

The local properties of bold signal fluctuations at rest monitor inhibitory control training in adolescents



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ABSTRACT

Inhibitory control (IC) plays a critical role in cognitive and socio-emotional development. Short-term IC training improves IC abilities in children and adults. Surprisingly, few studies have investigated the IC training effect during adolescence, a developmental period characterized by high neuroplasticity and the protracted development of IC abilities. We investigated behavioural and functional brain changes induced by a 5-week computerized and adaptive IC training in adolescents. We focused on the IC training effects on the local properties of functional Magnetic Resonance Imaging (fMRI) signal fluctuations at rest (i.e., Regional Homogeneity [ReHo] and fractional Amplitude of Low Frequency Fluctuations [fALFF]). Sixty adolescents were randomly assigned to either an IC or an active control training group. In the pre- and post-training sessions, cognitive ('Cool') and emotional ('Hot') IC abilities were assessed using the Colour-Word and Emotional Stroop tasks. We found that ReHo and fALFF signals in IC areas (IFG, ACC, Striatum) were associated with IC efficiency at baseline. This association was different for Cool and Hot IC. Analyses also revealed that ReHo and fALFF signals were sensitive markers to detect and monitor changes after IC training, while behavioural data did not, suggesting that brain functional changes at rest precede behavioural changes following training.

1. Introduction

Inhibitory control (IC) — the ability to resist automatism, temptations, distractions or interferences and to adapt to conflicting situations (Diamond, 2013) — plays a critical role in cognitive and socio-emotional development (Borst et al., 2015). Indeed, IC abilities in childhood and adolescence predict later academic and professional success (Diamond, 2013; Kim et al., 2013). Several studies have also shown that the development of complex skills, such as arithmetic or reading (Blair and Razza, 2007; Christopher et al., 2012; Cragg and Gilmore, 2014), reasoning (Houde and Borst, 2015), theory of mind (Marcovitch et al., 2015), decision-making (Cassotti et al., 2014) and creativity (Cassotti et al., 2016), rely on the increased efficiency of IC. IC is thus considered a core mechanism of typical as well as atypical development (Borst et al., 2015; Casey and Caudle, 2013; Diamond, 2013).

Several studies have shown that the ability to solve a conflict in

affectively neutral contexts (also referred to as 'Cool' IC, Aïte et al., 2018; Prencipe et al., 2011) develops linearly from childhood to adulthood in close relation to the protracted maturation of the prefrontal cortex (PFC, Gogtay et al., 2004; Luna et al., 2010, 2015). Indeed, IC relies on the activation of a number of PFC sub-regions (see recent fMRI meta-analyses: Criaud and Boulinguez, 2013; Simmonds et al., 2008; Swick et al., 2011), namely, the dorsolateral PFC, the ventrolateral PFC, the inferior frontal cortex (IFG), especially in the right hemisphere, the anterior part of the insula, and the anterior cingulate cortex (ACC). IC also elicits activation in other brain regions, such as the parietal cortex (Criaud and Boulinguez, 2013), the subthalamic nucleus (Aron and Poldrack, 2006; Aron et al., 2016) and the striatum (i.e., caudate nucleus and putamen) (Beste et al., 2018). Striatal regions, classically involved in learning (Seger, 2006, 2008; Seger and Cincotta, 2005, 2006), are also involved in IC partly because of their structural and functional connectivity to the PFC (Beste et al., 2018).

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The early development of limbic regions, such as the ventral striatum and the amygdala (Chein et al., 2010), contributes to making adolescence a specific period with higher emotional reactivity and lower IC abilities in affectively charged contexts (Hare et al., 2008; Somerville et al., 2011). Several studies have investigated the developmental trajectory of the abilities to solve a conflict in an affectively charged context (also referred to as ‘Hot’ IC). In contrast to the linear development of Cool IC, Hot IC follows a non-linear inverted U-shaped developmental trajectory, in which adolescents are less effective than children and adults in solving conflicts in affectively charged contexts (Aïte et al., 2018). These results are consistent with the dual system neurodevelopmental models (Shulman et al., 2016) supporting an adolescent-specific developmental trajectory of Hot IC. For instance, the “maturational imbalance” model (Casey and Caudle, 2013) proposes that lower Hot IC at adolescence would result from an imbalance between a hypersensitivity of the limbic network (involved in emotions) and the immaturity of the PFC (involved in the control of emotions). More recently, the “driven dual systems” model (Luna and Wright, 2016) emphasizes the role of a hyperactive socioemotional system associated with an inverted U-shaped trajectory of the subcortical limbic system (e.g., ventral striatum) but with cognitive control that would plateau in mid-adolescence rather than continuing to increase until early adulthood.

IC abilities develop with age but may also be improved by cognitive training (Dowsett and Livesey, 2000; Zhao et al., 2018).

Previous studies on typically developed children used IC training of medium duration (5–10 h over several weeks) and child friendly versions of the Stop Signal or the Go-NoGo tasks. Some studies reported no transfer, namely, IC training induced improvements on the trained tasks but not on the non-trained tasks (Thorell et al., 2009), while other studies detected a transfer, namely, an increased performance after IC training in not only the trained tasks but also the non-trained tasks (non-trained tasks involving either other executive functions such as working memory and task switching (Zhao et al., 2018) or abstract reasoning abilities (Liu, Zhu et al., 2015)). Of note, the results showed that such transfers on non-trained tasks had short-lived effects, i.e., they did not persist and were no longer evident 6 months after the IC training (Zhao et al., 2018). IC training in children was also associated with brain changes. Using EEG, Liu, Zhu et al. (2015) found, particularly in girls, a specific effect on the N2 component, a classical neuro-functional index of IC (Daurignac et al., 2006; Jonkman et al., 2007).

In adults, previous studies showed that IC training of short (i.e., 1 h) to medium duration (i.e., 5–10 h over several weeks) - based on the Stop Signal, Go-NoGo, Stroop or Simon tasks - led to increased performance either in the trained task only (Berkman et al., 2014; Manuel et al., 2013; Talanow and Ettinger, 2018; Zhao et al., 2018) or also in non-trained tasks, involving IC abilities (Millner et al., 2012) or decision-making processes (Verbruggen et al., 2012). Such IC training in adults also led to functional brain changes in regions of the IC network (Berkman et al., 2014; Chavan et al., 2015; Manuel et al., 2013; Spierer et al., 2013) and parietal cortices (Manuel et al., 2010). Furthermore, behavioural changes in a trained task, i.e., the Stop Signal Task (SST), were found to be related to activity changes in the right IFG (Berkman et al., 2014). No transfer of such a non-affective training task to a non-trained affective task (emotion regulation task) was observed at the behavioural level (Beauchamp et al., 2016). However, brain activation changes, in regions associated with training on the SST (Berkman et al., 2014), during the execution of an emotion regulation task, appear to be the result of an SST-based IC training (Beauchamp et al., 2016), suggesting that the brain is subject to fast plastic changes. Brain changes following IC training are not limited to changes (either increases or decreases) in local activity but also to changes in long-distance functional connectivity during IC tasks (Hu et al., 2017). In addition to studying the effects of IC training on functional connectivity during an IC task, resting-state fMRI (rs-fMRI) studies also reported the effects of IC training on functional connectivity at rest (Cao et al., 2016).

