Taking control! Structural and behavioural plasticity in response to game-based inhibition training in older adults

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Abstract

While previous attempts to train self-control in humans have frequently failed, we set out to train response inhibition using computer-game elements. We trained older adults with newly developed game-based inhibition training on a tablet for two months and compared them to an active and passive control group. Behavioural effects reflected in shorter stop signal response times were observed only in the inhibition-training group. This was accompanied by structural growth in cortical thickness of right inferior frontal gyrus (rIFG) triangularis, a brain region that has been associated with response inhibition. The structural plasticity effect was positively associated with time spent on the training-task and predicted the final percentage of successful inhibition trials in the stop task. The data provide evidence for successful trainability of inhibition when game-based training is employed. The results extend our knowledge on game-based cognitive training effects in older age and may foster treatment research in psychiatric diseases related to impulse control.

Introduction

Self-control is at the heart of human nature and frequently diminished in older age and psychiatric disease. Self-control interrupts the normal flow from intention to action. This ability to prevent and override unwanted thoughts, behaviours or emotions is integral to our functioning in daily life (Muraven et al., 1999), e.g. in traffic when you see that another car swerves into your blind spot just as you are about to switch lanes and you need to hit the brakes, or when trying to be polite during a conversation with a friend and not checking the mobile phone although you hear that a text message has just arrived. In experimental psychology, self-control is usually conceptualized under the construct of inhibition and frequently assessed using behavioural tasks like the stop signal task (Logan and Burkell, 1986). The stop signal task consists of a primary motor task, e.g. responding to a white arrow with a button press. If, however, a stop signal is presented (e.g. colour change to red), the participants are instructed to stop the ongoing motor response. The duration of the inhibition process can be derived from the reaction time data, a measure that has been termed stop signal reaction time (SSRT).

In the literature inhibition has been associated with a consistent network of brain regions comprising most prominently the prefrontal cortex, in particular the right inferior frontal gyrus (rIFG,(Aron et al., 2014). The rIFG is reliably activated during inhibition (for a meta-analysis see (Swick et al., 2011), and disruption of its integrity via lesions (Aron et al., 2003) or by means of transcranial magnetic stimulation (Verbruggen et al., 2010) results in substantial increases in SSRT.

Within the scope of the present study, we set out to train externally triggered inhibition. Interestingly, compared to the wealth of knowledge obtained on the training of various executive functions such as working memory (Klingberg, 2010; Kühn et al., 2012a), the literature on training of inhibitory control is relatively sparse. In two early studies, no effect of inhibition training was found (Logan and Burkell, 1986; Cohen and Poldrack, 2008) and several meta-analyses and large scale studies on the training of executive functions show mixed evidence for training effects and little or no evidence for transfer effects (Owen et al., 2010; Melby-Lervåg and Hulme, 2013). The lack of research in this area can most likely be attributed to the fact that inhibition is widely regarded as “untrainable” (Gray et al., 2003). However, recent findings from cognitive neuroscience provide evidence for the existence of training effects. One study used an

adaptive stop task design over a training period of three weeks showing decreases in rIFG activation during implementation of control, and increases in lateral prefrontal cortex during the cue phase (Berkman et al., 2014). The authors argue that transfer effects in the domain of inhibition might be difficult to find, because particular contingencies of the cue stimuli are learned, which are highly task specific. Recently, several authors have suggested that training with video games results in surprisingly wide transfer effects (Cardoso-Leite and Bavelier, 2014). In a previous study, we have been able to demonstrate structural changes in a brain network involved in spatial navigation after a two-month training period with a platform game that places high demands on 3D orientation (Super Mario 64), accompanied by changes in an untrained orientation task (Kühn et al., 2013).

Based on this prior evidence, we set out to design a video game-like training task that encompassed elements of response inhibition. Throughout the training intervention, difficulty level was increased by introducing faster switches between the inhibition stimuli and more items that required inhibition. We predicted structural increases in rIFG, based on the abovementioned evidence linking response inhibition to the integrity of rIFG, in particular in rIFG orbitalis and triangularis based on a previous meta-analysis on inhibition tasks (Simone Kühn, Brass, & Gallinat, 2013) and behavioural effects in a classical stop signal task. We selected cortical thickness as the parameter of interest since it has previously been suggested to be a more sensitive parameter with a higher signal-to-noise ratio compared to voxel-based morphometry (Dickerson et al., 2008; Hutton, Draganski, Ashburner, & Weiskopf, 2009; Salat et al., 2004). Moreover, cortical thickness measures have been considered to be more easily interpretable than the probabilistic grey matter volumes in VBM (Lehmann et al., 2011). Since older age has been associated with a decrease in the capacity to inhibit (Kramer et al., 1994), most likely associated with the widely described age-related decline in the frontal lobe (Fjell et al., 2009), we selected a sample of adults aged 60 and above, where a realistic need to train self-control can be expected.

