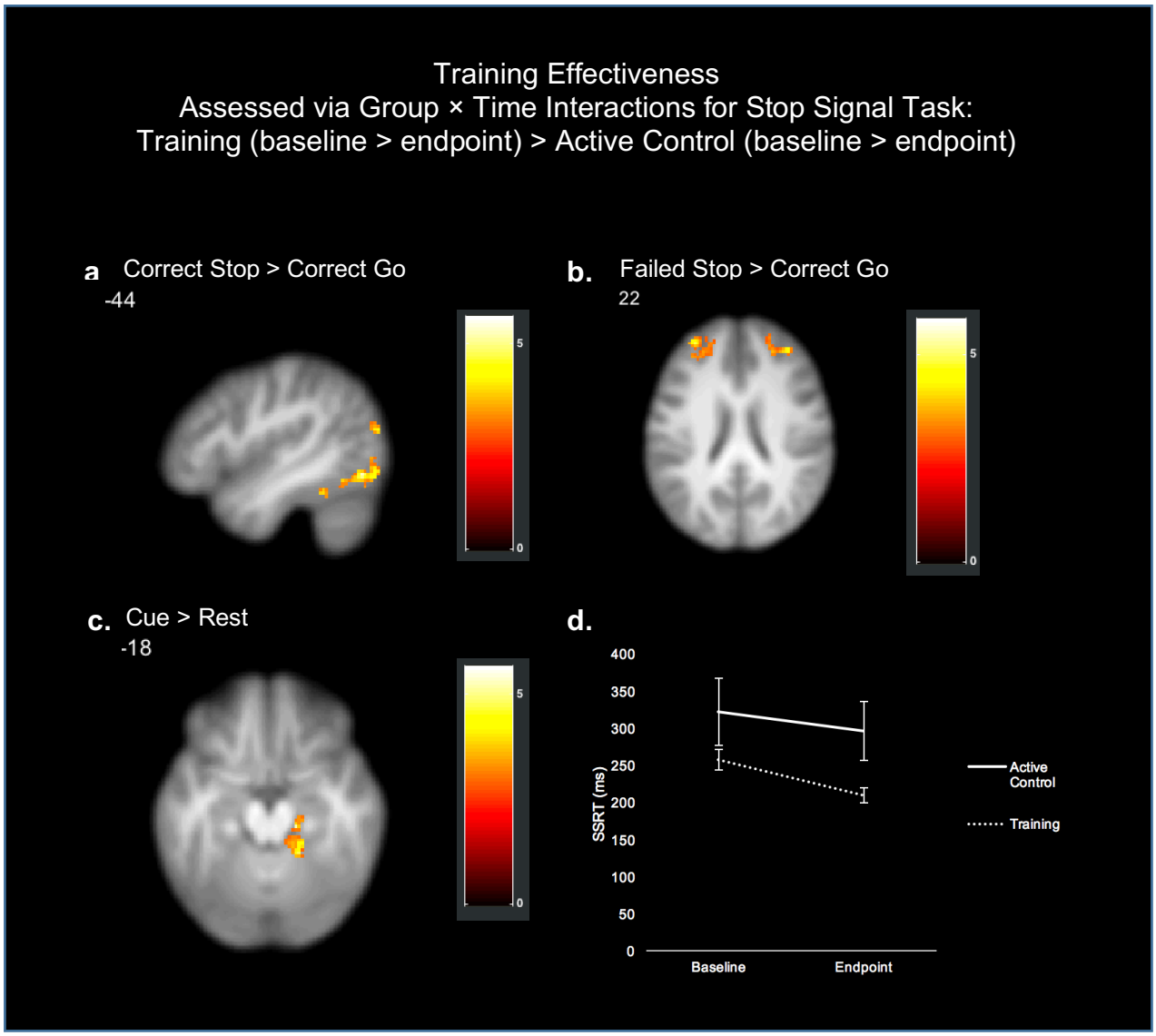

Figure 2. *Group × time interactions in brain and behavior during IC implementation and preparation on the Stop Signal Task*. The training group demonstrated significant increases in activation from baseline to endpoint compared to the active control group in the precuneus during successful IC implementation (a) and in bilateral middle frontal gyrus during failed IC implementation (b). During IC preparation, the training group showed significant increases in activation in the cerebellum and hippocampus from baseline to endpoint compared to the control group (c). Behaviorally, the training group did not show significantly different changes in SSRT

over time compared to the control group, $F(1,15) = .977$, $p = .339$, $\eta_p^2 = .061$; however, the effect was in the expected direction and the training group did show significant improvement in SSRT over time, $F(1,15) = 10.489$, $p = .006$, while the active control group did not, $F(1,15) = 1.487$, $p = .241$ (d).