Recent brain imaging studies also showed that (i) local properties of BOLD signal oscillations at rest, namely, the Regional Homogeneity (ReHo, Jiang and Zuo, 2016; Zang et al., 2004) and the fractional Amplitude of Low Frequency Fluctuations (fALFF, Zou et al., 2008) of the spatio-temporal coherence and amplitude of the local BOLD fluctuations, can serve as non-invasive proxies of brain metabolism (Aiello et al., 2015); and (ii) individual differences in these BOLD fluctuations at rest are related to individual differences in Cool IC efficiency in adults (Liu, Chen et al., 2015 for ReHo and Hu et al., 2014 for fALFF).

In this context, we tested whether ReHo and fALFF at baseline (before training) are associated with Cool and Hot IC efficiency in adolescents aged 16–17 years old. We focused on the critical role of two cortical regions (i.e., the IFG and ACC) and two subcortical regions (i.e., the caudate nucleus and putamen) playing a critical role in IC. In line with previous findings, we anticipated correlations at baseline between IC efficiency and ReHo and fALFF signals in these regions (Hu et al., 2014; Liu, Chen et al., 2015). We also anticipated different correlation patterns in Cool IC compared to Hot IC tasks. In addition, we also tested the effect of a computerized 5-week IC training compared to an active control training in adolescents on Cool and Hot cognitive control efficiency and on the local properties of BOLD fluctuations at rest (i.e., ReHo and fALFF). Note that comparing the effect of IC to an active control training group allowed us to control for test-retest effects (see, e.g., Diamond and Ling, 2016). In line with previous studies, we anticipated behavioural changes after IC training on the trained task (i.e., Cool Stroop task) (Berkman et al., 2014; Zhao et al., 2018) but not on the affective non-trained task (i.e., Hot Stroop task) (Beauchamp et al., 2016). We also expected functional changes after IC training in the cortical (i.e., the ACC and IFG) and subcortical (i.e., the caudate nucleus and putamen) regions of the IC (e.g., Beauchamp et al., 2016; Berkman et al., 2014).

2. Materials and methods

2.1. Participants

Sixty healthy adolescents, aged 16 to 17 years old (mean age 16.78 ± 0.49 y.o, 21 males), were recruited from high schools in Paris (France), coming from high-income families (mean income/month: $4375\text{€} \pm 1100\text{€}$). The recruited participants were all of the regular age for their grade. Participants were randomly assigned to two different trainings: the Inhibitory Control (IC) group ($n = 32$, 16.85 ± 0.53 y.o, 11 males) and the Active Control (AC) group ($n = 28$, 16.71 ± 0.44 y.o, 10 males; for more information, see the ‘Training procedure’). A computerized algorithm (randoweb) was used to ensure a balanced male to female ratio between the two training groups. Eight participants were discarded from the training analyses because they did not reach the minimum number of 15 training sessions and thus (i) did not have sufficient training (i.e., at least 15 sessions of 15 min, which means a minimum of 3 h 45 min) and/or (ii) stopped the training too early before the post-training session. Therefore, the sample for these training analyses included 52 participants (IC: $n = 28$, 16.83 ± 0.53 y.o, 8 males; AC: $n = 24$, 16.72 ± 0.44 y.o, 7 males). The participants in the AC and the IC groups completed an average of 24.21 ± 1.72 ([20–26]) and 24.96 ± 2.10 ([21–33]) training sessions, respectively. There was no performance difference at baseline (pre-training session) between the groups for the Cognitive Stroop Task (AC: 86.56 ± 88.45 vs. IC: 61.95 ± 89.55 , $F(1,50) = 0.987$, $p = .325$, $\eta_p^2 = 0.019$) or for the emotional version of the Stroop task (AC: 62.61 ± 123.81 vs. IC: 49.94 ± 80.10 , $F(1,50) = 0.197$, $p = .659$, $\eta_p^2 = 0.004$). All participants were right-handed, as determined by the Edinburgh Handedness Inventory (Oldfield, 1971), born full-term, had normal or corrected-to-normal vision, had no history of neurological disease, and had no cerebral abnormalities. Parents or legal guardians gave written consent, and all adolescents agreed to participate. All participants were tested in accordance with the national and international norms that govern the

use of human research participants. This study was approved by a national ethics committee (IRB 2015-A00811-48).

2.2. Experimental procedure

During the training period, each participant performed 25 training sessions on electronic tablets at home, 15 min per day, 5 days a week for 5 weeks. The participants were randomly assigned to the IC group or the AC group using a single-blind design. During the training period, each participant in the IC group performed both the classic version of the Stroop task (*Colour-Word Stroop task / Cool Stroop task*) and the *Stop Signal Task (SST)*, and each participant in the AC group answered knowledge- and vocabulary-based questions (Jaeggi et al., 2011). To limit assessor-related bias, instructions and responses were given through the electronic tablets. This procedure ensured that all participants were exposed to similar experimental demands and similar levels of motivation (Zhao et al., 2018). This training programme was designed by the authors.

In before (pre-test) and after (post-test) training sessions, participants performed a battery of cognitive tests (~2 h) and a multimodal MRI acquisition (~1 h 30). During the cognitive evaluation, the participants individually performed different cognitive tests involving executive functions (i.e., working memory, flexibility and inhibition), including an affectively neutral (*Colour-Word Stroop Task / Cool Stroop*) and an affectively charged (*Emotional Stroop Task / Hot Stroop*) version of the Stroop task, following instructions displayed on the computer screen. We focused on these two versions of the Stroop task because they are sensitive to developmental differences in Cool versus Hot IC (Aïte et al., 2018). Indeed, Aïte et al. (2018) reported a linear development of Cool IC abilities and a quadratic developmental trajectory of Hot IC abilities from childhood to adulthood, showing that adolescence is a critical developmental period during which adolescents are less efficient than both children and adults in solving conflicts in affectively-charged contexts. The MRI session included anatomical and resting state functional sequences. Other MRI acquisition sessions — functional MRI during the Stop-Signal Task, Attention Network Task, Dot Task and Delayed Discounting Task along with a diffusion MRI sequence — out of the scope of the present study, were also acquired.