Materials & Methods

Participants

Fifty three healthy participants (mean age=69 years, SD=4.2, range 62-78, 27 females) were recruited from the student body of the Senior University, Berlin and by means of flyers and internet advertisements. The advertisement did mention that we were recruiting for a cognitive

training study but did not specify which training effects we expected. Moreover participants were randomly assigned to the different groups ruling self-selection effects out. The sample size was based on estimates from a previous study with a similar design and similar outcome measures (S Kühn, Gleich, Lorenz, Lindenberger, & Gallinat, 2014). Based on this previous study with an effect size of 0.65 we aimed for recruiting 17 participants per group to achieve a power of 0.80 and alpha error of 0.05. After complete description of the study, the participants' informed written consent was obtained. The local ethics committee of the Charité University Clinic, Germany, approved of the study. Cognitive status was assessed with the Mini Mental State Examination (MMSE, Folstein et al., 1975). All participants reached a MMSE score of 25 or higher (mean MMSE score=28.45, SD=1.14; range 25-30) indicating they were cognitively intact. An exclusion criterion was previous experience with a tablet computer. According to personal interviews (Mini-International Neuropsychiatric Interview) participants were free of mental disorders. In addition, exclusion criteria for all participants were abnormalities in MRI, general medical disorders and neurological diseases. The participants received a financial compensation for the testing sessions, but not for the training itself.

Training Procedure

The participants were randomly assigned to one of three groups. The inhibition game group (n=20, mean age=69.6, SD =4.5, 11 females) played an inhibition game on a tablet (Samsung Galaxy Tab 3) over a period of eight weeks. The active control group was introduced to a tablet-based cognitive training platform (n=15, mean age=68.4, SD =4.7, 7 females) that ran on the same model. This group was included to control for the fact that participants in the inhibition-training group also received a novel technical device to interact with. The passive control group (n=18, mean age=69.6, SD =3.5, 9 females) was not given a tablet and had no task but underwent the same testing procedure as the two other groups.

Both training groups were asked to train the game or with the cognitive training platform for approximately 15 min a day. However, we intentionally compensated the participants only for the sessions in which they came to the lab for testing. Our previous research, in which we used a similar procedure, suggests that the perceived fun while engaging in an intervention is positively associated with brain plasticity (Kühn et al., 2014) and we speculate that enforcing longer training sessions and therewith forcing participants to engage longer than they feel like, may impair motivation and therewith the hypothesized training effects.

Inhibition game

The inhibition game (developed using the Unity platform) consisted of target objects (mostly specific types of food, 35 items in total) that appeared on a buffet at the top of the screen and a plate that was displayed at the bottom of the screen (*Figure 1*) (the game "Schiff Ahoi" can be downloaded via https://mpibox.mpib-berlin.mpg.de/f/06bf74aad2/). At the beginning of the game, the task was fairly simple, namely to move the target items from the buffet onto the plate as quickly as possible by means of swiping gestures. A timer to the left of the plate displayed how much time participants had left to displace the items (on each trial, the timer started at 1 min 30 seconds and ran down to 0). Successful placement of the target item onto the plate coincided with a pleasant, while unsuccessful placement coincided with an unpleasant sound. Also, after an item had been swiped away from the buffet, a new one appeared after a short delay to ensure that participants were constantly encouraged to speed up their performance and translocate as many objects as possible. Once participants were familiar with the basic task, inhibition items were introduced and displayed on the red napkin (with the label "NEIN", "no" in German on it) located to left of the plate. Participants were specifically instructed not to drag the inhibition items onto the plate, if they appeared on the buffet. Likewise, incorrect selection or translocation of an inhibition item coincided with an unpleasant sound. The display of the inhibition items on the napkin stayed visible during game play, so that participants did not need to memorize the items, however with growing number of inhibition items this is what participants reported doing. To increase the general tendency to respond, more than one target item appeared on the buffet and the items disappeared after a short time, therewith withdrawing a chance to collect another item. Moreover inhibition items were less frequently presented compared with target items (about 25% inhibition items, 75% target items). Inhibition items were frequently exchanged between different trials, in order to prevent training of specific S-R associations and to promote cognitive flexibility. Moreover, task difficulty was gradually increased: participants started out with non-food objects as inhibition items, and then advanced to food items that became more and more difficult to discriminate from the target items in terms of food group, colour etc. Additionally, the number of inhibition items that needed to be avoided was increased from one up to twenty to make the task even more difficult. Moreover, inhibition items did not exclusively occur as inhibition items, but also appeared as target items in other trials.

Performance feedback was provided online through points awarded for correctly placed target items by a counter that was located above the timer on the left side of the screen. Accordingly,

points were subtracted for inhibition items that were mistakenly touched. To make the game more appealing to an older population, it was set on a recreational cruise ship and called "Schiff Ahoi!" (ship ahoy!). Participants embarked on a virtual cruise of the Mediterranean Sea and could make their ship travel forward on a nautical chart, depending on the amount of points they collected. Throughout their journey, participants arrived at eight different cities along the Mediterranean coastline (e.g. Livorno, Rome, Monte Carlo) and upon arrival at each of these cities they were rewarded with a special virtual postcard.