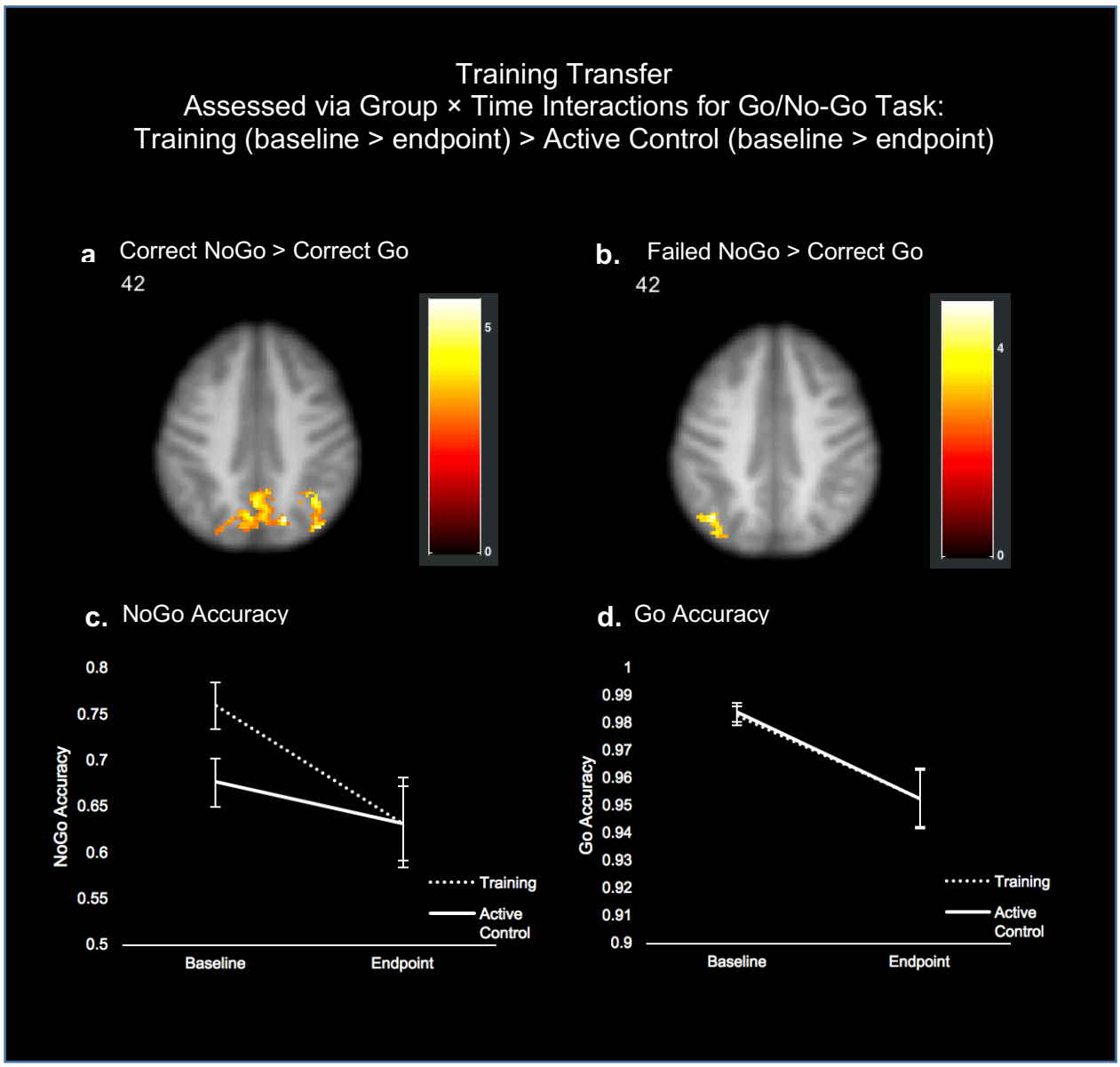

Figure 3. *Group × time interactions in brain and behavior during IC implementation on the Go/No-Go task.* The training group demonstrated significant increases in activation from baseline to endpoint compared to the active control group in the right cuneus and angular gyrus during successful IC implementation (a) and in left angular gyrus during failed IC implementation on the Go/No-Go task (b). Behaviorally, the training group did not show significantly different changes in NoGo Accuracy over time, $F(1,16) = .389$, $p = .373$, $\eta_p^2 = .05$,