2.2.1. Training sessions

In both IC and AC trainings, the level of difficulty was increased progressively and adapted in real time to the learning curve of each participant in order to maintain the motivation of the participant and to prevent automaticity (Buschkuhl et al., 2012; Green and Bavelier, 2008; Klingberg, 2010). All tasks were implemented on tactile tablets using E-prime 2.0.10 (Psychology Software Tools, Pittsburgh, PA).

Since (i) IC is a multidimensional construct (Diamond, 2013) and (ii) transfer effects can be potentially larger when the same cognitive function is trained with different tasks (Buschkuhl et al., 2012; Green and Bavelier, 2008), IC training included two tasks involving interference control (*Colour-Word Stroop task / Cool Stroop task*) and response inhibition (*Stop Signal Task*).

In the *Colour-Word Stroop task*, participants were instructed to identify the ink colour (e.g., blue) of a printed word denoting a colour by pressing one of the four colour buttons (i.e., blue, green, yellow, red) on the tactile tablet. The word colour and the ink colour could be either congruent (e.g., “blue” written in blue) or incongruent (e.g., “blue” written in red). In addition, we designed control items (i.e., colour word written in black) in which participants were instructed to determine the colour denoted by the word. Control items were intended to force participants to encode the colour of the word throughout the training sessions. Words were presented on the centre of the screen in a 24-pt Bold Arial Font. The level of difficulty increased in the congruent and incongruent Stroop items as the stimulus onset asynchrony (SOA) decreased between the presentation of the word (written in light grey) and the colouring of this word in one of the four ink colours (blue,

yellow, green or red, see, e.g., Appelbaum et al., 2014). At the beginning of the training, the SOA was set at 450 ms (Level 1) and decreased by 50 ms intervals at each level of task difficulty (up to an SOA of 100 ms in Level 8). At each level, participants performed 13 control, 13 congruent, and 13 incongruent Stroop items.

In the SST, participants were instructed to press one of two response buttons on the tactile tablet to indicate the direction of an arrow presented on the screen and to withhold their responses if an auditory signal (i.e., stop signal) was presented after the presentation of the arrow (e.g., Aron et al., 2014). The task difficulty was also adjusted to the participants’ level. The time interval between the presentation of the arrow and the stop signal (i.e., the SOA) was manipulated. To increase the difficulty, the SOA was increased, and to decrease it, the SOA was reduced. On Level 1, the SOA was set at 100 ms and was increased by 50 ms intervals at each level of task difficulty (up to an SOA of 450 ms in Level 8). At the beginning of each training session, participants performed 16 Go trials. Then, each level in each training session consisted of 30 Go trials and 10 Stop trials.

The AC training consisted of knowledge- and vocabulary-based tasks of increasing difficulty (see Jaeggi et al., 2011). In each task, 4-choice trivia-like questions were presented, and participants were asked to answer by pressing one of the four answers presented on the screen. A maximum of 30 s was allowed for participants to answer each question. An online pre-test, administered to more than 1600 adolescents, was used to categorize the questions into 8 difficulty levels for each task. Ten questions were finally chosen for each difficulty level.

On any given level, for the four tasks, the task difficulty was increased when participants achieved 90% accuracy, decreased when participants failed to achieve 70% accuracy, and remained the same when participants reached between 70% and 90% accuracy. Each training session consisted of several blocks during which the participants had to earn a maximum number of points to upgrade level. For each task and each training session, participants started the session with the difficulty level just below the one they achieved during the previous training session. At the end of each training session, the participants were asked to complete a short auto-evaluation questionnaire on their motivation and engagement during the session, which provided the experimenters with details regarding (i) the number of sessions performed during the training phase and (ii) the quality of the training.

To determine whether the adolescents progressed in the IC and AC training groups, we ran separate t-tests on the average level of difficulty reached by the participants in the first and last sessions. We found a significant difference between the two sessions in the AC group (first session: 2.26 ± 0.22 , last session: 6.44 ± 0.40 ; $t(26) = -12.71$, $p < .001$, $d = 2.45$) and in the IC group (first session: 2.33 ± 0.13 , last session: 5.08 ± 0.20 ; $t(31) = -14.05$, $p < .001$, $d = 2.48$). Importantly, participants made progress from the first to the last training session in both the AC and the IC training groups.

2.2.2. Evaluation of cool and hot inhibitory control

Both tasks were implemented with E-prime 2.0.10 (Psychology Software Tools, Pittsburgh, PA) and performed individually on a laptop computer with a resolution of 1366×768 pixels and a refresh rate of 60 Hz.

For the *Colour-Word Stroop task*, we designed sixteen standard Stroop items combining four different colour names (red, green, blue and yellow) with the four corresponding ink colours (RGB colour codes: 255;0;0, 0;255;0, 0;0;255, and 255;255;0, respectively). Four items were congruent (e.g., “red” written in red), and 12 were incongruent (e.g., “red” written in blue). Items were displayed in the centre of the screen in 24-pt Bold Courier New on a grey background (RGB code 135;135;135). The participants were instructed to identify the ink colours while ignoring the meaning of the words presented.

In the *Emotional Stroop task*, four black-and-white photographic images depicting happy, angry, sad, and fearful faces (two males and two females), taken from the *NimStim* set of facial expressions

(Tottenham et al., 2009), were combined with four words naming the corresponding emotions (e.g., happiness, anger, sadness and fear) to create four congruent items (e.g., the fearful face with “fear” written underneath) and 12 incongruent items (e.g., the fearful face with “anger” written underneath). The faces with the word written underneath were presented in the centre of the screen on a grey background (RGB code 135;135;135). The participants were instructed to indicate the emotion of the facial expressions while ignoring the word written underneath.