Cognitive training platform

The cognitive training platform was a mobile application (programmed using PHP) developed with the aim of providing a comprehensive tablet-based cognitive stimulation program tailored to the needs of elderly and inexperienced tablet users (a detailed description of the cognitive training platform can be found here https://mpibox.mpib-berlin.mpg.de/f/b692480209/). The platform consisted of six different cognitive tasks that participants could practice, namely a music memory task, a mental arithmetic task, a picture memory task, a mental rotation task, a version of the Stroop task, and a semantic category task. Task difficulty was individually adapted based on participant's task performance: exercises became more difficult as participant's performance improved and vice versa. Within each cognitive training session, five exercises were randomly selected and presented in a random order. The duration of a single training session was approximately 15 minutes, with each exercise taking about two minutes. Participants were instructed to perform at least one training session daily over a period of eight weeks. After completing an exercise, participants were presented with a performance graph in order to track their individual performance. The cognitive training function was complemented by the information and communication functions. These features were included in the platform to inform participants about the importance of maintaining a mentally active lifestyle in later life and to facilitate social engagement.

Scanning Procedure

Structural images were collected on a Siemens Tim Trio 3T scanner (Erlangen, Germany) with a 12-channel head coil. The structural images were obtained using a three-dimensional T1-weighted magnetization prepared gradient-echo sequence (MPRAGE) based on the ADNI

protocol (www.adni-info.org) (repetition time=2500 ms; echo time=4.77ms; TI=1100ms, acquisition matrix=256×256×176, flip angle=7°; 1x1x1mm^3 voxel size).
Functional images were acquired using a T2*-weighted echo planar imaging (EPI) sequence sensitive to blood oxygen level dependent (BOLD) contrast (TR=2000ms, TE=30ms, image matrix=64×64, FOV=216 mm, flip angle=80 º, voxel size 3×3×3mm^3, 36 axial slices).

fMRI stop signal paradigm

Participants completed an adaptive stop signal paradigm (Logan et al., 1984) (Presentation software) while fMRI data was collected. This was the only task assessing response inhibition that we acquired as at pre- and post-test as a measurement of inhibition. The stop task consisted of trials in which a right or left button press was required (go trials) and trials in which an already initiated motor command had to be withheld (stop trials). Participants were instructed to respond as fast as possible to a white arrow pointing either to the right or left by pressing a right or left button (using right and left index finger, respectively). For stop trials (25% of trials), participants were instructed to stop their response when the white arrow changed its color to red after a certain delay (stop signal delay, SSD). The adaptive character of the task was achieved by a continuous adaption of the SSD using two independent staircases in order to reach a performance level of approximately 50% successfully inhibited responses. The staircases started at 150 and 200 ms, respectively. A staircase was incremented in case of a successful stop trial (no button press) or decremented in case of an unsuccessful stop trial (executed button press) by 50 ms. Staircases were updated independently in a pseudo-randomized balanced fashion. The mean SSD during the pretest was used as a starting value for the two staircases of the experiment. During the experiment, the SSD was also updated continuously in the same way as described for the pretest.
All trials started with a cue, which lasted for 500 ms; during this time a white circular ring was presented in the center of the screen. Subsequently, an arrow appeared in the center of the ring either pointing to the right (>) or left (<). The direction of the arrow was balanced across the experiment in a pseudo-randomized order. A go trial (144 of 192 trials) ended in the moment of a button press, but lasted a maximum of 1000ms. In the stop trials (48 of 192 trials) the arrow and the ring changed their color to red once the adaptive SSD had elapsed, indicating the response should be withheld. Stop trials also lasted a maximum of 1000 ms and ended, if the participant did not withhold the response. At the end of each trial, a blank black screen was presented and the following trial started after a variable delay ranging from 0.5 to 4s (mean=1 s) that was

characterized by an exponentially decreasing function. Additionally, 24 nullevents were pseudo-randomly uniformly interspersed over the 192 experimental trials.

Before the scanning session, participants were familiarized with the task in a standardized procedure and performed a behavioral pretest session containing 96 trials (72 go and 24 stop trials) also using their right and left index finger to respond. This pretest was used to estimate the individual SSD using two independent staircases.

We had to exclude the behavioral data of five participants due to technical failure resulting in logfiles not being recorded.

Logan and Cowan suggested that go and the stop processes are two independent processes, which compete against each other (Logan et al., 1984). When the probability of responding on a stop-signal trial different from 0.50, which was the case in the present data set, the integration method to compute SSRT is recommended (Verbruggen et al., 2013). According to this method SSRT is estimated by subtracting mean SSD from the finishing time of the stop process which is determined by integrating the go RT distribution (RTs are rank-ordered and then the nth RT is selected, with n being the result of a multiplication of the number of no-signal trials in the distribution by the probability of responding).

The resulting SSRT is an estimation of the length of inhibition process and thus a measure of inhibition performance. We excluded two participants from the SSRT analysis due to very slow responding at pretest.

Data Analysis

Cortical thickness

Cortical segmentation was performed using the FreeSurfer image analysis suite (http://surfer.nmr.mgh.harvard.edu/). The technical details of these procedures have been described thoroughly elsewhere (Fischl, 2012). Briefly, this program uses intensity and continuity information from MR volumes to reconstruct and measure cortical thickness, and provides valid measures at submillimeter resolution. Assessments of test–retest reliability of FreeSurfer have revealed high intra-class correlations of .994 for MPRAGE sequences (Wonderlick et al., 2009) and high consistency of absolute within-subject measures of cortical thickness assessed in intervals of minutes to weeks with variations of only≤.05 mm (Wang et al., 2008).