or Go Accuracy over time, $F(1,16) = .7$, $p = .415$, $\eta_p^2 = .042$, compared to the control group. NoGo Accuracy declined significantly over time within the training group, $F(1,16) = 7.316$, $p = .016$, but not in the active control group, $F(1,16) = 1.024$, $p = .327$ (c). Go Accuracy significantly decreased in both the training group, $F(1,16) = 17.824$, $p = .001$, and the control group over time, $F(1,15) = 5.916$, $p = .027$ (d).

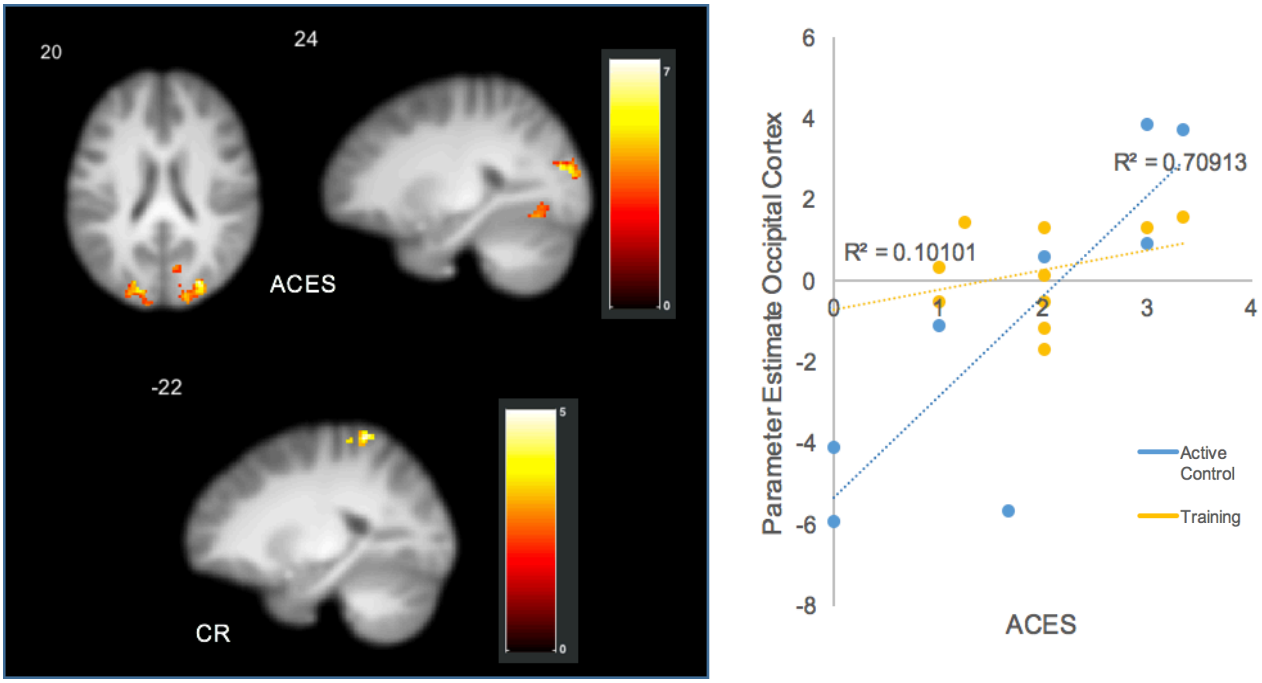

Figure 4. *Association between changes in activation during IC preparation (Cue > Rest) with ACES (top left) and cumulative risk (bottom left).* Parameter estimates from the occipital cluster plotted with ACES by group (right), demonstrating a stronger relationship between activation in this area and ACES in the control group compared to the training group.