For both the Cool Stroop and the Hot Stroop tasks, the participants responded by manually pressing two keyboard buttons with their left and right index fingers (the ‘s’ button for yellow or blue and the ‘l’ button for red or green in the Cool Stroop task; the ‘d’ button for happiness or sadness and the ‘k’ button for anger or fear in the Hot Stroop task). Each key was labelled with a sticker of the corresponding colour or emotion. Each trial started with the presentation of a black fixation cross on a grey background for 1500 ms, and then one of the colour words or faces / emotional words was displayed for a maximal duration of 3000 ms. The participants were asked to answer as quickly as possible while maintaining high accuracy. The response times (RTs) were measured from the stimulus onset to the button press. For each Stroop task, participants performed a block of 64 trials (i.e., 32 congruent and 32 incongruent trials), preceded by two training blocks. In the first training block, participants learned to associate each response button to the corresponding colour or emotion by pressing the key on the keyboard corresponding to the colour dot or facial expression presented on the screen (each colour dot or facial expression was presented two times for a total of 8 trials). In the second training block, participants performed 6 congruent and 6 incongruent Stroop items and received feedback on the correctness of their answers. The presentation of the trials was randomized in both training and experimental blocks. For both tasks, for each participant, we computed the mean RT for each condition (i.e., congruent [C] and incongruent [I]) on correctly performed trials. Then, the Stroop score (i.e., the interference score [IS], which is the difference in RTs between congruent and incongruent items), was computed for each participant, where a higher Stroop score revealed lower IC efficiency. Stroop scores were screened and cleaned for possible aberrant values using a nonparametric approach: values lower than median - 2 MAD (MAD: median absolute deviation) or greater than median + 2 MAD were considered outliers. Data imputation, based on the median value over the whole sample, was also applied to replace any missing data and outliers. Receptivity of cognitive training was assessed from the relative change after training (i.e., relative change = (post - pre) / pre) for both Stroop scores (i.e., *Colour-Word Stroop task* and *Emotional Stroop task*). For each task, the relative change after training was computed from Stroop scores already screened and cleaned for aberrant values. Then, data imputation, based on the median value over the whole sample, was applied to replace any missing data and outliers. This procedure was used to obtain as much data as possible and thus to increase the statistical power of our statistical analyses.

2.3. MRI acquisition

Functional MRI data were acquired at the CIREN facility using a 3 T MRI scanner (GE, DISCOVERY MR750 3 T MR System, United States). We acquired anatomical MRI data using a high-resolution 3-D T1-weighted gradient sequence (field of view = 256 mm, slice thickness = 1 mm, matrix size = 256 x 256 mm, resolution = 1 mm³, flip angle = 11°, repetition time = 8.2 ms, echo time = 3.2 ms, inversion time = 400 ms) and an rs-fMRI using a T2*-weighted echo-planar imaging (EPI) sequence (field of view = 192 mm, slice thickness = 3 mm, 42 slices, matrix size = 64 x 64 mm, resolution = 3 x 3 x 3 mm³, flip angle = 90°, repetition time = 2000 ms, echo time = 23 ms). During the rs-fMRI sequence, the participants were asked to lay still with their eyes closed, but not to fall asleep, instead to try to think of

nothing at all, and in the case of a sticky thought, to think of a starry sky.

2.4. MRI analysis

2.4.1. Preprocessing of rs-fMRI data

MRI preprocessing and statistical analyses were performed using SPM12 (Wellcome Department of Imaging Neuroscience, London, UK) running on MATLAB 2014b (Mathworks Inc., Natick, USA) with dedicated toolboxes (the advanced version of Data Processing Assistant for Resting-State fMRI, DPARSF; Yan and Zang, 2010, <http://www.restfmri.net>) and ArtRepair (<http://cibsr.stanford.edu/tools/human-brain-project/artrepair-software.html>; Mazaika et al., 2007). These software were used to pre-process the fMRI data and compute the ReHo and fALFF images. An in-house MATLAB function was used to estimate the median value of the ReHo and fALFF signals within individual Regions of Interest (ROIs) derived from the AAL2 atlas (Rolls et al., 2015; Tzourio-Mazoyer et al., 2002).

A seven-step approach was used to preprocess the rs-fMRI data. The first 10 time points were removed to avoid the non-equilibrium effects of magnetization, and the remaining 168 time points of functional BOLD images were then processed as follows:

- 1 Slice time corrected for interleaved acquisition.
- 2 Realigned to correct for head movement by coregistering all the subsequent volumes to the first time point.
- 3 Repaired if necessary, using ArtRepair, for volumes with movements (rapid motion threshold > 0.5 mm / TR) using linear interpolation from the nearest unrepaired scans.
- 4 Spatially normalized. To normalize functional images, each participant's T1-weighted images were coregistered to the mean functional images and were subsequently segmented into grey matter (GM), white matter (WM), and cerebrospinal fluid (CSF). The parameters obtained from the segmentation were used to normalize each participant's functional images onto the Montreal Neurological Institute (MNI) space.

These functional images were then processed as follows:

- 5 Resampled to a voxel size of 3 x 3 x 3 mm³.
- 6 Smoothed with an 8 mm FWHM Gaussian Kernel. This smoothing step, during preprocessing, was applied only for fALFF analysis, and not ReHo analysis, to prevent artificially increasing the regional similarity (Yan and Zang, 2010). The smoothing of ReHo maps was thus performed after ReHo calculation.
- 7 To remove BOLD signal fluctuations unrelated to neural activity, the 6 head motion parameters plus their derivatives and the corresponding squared items (Friston 24; Friston et al., 1996) as well as WM, CSF and global mean signal were regressed out as nuisance variables; linear trend was also removed from each voxel's time course.

2.4.2. Estimation of ReHo and fALFF signals

If low-frequency fluctuations (0.01-0.1 Hz) of the BOLD signal at rest reflect spontaneous neural activity (Lu et al., 2007), then high-frequency oscillations capture physiological signals such as cardiac and respiratory signals (Cordes et al., 2001). Before ReHo estimation, data were therefore bandpass filtered (0.01-0.1 Hz) to minimize any confounding physiological effects. ReHo was then computed at the voxel level by calculating the Kendall's coefficient of concordance (Kendall and Gibbons, 1990) of the BOLD time series of 27 neighbouring voxels (Zang et al., 2004). ReHo is thus defined as the spatio-temporal coherence of the signal of a voxel with the signal of its nearest neighbours (Zang et al., 2004). The ReHo maps were finally smoothed with an 8 mm FWHM Gaussian Kernel.

The regional spontaneous activity was also examined using the

complementary ALFF measure (Biswal et al., 1995). ALFF reflects the intensity of regional spontaneous brain activity (Zou et al., 2008) and is particularly sensitive to physiological noise. The fractional Amplitude of Low Frequency Fluctuations (fALFF) — defined as the total signal amplitude within the low-frequency range (0.01–0.1 Hz) divided by the total signal amplitude of the entire detectable frequency range (i.e., 0.01–0.25 Hz; Song et al., 2011) — was therefore used as it improves the sensitivity and specificity in detecting spontaneous brain activities (Zou et al., 2008).