All reconstructed data were visually checked for segmentation accuracy at each time point. No manual interventions with the MRI data had to be performed. We used the longitudinal processing scheme implemented in FreeSurfer to account for the repeated-measurement design in the processing stream. Both time points were first processed with the cross-sectional stream. Then, a base template was created from both time points, which operates as an initial estimate for the segmentation and surface reconstruction. The two measurement time points were then registered to this template to ensure non-biased analysis. We used the Desikan-Killiany surface-based cortical labelling protocol (Desikan et al., 2006) to estimate cortical thickness in the a priori defined regions: right inferior frontal gyrus with its subregions orbitalis, triangularis and opercularis. Additionally we selected three regions that have been shown to improve in other cognitive training approaches such as working memory training, namely bilateral anterior cingulate cortex (ACC, Desikan-Killiany "sulcus and gyrus of the anterior cingulum"), bilateral dorsolateral prefrontal cortex (DLPFC, Desikan-Killiany "gyrus and sulcus of middle frontal gyrus") and bilateral precuneus (Desikan-Killiany "gyrus of precuneus") to test for the specificity of the effects. Since we had the a priori hypothesis to find training-related increases in rIFG, we computed a group x time repeated-measures ANOVA for the three subregions of the rIFG with the Bonferroni corrected *p*-value of 0.0166. We computed intra-class correlations in order to determine the test-retest reliability.

We computed Pearson correlation coefficients between change in cortical thickness of rIFG triangularis over time (posttest – pretest) and the time participants spent playing the inhibition game as well as the percentage of successfully inhibited stop trials at posttest.

fMRI data analysis

Functional imaging data was analyzed using Statistical Parametric Mapping software package (SPM8). EPIs were corrected for slice timing and head motion and transformed into the stereotactic normalized standard space of the Montreal Neuroimaging Institute (MNI) using the unified segmentation algorithm. Finally, EPIs were resampled (voxel size=3x3x3mm^3) and spatially smoothed with a 3D Gaussian kernel of 6mm full width at half maximum.

A general linear model (GLM) with a full-factorial design was applied on the 2nd level. On single subject level, event-related separate regressors were included for the cue, as well as for go trials, successful stop trials, and unsuccessful stop trials at the time of arrow presentation. Additionally, a regressor of no interest was included that modeled invalid trials in which a participant did not

respond during go trials or made discrimination errors (e.g. pressed the right button when a left-directed arrow was presented) at the time of arrow presentation. Finally, the six rigid body movement parameters were also included in the single subject GLM. Differential t-contrasts for successful stop trials versus go trials were calculated and taken to group level analysis. On the second level, these differential t-contrast images were entered into a one-sample *t*-test. Whole brain results were corrected for multiple comparisons using a family-wise error threshold of $p<0.05$. The resulting maps were overlaid onto a normalized T1 weighted MNI template (colin27) and the coordinates reported correspond to the MNI coordinate system. From the cluster in rIFG/anterior insula in the contrast successful stop vs. go trials we extracted BOLD signal using MATLAB.

Results

Participants did not differ between groups in terms of gender ($p>0.45$), age ($p>0.88$) or education ($p>0.17$). On average, participants spent 12.6 hours (SD=7.9) ranging from 2.5 to 26.7 hours actively playing the inhibition game and 10.1 h (SD=4.4) ranging from 4 to 16.3 h on the cognitive training platform.

Structural plasticity in rIFG

In line with our a priori hypotheses, we found a significant interaction between group and time in cortical thickness of the rIFG triangularis ($F(2,50)=7.519$, $p=0.001$, $\eta^2=0.23$, observed power: 0.93, *Figure 2A*). However, we did not observe the same effect in rIFG opercularis ($F(2,50)=0.552$, $p=0.579$) nor in rIFG orbitalis ($F(2,50)=0.951$, $p=0.393$). Post-hoc paired *t*-tests revealed that the cortical thickness increase was significant in the inhibition-training group, $t(20)=3.32$, $p=0.004$, Cohen's d = 0.74, but not for the active control group training on the cognitive training platform ($p=0.667$) and the passive control group showed a decrease between pre- and posttest, $t(18)=-2.53$, $p=0.022$, Cohen's d = 0.60. Between-group *t*-tests revealed a significant difference between the inhibition game and passive control group, with the inhibition-training group showing higher cortical thickness at posttest, $t(36)=2.25$, $p=0.031$, Cohen's d = 0.75. Importantly, at pretest, the groups did not differ significantly from one another ($p>0.40$) and the time x group interaction was likewise significant when excluding the passive control group

(that showed a significant decrease) and only considering the inhibition training group and the active control group ($F(1,33)=5.814$, $p=0.022$, $\eta^2=0.15$). In order to estimate the reliability of our FreeSurfer measures we computed intra-class correlations (triangularis: 0.945, opercularis: 0.924, orbitalis: 0.950), indicating a high degree of reliability.

To test for the specificity of the observed training effects in rIFG triangularis we computed the time x group interaction also for ACC, DLPFC and precuneus. In none of the regions we observed a significant effect (ACC: $F(2,50)=0.009$, $p=0.99$; DLPFC: $F(2,50)=1.02$, $p=0.368$; precuneus: $F(2,50)=2.38$, $p=0.103$). Notably, the inhibition training group showed a decrease in precuneus, but even though the *p*-value may be not to far from significance the pattern of results was clearly different from our hypothesized finding.