To increase the signal-to-noise ratio, ReHo and fALFF values were extracted from the AAL2 atlas (Rolls et al., 2015; Tzourio-Mazoyer et al., 2002) and averaged over the critical brain regions of the IC network: two cortical regions (the ACC and the IFG) and two sub-cortical regions (the caudate nucleus and the putamen) (see Fig. 2).

2.5. Statistical analysis

To confirm that ReHo and fALFF signals were associated with IC efficiency (Hu et al., 2014; Liu, Chen et al., 2015; Tian et al., 2012), we conducted univariate linear models with Stroop interference scores as the co-variable and brain hemispheres (i.e., “right” vs. “left”) as the within-factor. Both the Colour-Word Stroop task (Cool IC) and the Emotional Stroop task (Hot IC) were analysed. Data from participants in both the AC and IC training groups were pooled into a common sample as was done in the pre-test session; participants had not yet followed any training.

Univariate linear models were used to test whether the relative changes in Stroop scores after training in both the Cool and the Hot Stroop tasks differed between the training groups (i.e., CA vs. CI). Relative (i.e., relative change = (post - pre) / pre), instead of absolute (i.e., post - pre), changes were used in the analyses to control for baseline variability.

We then tested whether the ReHo and fALFF signals changed after 5 weeks of IC training, i.e., whether ReHo and fALFF might also be sensitive biomarkers of IC training. Thus, for each ROI, a univariate linear model analysis was conducted with group (“AC” vs. “IC”) as the between-factor and brain hemisphere (“right” vs. “left”) as the within-factor. The dependent variable corresponded to the relative difference in ReHo or fALFF signals between the pre-test and post-test. To test whether the whole pattern of relative regional changes (i.e., pattern of relative changes including all the ROIs selected) differed between the two groups (i.e., “AC” vs. “IC”), we then carried out multivariate linear models for ReHo and fALFF separately.

The main effects and interactions were investigated with F-tests. A two-tailed p-value of less than .05 was considered statistically significant. The analyses were not corrected for multiple comparisons but were controlled for the age and sex. We also controlled for the high school attended by the participants to control for possible fixed effects associated with the affiliation to specific high schools. All statistical analyses were carried out with R software version 3.3.2 software (<http://www.r-project.org/>) and the ‘car’ and ‘effects’ packages.

3. Results

3.1. Behavioural analyses

The analysis of the cognitive changes after training, tested by comparing the relative changes after training for both Cool and Hot Stroop scores between the AC and IC groups, did not reveal significant group-specific training effects for the Cool Stroop ($F(1,50) = 0.379$, $p = .541$, $\eta_p^2 = 0.008$) or for the Hot Stroop ($F(1,50) = 0.214$, $p = .645$, $\eta_p^2 = 0.004$) scores (see Fig. 1 and Supplementary Material).

3.2. ReHo / fALFF and IC efficiency

Univariate linear model analyses revealed the main effects of the

Cool Stroop score on the fALFF signal, with positive associations between the Cool Stroop score and the fALFF signals in bilateral ACC ($F(1,45) = 6.16$, $p = .017$, $\eta_p^2 = 0.12$) and IFG ($F(1,45) = 8.01$, $p = .0069$, $\eta_p^2 = 0.15$) (see Fig. 2). There was no significant association between the Cool Stroop score and the ReHo signals.

Regarding Hot IC, analyses revealed the main effects of the Hot Stroop score on the ReHo signal with positive associations between the Hot Stroop score and the ReHo signals in the bilateral caudate nucleus ($F(1,45) = 4.25$, $p = .045$, $\eta_p^2 = 0.08$), putamen ($F(1,45) = 4.19$, $p = .047$, $\eta_p^2 = 0.08$) and ACC ($F(1,45) = 6.45$, $p = .015$, $\eta_p^2 = 0.12$) (Fig. 2). Similar results were observed for fALFF, with positive associations in the bilateral caudate nucleus ($F(1,45) = 7.95$, $p = .0071$, $\eta_p^2 = 0.15$) putamen ($F(1,45) = 8.16$, $p = .0065$, $\eta_p^2 = 0.15$) and ACC ($F(1,45) = 10.77$, $p = .0020$, $\eta_p^2 = 0.19$) (Fig. 2). For both ReHo and fALFF, analyses also revealed an interaction between the Hot Stroop interference score and hemisphere within the putamen (ReHo: $F(1,45) = 5.05$, $p = .030$, $\eta_p^2 = 0.10$; fALFF: $F(1,45) = 8.56$, $p = .0054$, $\eta_p^2 = 0.16$), showing stronger associations between ReHo/fALFF signals and interference score within the left rather than the right hemisphere (Fig. 2).

3.3. ReHo and fALFF sensitivity to IC training

Univariate linear model analysis of relative changes in ReHo signal revealed a significant group-by-hemisphere interaction in the caudate nucleus ($F(1,37) = 5.01$, $p = .031$, $\eta_p^2 = 0.12$) (see Fig. 3 and Table 1). A similar group-by-hemisphere interaction ($F(1,37) = 5.75$, $p = .022$, $\eta_p^2 = 0.13$) was detected for the relative change of the fALFF signal within this region (see Fig. 3 and Table 2). In the right hemisphere, ReHo and fALFF signals increased after training in the AC group and decreased in the IC group, while in the left hemisphere, ReHo and fALFF signals increased in both AC and IC groups (see Fig. 3 and Tables 1–2). A main group effect was also detected for the fALFF relative change within the putamen ($F(1,37) = 4.50$, $p = .041$, $\eta_p^2 = 0.11$), with a fALFF signal increasing after training for participants in the AC group and decreasing for participants in the IC group (see Fig. 3 and Table 2). Univariate analysis did not reveal other significant results in the sub-cortical or the cortical brain regions.

The multivariate analysis on the whole pattern of relative changes after training indicated a significant main group effect for ReHo ($F(8,30) = 2.77$, $p = .02$, $\eta_p^2 = 0.42$) and fALFF ($F(8,30) = 2.45$, $p = .03$, $\eta_p^2 = 0.39$) (Fig. 3), showing that ReHo and fALFF change patterns differed between the IC and AC groups.

4. Discussion

Consistent with the findings of previous studies in adults (Deng et al., 2016; Liu, Chen et al., 2015; Takeuchi et al., 2015), we found that ReHo and fALFF signals were associated with IC efficiency during adolescence. Importantly, we are the first to provide evidence that the relation between ReHo and fALFF signals differ according to the type of IC tasks, namely, cognitive (Cool) or emotional (Hot) Stroop tasks, in adolescents.

We found that the fALFF signal in the IFG and ACC, a non-invasive proxy of regional brain metabolism (Aiello et al., 2015), was positively correlated with the Cool Stroop interference score. Hence, a lower fALFF signal was associated with a higher IC efficiency in adolescents. In the current study, neural activity at rest was investigated from the analysis of local properties of BOLD fluctuations, complimenting previous studies on IC at adolescence, based on functional and structural connectivity. Resting-state fMRI studies reported functional connectivity changes within the executive network, encompassing the fronto-parietal and the cingulo-opercular networks, with decreased short-range connections (correlations between close regions, i.e., ‘segregation’) and increased long-range connections (correlations between distant regions, i.e., ‘integration’) during development (Fair et al., 2007,

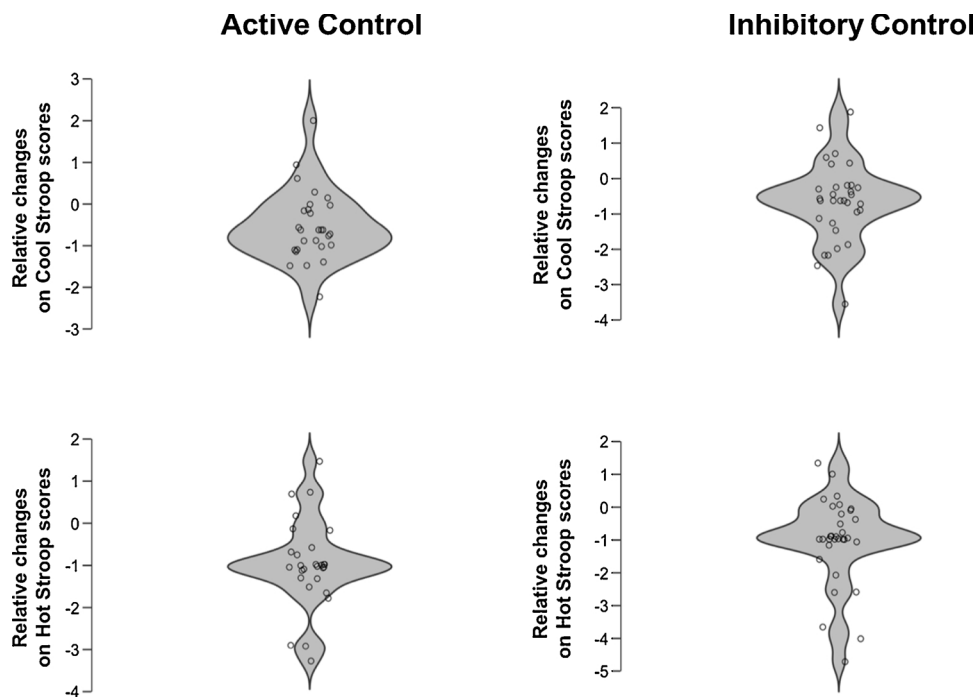


Fig. 1. Relative cognitive changes after training. These violin plots represent the relative changes after training [relative change = (post - pre) / pre] in both the Cool Stroop (first row) and the Hot Stroop (second row) scores, for both training groups: Active Control (left) and Inhibitory Control (right). Each dot represents a participant data. Data imputation, based on the median value over the whole sample, was applied to replace any missing data and outliers.

2009). Recently, a diffusion MRI study investigated the structural connectivity during development and revealed that both modular segregation and network efficiency are associated with enhanced executive performance and also mediate the improvement of executive functioning with age (Baum et al., 2017; Satterthwaite et al., 2013). At the cellular level, the myelination process, which enables more effective long-distance neural pathways, favours integration, whereas synaptic pruning favours segregation (Fair et al., 2007, 2009).

A previous study on adults using a Multi-Source Interference Task (combining the Stroop, Simon and flanker effects) reported a negative correlation between fALFF signal and interference score (Deng et al., 2016). We suspect that such inversion of the relation between fALFF and IC efficiency from adolescence to adulthood might stem from the protracted maturation of the prefrontal regions (Gogtay et al., 2004; Luna et al., 2010, 2015), and in particular of the non-linear cortical thickness changes characterized by a thickening of the cortex from childhood to adolescence followed by cortical thinning from adolescence to adulthood (Giedd and Rapoport, 2010; Gogtay and Thompson, 2010) associated with functional segregation (Fair et al., 2007, 2009).

ReHo and fALFF signals in subcortical (caudate nucleus and putamen) and cortical (ACC) regions were positively correlated with the Hot Stroop interference score, showing that adolescents with higher ReHo and fALFF signals within these brain regions of the IC network had lower IC efficiency. These findings provide additional evidence for the role of the caudate nucleus and the putamen, sub-regions of the striatum, in solving conflict in an affectively charged context (Chein et al., 2010; Hare et al., 2005). We also found a stronger association between Hot IC efficiency and ReHo / fALFF signals in the putamen in the left compared to the right hemisphere. This leftward asymmetry may be associated with the hemisphere-specific maturational changes that occur during adolescence, with a greater decrease of putamen volume in the left hemisphere compared to that of the right hemisphere (Dennison et al., 2013). Hence, the putamen in the left hemisphere, by maturing earlier than the putamen in the right hemisphere, might play a greater role in solving conflict in an emotional context during adolescence. The association between performance in the Hot Stroop task and the ReHo and fALFF signals within the dorsal part of the ACC suggests that the Hot Stroop task might also require conflict detection and conflict resolution processes similar to those involved in affectively

neutral contexts (Botvinick, 2007; Simon et al., 2015).

In addition to the association observed between the ReHo and fALFF signals and the Cool and Hot IC efficiencies at baseline, we also found IC training-related changes in these two measures of BOLD signal fluctuations at rest in the sub-regions of the striatum (i.e., caudate nucleus and putamen), key regions of the inhibitory control network (Beste et al., 2018; Grahn et al., 2008; Rubia et al., 2006) but also involved more generally in learning (Seger, 2006, 2008; Seger and Cincotta, 2005, 2006). These changes in striatal regions (i.e., the caudate nucleus and putamen) after a IC training are consistent with previous studies reporting (i) an increased caudate activation in the Stop versus Go condition during an SST task (Berkman et al., 2014) and (ii) fronto-basal changes by SST practice (Manuel et al., 2013; Spierer et al., 2013). These results are thus in line with fMRI studies reporting activations within the sub-thalamic nucleus (Aron and Poldrack, 2006; Aron et al., 2016) and the striatum (Beste et al., 2018) during IC tasks. The involvement of the striatal regions in IC is partly due to their structural and functional connectivity to the PFC (Beste et al., 2018). These ReHo and fALFF changes related to IC training were also found to be hemisphere-dependent. This hemispheric specificity is in line with previous studies in adolescents (Houdé et al., 2010; Rubia et al., 2006) and in adults (Garavan et al., 1999), which reported a rightward hemispheric dominance for response inhibition. For instance, Rubia et al. (2006) reported increased fronto-striatal activations, especially in the right caudate and putamen, from adolescence to adulthood in motor and cognitive IC tasks. Moreover, a meta-analysis of functional MRI studies in children and adolescents reported an age- and hemisphere-specific activation during executive tasks, with a larger activation in the right than in the left anterior insular cortex (AIC, a region involved in cognitive control; Bunge et al., 2002; Dosenbach et al., 2006) in adolescents but not in children (Houdé et al., 2010). Taken together, these different studies support the notion that the IC neural network is right-lateralized with an increasing lateralization with age (Houdé et al., 2010; Rubia et al., 2006).