We found a significant association between cortical thickness change in rIFG triangularis and the duration participants played the inhibition game ($r(20)=0.623$, $p=0.003$, *Figure 2B*), reflecting that participants who played the game more frequently showed stronger increases in cortical thickness. This relationship between time spent training and cortical thickness change was not present in the active control group ($r(15)=0.27$, $p=0.924$).

Behavioral plasticity effects

On the behavioural level, we observed evidence for plasticity as well. In a classical stop signal task that participants performed before and after training, we found a significant time x group interaction effect (Table 1,$F(2,45)=3.554$, $p=0.037$, $\eta^2 = 0.136$) and a significant decrease of SSRT in the inhibition game group ($t(17)=3.166$, $p=0.006$, Cohen's d = 0.75) but neither for the active control group ($t(14)=-0.808$, $p=0.433$) nor for the passive control group ($t(14)=1.19$, $p=0.254$). We observed no significant group differences at pretest, except for a marginally significant difference in SSRT computed with the integration method between the inhibition and active control group ($t(32)=-1.74$, $p=0.092$).

Interestingly, we found a positive association between cortical thickness increase in rIFG triangularis and the percentage of successfully inhibited stop trials at posttest in the inhibition training group ($r(20)=0.52$, $p=0.018$, *Fig. 2C*). It is noteworthy that this correlation was in part driven by a single participant, however, statistically the values of the participant are not outliers.

Functional plasticity in rIFG during stop signal task

As previously reported in the literature we found significant activation in rIFG/anterior insula when comparing successful stop with go trials across all groups in the fMRI data acquired during stop task performance at pretest (peak coordinate at 48 17 22, *Fig. 2D*, Table 2), next to the typical activation pattern including pre-supplementary motor area (preSMA) and bilateral parietal lobe. When comparing signal change extracted from the rIFG/anterior insula ROI of the contrast successful stop vs. go across at pretest collapsed across all groups, we found a significant decrease over time only in the inhibition-training group ($t(14)=-2.30$, $p=0.038$, Cohen's d = 0.61), whereas the signal did not change in the two control groups ($p>0.81$). However, most likely due to the smaller sample size in the fMRI task the interaction of group and time did not reach significance ($p=0.217$).

Discussion

Within the scope of the present study we detected structural neural changes as well as behavioural plasticity effects resulting from a tablet-based inhibition-training intervention in older adults. We found structural increase in rIFG triangularis cortical thickness uniquely in the inhibition training group. Moreover, this group showed the strongest behavioural transfer effects to a classical stop signal task as well as a decrease in functional activation of rIFG/anterior insula during stop task performance.

Structural plasticity effects of inhibition training

In line with our a priori hypothesis, we found a 2.2% increase in cortical thickness of rIFG triangularis in the inhibition game group compared to a stable or reverse pattern in the active and passive control groups. The localisation of the observed effect fits partially to a recent study that has shown increases in grey matter volume in rIFG orbitalis and modulation of white matter microstructure in rIFG triangularis in response to two weeks training with a Go/NoGo task in young adults (Chavan et al., 2015). Moreover we were able to demonstrate that the pattern of results is specific for the rIFG triangularis and is not observed in brain regions such as ACC, DLPFC or precuneus.

Interestingly, we additionally found a significant relationship between thickness changes and the time participants spent playing that resembles a dose-response relationship. That is, the more

participants deliberately played the inhibition game, the more rIFG cortical thickness they gained. However, since we did not experimentally manipulate how much participants played the game, we cannot draw any conclusions on causality.

Previous studies on patients with brain lesions have provided evidence that integrity and volume of the rIFG are related to stop signal inhibition performance (Aron et al., 2003). Evidence for a causal association between prefrontal cortex and inhibition performance comes from a tDCS cognitive training study in which stimulation of prefrontal cortex (the target was referred to as rIFG, although the spatial resolution of tDCS is most likely not precise enough to limit stimulation to this area) improved training effects in a stop signal task (Ditye et al., 2012).

Consistent with the link between rIFG and inhibition, structural reductions in prefrontal cortex have been associated with higher impulsivity (Schilling et al., 2012a; 2012b). In line with these findings, a study on elderly subjects has found a positive association between bilateral cortical surface area in dorsolateral prefrontal cortex and the ability to delay gratification (Drobetz et al., 2014). This evidence for far-reaching associations between prefrontal cortex integrity and impulsivity and the ability to control oneself suggests that the present response inhibition training may constitute a potential means to foster self-control in general.

It has been shown that in particular IFG shows a rapid decline over the course of aging (Raz et al., 2005) and this may contribute to the observed decline in cortical thickness in rIFG in the passive control group, however the effect may also be due to measurement error.

Behavioural plasticity effects of inhibition training

In the present behavioural data, we found evidence for plasticity in a classical stop signal task, with the inhibition training group showing the strongest decrease in SSRT due to training. Moreover, the structural changes in rIFG cortical thickness were associated with behavioural performance. In the inhibition game group a positive correlation between cortical thickness plasticity in rIFG and a higher percentage of successful inhibition trials in the stop task at posttest was observed.