Given that a 5-week computerized IC training induced changes in brain function, assessed by ReHo and fALFF signals at rest, we argue that such proxies of regional metabolism (Aiello et al., 2015) could provide more sensitive markers of the potential effect of intensive and sustained cognitive training compared to behavioural outcomes. This

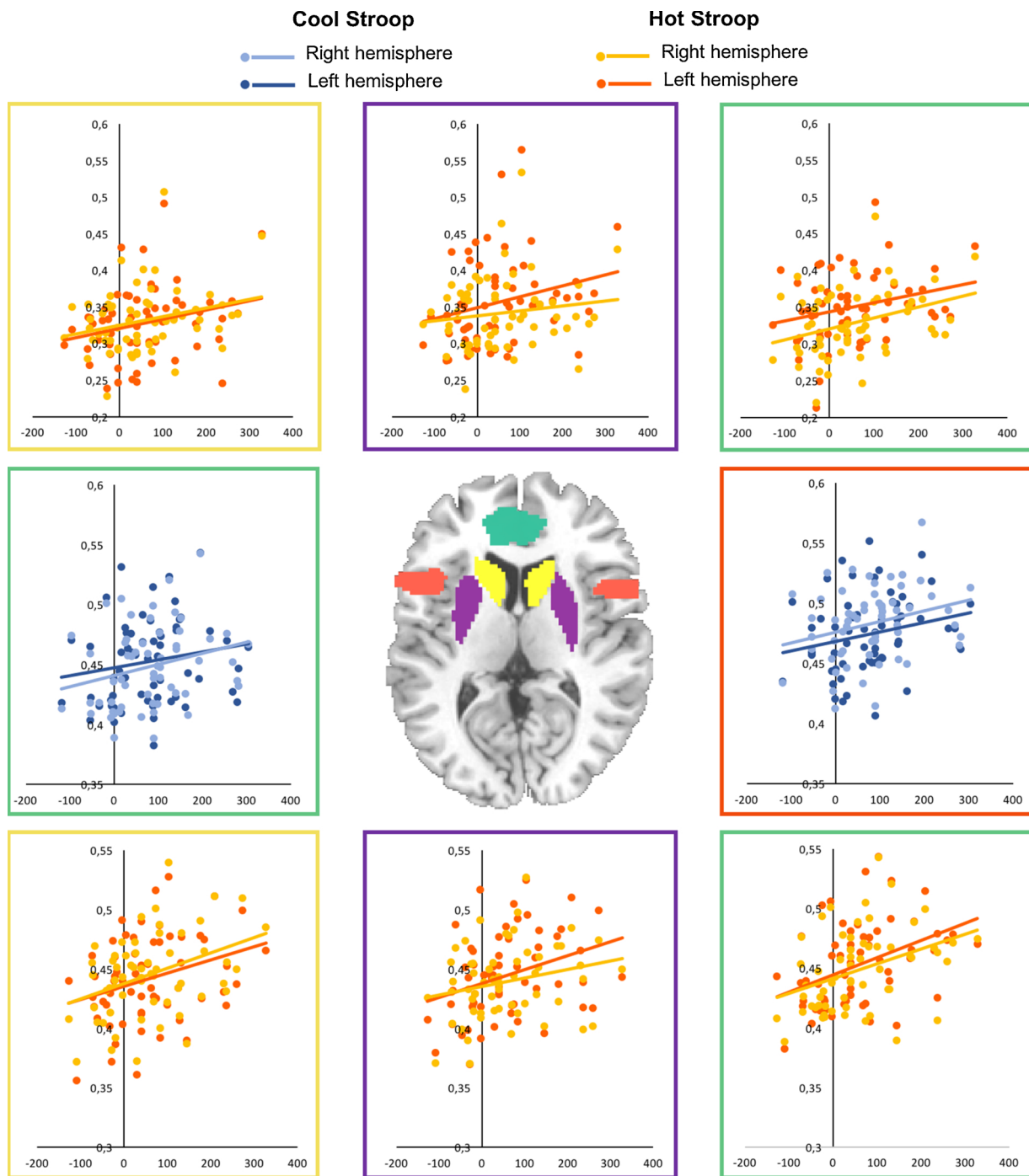


Fig. 2. Correlations between ReHo / fALFF signals and Inhibitory Control (IC) efficiency assessed with the Cognitive Stroop Task (Cool IC) and the Emotional Stroop task (Hot IC). Regions of Interest (ROI), represented on an axial slice (middle panel), were derived from the standard AAL2 atlas and colour coded as follows: caudate nucleus in yellow, putamen in purple, ACC in green, and IFG in orange. Graphs on the top of the figure correspond to the ReHo signal, and graphs in the middle and bottom correspond to the fALFF signal. Blue lines / dots on the graphs are used for Cool Stroop data and orange lines / dots for Hot Stroop data. Box colours are as described above, with the dispersion graph ReHo / fALFF versus interference score of Cool / Hot Stroop task codes for the analysed ROI. Dark and light lines / dots represent data from the left and right hemispheres, respectively. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

combination of brain changes associated with the lack of behavioural changes after cognitive training was recently observed by [Beauchamp et al. \(2016\)](#), who did not find behavioural changes but detected activation changes, during an emotion regulation task, in the left IFG and supramarginal gyrus, after an SST-based IC training. Notably, unlike the study by [Beauchamp et al. \(2016\)](#), which investigated task-evoked BOLD signal changes, the present study measured spontaneous BOLD signal fluctuations at rest. Such functional changes at rest may

reflect the consolidation of previous experience ([Lewis et al., 2009](#)), which in turn may lead to behavioural changes in the near future. On the other hand, the lack of training-induced cognitive changes may have also resulted from slight differences between the cognitive Stroop trained task and the cognitive version of the Stroop task performed during the pre- and the post-training sessions. Indeed, while improvements are often observed in the trained tasks, little or no transfer may be detected for non-trained tasks even if they are very similar to the