This evidence clearly challenges the long held view that inhibition is “untrainable” (Gray et al., 2003). Our findings support the evidence of training-related decreases in SSRT as previously presented (Manuel et al., 2010; Berkman et al., 2014), however, the presented results go beyond these studies by showing plasticity effects in response to an inhibition training regimen that bears

not much surface similarity in terms of stimulus material or response format to the stop signal task.

Our findings are in line with a previous behavioural study in which older adults were trained with computer-based cognitive training games over a period of seven weeks, whereas a control group answered quiz questions about documentaries (van Muijden et al., 2012). Similar to our results, the experimental group showed plasticity effects in a stop signal task. Moreover a recent study trained healthy young participants with a commercial video game that was hypothesized to train inhibition and another group with a stop signal reaction time task (Biggs et al., 2015). In both groups participants showed training gains in a video game in which participants were supposed to shoot enemies but avoid shooting civilians. Both inhibition training approaches lead to a significant reduction in civilian casualties in comparison to a visual search-training group. However, the effects of the present inhibition game intervention go beyond these previous results, since we unveil the underlying brain structural plasticity effects and demonstrate that inhibition training effects can likewise be achieved in an older population.

Functional neural plasticity effects of inhibition training

Brain activation during stop task performance showed significant activation in rIFG across all participants at pretest, verifying that rIFG is indeed involved in stop task performance (Aron et al., 2004). Moreover, we found a reduction of activity in rIFG when comparing successful stop trials with go trials at posttest relative to pretest in the inhibition-training group. This is in line with the previous stop signal training study (Berkman et al., 2014). Importantly we find similar training-related reductions in rIFG in an older population, since previous studies have shown decreases in rIFG during inhibition task performance with age (Sebastian et al., 2013; Coxon et al., 2016). Based on these age-related decreases in rIFG activity, one may have hypothesized that training effects should present themselves as increases in BOLD activity, rather than decreases. However, the present data reveals training-related decreases of activity in rIFG in older adults similarly as previously demonstrated in younger adults (Berkman et al., 2014). This hints at the possibility that functional plasticity follows the same efficiency principles and mechanisms in older as in younger participants. In line with the observed effects, previous cognitive training studies targeting working memory (Heinzel et al., 2014) or multiple cognitive domains (Kühn et al., 2011) or sustained engagement in learning novel leisure time activities such as digital photography and quilting (McDonough et al., 2015) have shown similar decreasing BOLD

effects in task-related brain regions after training in older adults. The present study stands out by showing that these functional activity decreases are not only accompanied by improved performance, but also by structural plasticity effects in the very same brain regions.

Limitations

The relatively small sample size is a limitation of the present study. Future studies may select the neuropsychological tasks in the cognitive training battery more conservatively when using this intervention as a control. Our battery contained a Stroop task, which may likewise be assumed to train inhibition. Moreover future studies may focus on training of other aspects of self-controls such as delay discounting or decision-making and should attempt to assess transfer effects onto day-to-day behaviour indicative of better self-control, such as successful adherence to dietary regimens.

Conclusion

The present study has demonstrated that inhibition can be trained in older adults. Importantly, at the same time structural plasticity effects were observed in rIFG that were positively associated with the time participants engaged in playing the inhibition-training game. Moreover, these structural gains were shown to be behaviourally relevant resulting in higher percentages of successful inhibition trials in the stop task at posttest.

These pronounced plasticity effects in older participants should encourage researchers to utilize game-design mechanisms when developing training regimens. Future research should include the assessment of global transfer effects into daily life, such as success in dieting or success in exerting self-control over unwanted habits such as smoking and alcohol intake. Since lack of self-control plays a prominent role in many impulse-related psychiatric diseases, future studies should test whether our inhibition training may facilitate the ability to regain control.

Author contribution

S.K., M.W., M.H., J.O'S., A.S., conducted the experiments, S.K., E.S-T., J.G., R.C.L. designed the experiments and wrote the paper, R.C.L. analysed the fMRI data, M.B. analysed the sMRI data, S.B., T.B. programmed the game, all authors read and approved the manuscript.

Conflict of interest

The authors have no conflict of interest.

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Figure captions

Figure 1: Screenshot from the inhibition game.

Figure 2: A) left: Structural plasticity in right inferior frontal gyrus (rIFG) triangularis cortical thickness of the inhibition training group (depicted in yellow), right bar graph depicting significant time x group interaction; B) scatterplot of the association between cortical thickness change in rIFG and duration of inhibition game training; C) scatterplot of the association between cortical thickness change in rIFG and percentage of successful inhibition at posttest in the inhibition training group; D) left: fMRI contrast of successful stopping vs. go at pretest across all groups, black arrows indicate the cluster in rIFG/anterior insula, right: Significant decrease of BOLD activity in rIFG/anterior insula in the inhibition-training group.

Table 1

Behavioural data of the pre- and posttest stop signal task performance (means and standard deviation in brackets)

	Passive Control Group		***Tablet Control Group***		***Inhibition Game Group***	
	n=15		n=15		n=18	
	Pretest	***Posttest***	***Pretest***	***Posttest***	***Pretest***	***Posttest***
Go RT	625 ms (65)	653 ms (78)	695 ms (103)	643 ms (93)	637 ms (81)	639 ms (78)
Failed Stop RT	566 ms (62)	588 ms (60)	617 ms (87)	591 ms (85)	567 ms (68)	580 ms (64)
SSD	277 ms (63)	315 ms (72)	358 ms (103)	307 ms (102)	271 ms (94)	296 ms (87)
Percent successful stopping	54.7 (3.9)	54.2 (3.3)	56.1 (4.1)	53.9 (4.3)	54.3 (5.5)	54.6 (4.0)
Percent unsuccessful go	3.0 (5.0)	2.2 (3.3)	1.3 (1.1)	1.5 (1.2)	1.9 (2.3)	1.8 (2.0)
SSRT integration method	323 ms (41)	312 ms (32)	310 ms (31)	318 ms (35)	338 ms (57)	314 ms (48)

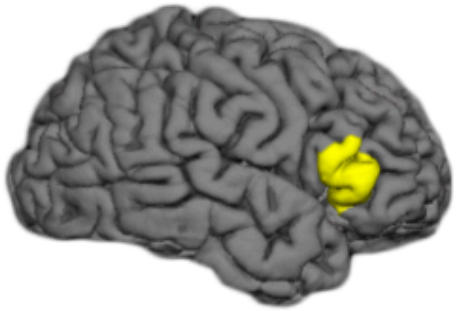
Table 2

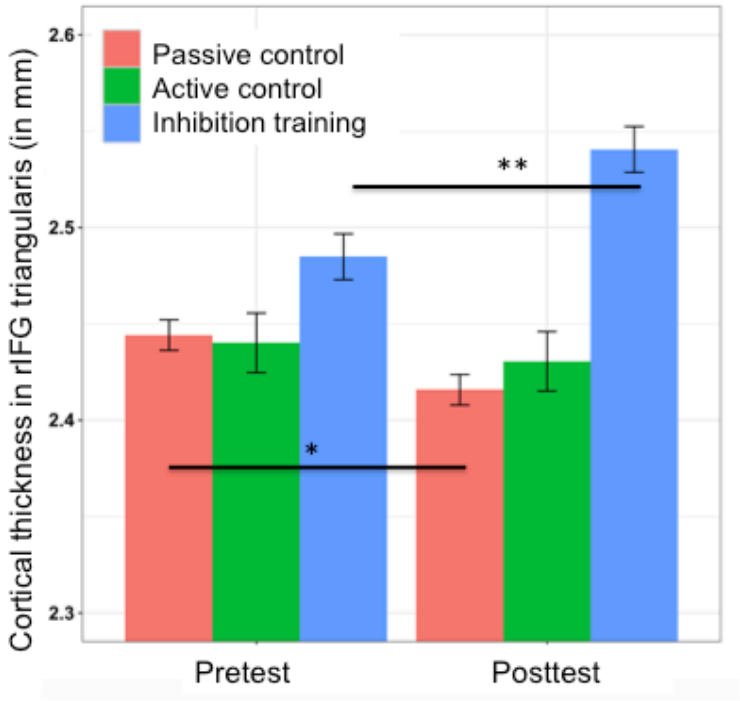
Successful stop > Go across all groups at pretest (family-wise error corrected $p < 0.05$)

Brain structure	*BA*	*peak coordinates (MNI)*	*T (peak)*	*Cluster size (vox)*
Left occipital gyrus	18	-21, -100, -2	11.47	386
Right lingual gyrus	18	24, -88, -11	10.47	369
Right inferior frontal gyrus (opercularis)	44	39, 5, 31	6.83	152
Right inferior frontal gyrus (orbitalis)	47	33, 23, -8	8.58	85
Left inferior frontal gyrus (orbitalis)	45	-30, 20, -8	7.51	36
Right supramarginalgyrus	40	60, -43, 40	6.41	32
Right angular gyrus	7	30, -58, 43	6.23	26
Left inferior frontal gyrus (triangularis)	46	-48, 26, 31	5.8	5
Pre-supplementary motor area	6	9, 32, 49	5.81	4

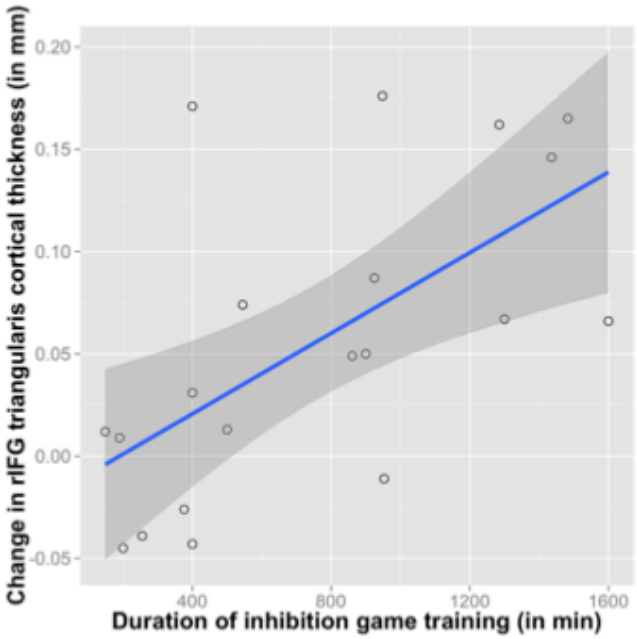

0:43
35
NEIN
For educational use only

A

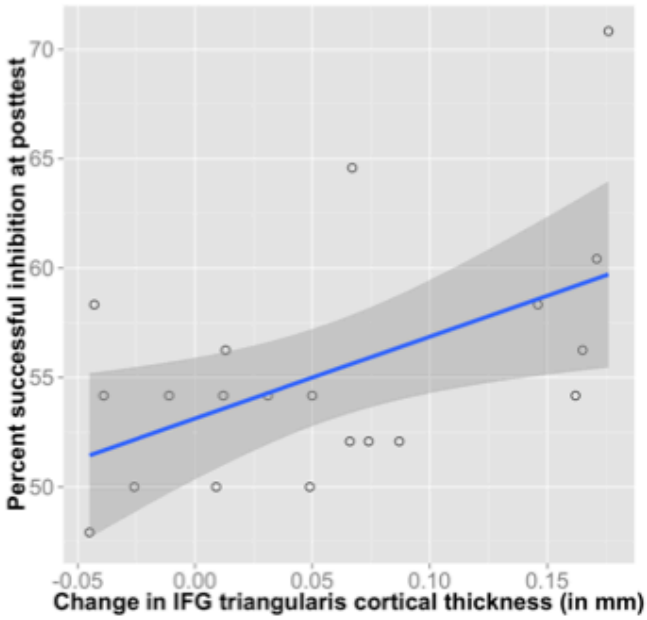



Passive control
Active control
Inhibition training
Cortical thickness in rIFG triangularis (in mm)
2.6
2.5
2.4
2.3
**
*
Pretest
Posttest

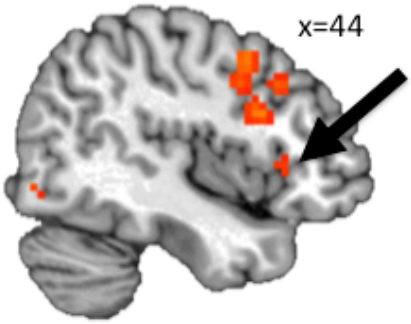
B


Change in rIFG triangularis cortical thickness (in mm)
0.20
0.15
0.10
0.05
0.00
-0.05
400
800
1200
1600
Duration of inhibition game training (in min)

C


Percent successful inhibition at posttest
70
65
60
55
50
-0.05
0.00
0.05
0.10
0.15
Change in IFG triangularis cortical thickness (in mm)

D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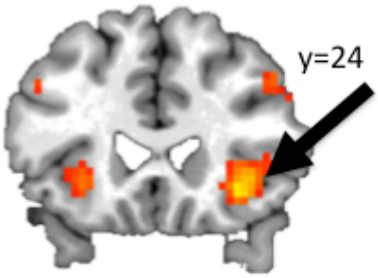
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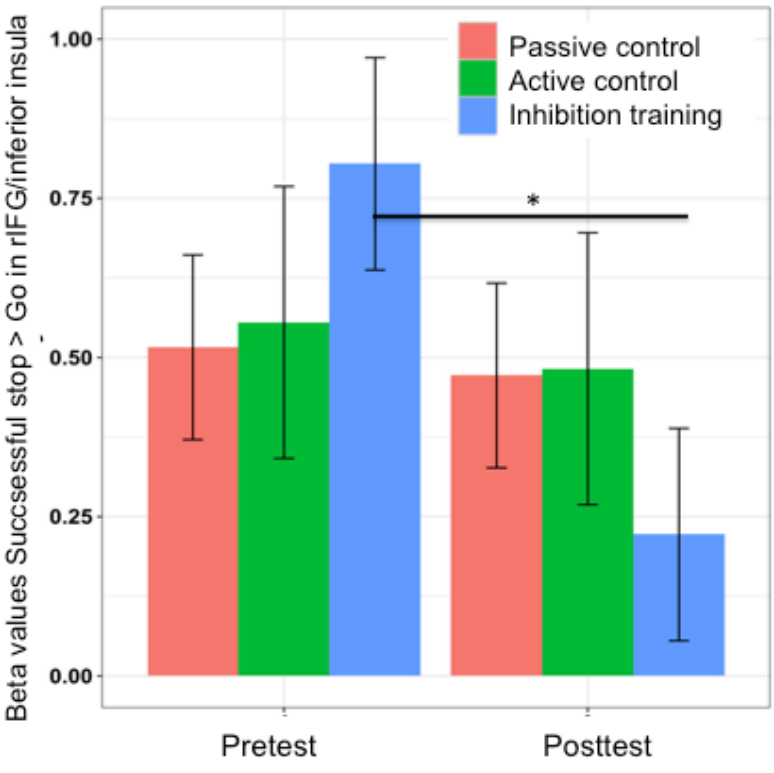
Passive control
Active control
Inhibition training
Beta values Successful stop > Go in rIFG/inferior insula
1.00
0.75
0.50
0.25
0.00
*
Pretest
Posttest