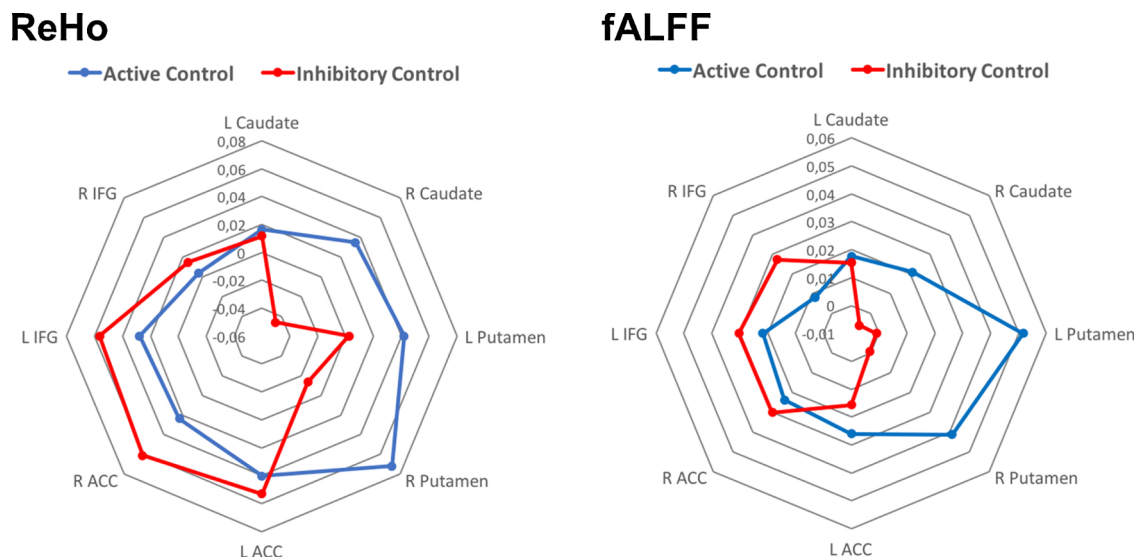


Fig. 3. Global patterns of the relative changes of ReHo and fALFF after training. The radar graphs represent relative changes in the ReHo signal (left panel) and the fALFF signal (right panel) in the subcortical (caudate nucleus, putamen) and cortical (ACC, IFG) regions of the IC network in the Inhibitory Control (in red) and Active Control (in blue) training groups. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

trained tasks (Green and Bavelier, 2008). Regarding the emotional IC, the lack of performance increase in the Hot Stroop task after a Cool Stroop training is consistent with a previous study reporting no transfer effect from a non-affective training task to a non-trained affective task (Beauchamp et al., 2016). As already suggested by previous studies (Green and Bavelier, 2008; Schmidt and Bjork, 1992), we may have to vary the task items to be learned and the context in which they appear during the training phase to attempt to facilitate the transfer from the trained task to non-trained tasks (e.g., Hot Stroop task). Indeed, this may force the participants to extract general principles about the trained task and thus may ensure that the learned skills are reused. Moreover, given that functional changes in the brain following IC training seem to precede behavioural changes, we suspect that increasing the training dose by increasing the session duration and / or the number of sessions (Beauchamp et al., 2016; Jolles and Crone, 2012; Kelly and Garavan, 2005) may facilitate the training transfer and thus enable the detection of changes at the behavioural level.

The present study has several limitations that call for caution when interpreting the results. First, despite the large sample size associated with a longitudinal design, the statistical effects are moderate. Our findings should thus be taken with caution and replicated with a larger group of independent samples. Future studies should investigate the effects of IC training at both the brain and behavioural levels not only on adolescents but also on younger and older participants (i.e., children

and young adults) to determine whether the IC training-related ReHo and fALFF signal changes are training- or age-specific. In addition to an immediate post-training effect, future work should also test the possible lasting effects (e.g., 3- or 6-months follow-up sessions) of an IC training. Furthermore, developmental studies, involving children, adolescents and adults should also investigate to what extent age can, or not, modulate these effects (Zhao et al., 2018).

In conclusion, we demonstrated for the first time that ReHo and fALFF signals, i.e., local properties of the BOLD signal fluctuations, provide information on the relationship between individual differences in the activity of the brain at rest and individual differences in both Cool and Hot IC efficiency and may also help monitor the effects of IC training. Future studies should determine whether ReHo and fALFF signals before training could possibly constitute reliable predictors of potential IC efficiency gain after training in both typical and clinical populations.

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Table 1

Relative changes in ReHo after training in the Active Control (AC) and Inhibitory Control groups (IC). Data for the AC and IC training groups are represented as the means ± standard errors. The main and interactive effects are derived from univariate linear models with group (“AC” vs. “IC”) as the between-factor and brain hemisphere (“right” vs. “left”) as the within-factor. Analyses were controlled for the age, sex, and high school of the participants.

ROIs	AC Mean (± SE)	IC Mean (± SE)	Statistics			
			Group effect		Group x Hemisphere	
			F-value	p-value	F-value	p-value
R ACC	0.024 (0.028)	0.061 (0.032)	0.60	0.443	0.64	0.429
L ACC	0.040 (0.023)	0.053 (0.033)				
R IFG	0.004 (0.24)	0.015 (0.020)	0.42	0.522	0.55	0.464
L IFG	0.028 (0.021)	0.056 (0.026)				
R Caudate	0.035 (0.029)	-0.046 (0.024)	1.42	0.241	5.01	0.031
L Caudate	0.016 (0.027)	0.012 (0.034)				
R Putamen	0.072 (0.026)	-0.013 (0.031)	1.61	0.213	0.59	0.446
L Putamen	0.042 (0.029)	0.002 (0.037)				

Table 2

Relative changes in fALFF after training in the Active Control (AC) and Inhibitory Control groups (IC). Data for the AC and IC training groups are represented as the means \pm standard errors. The main and interactive effects are derived from univariate linear models with group ("AC" vs. "IC") as the between-factor and brain hemisphere ("right" vs. "left") as the within-factor. Analyses were controlled for the age, sex, and high school of the participants.

ROIs	AC (Mean \pm SE)	IC (Mean \pm SE)	Statistics			
			Group effect		Group x Hemisphere	
			F-value	p-value	F-value	p-value
R ACC	0.024 (0.015)	0.030 (0.014)	0.05	0.828	2.95	0.094
L ACC	0.026 (0.017)	0.016 (0.015)				
R IFG	0.008 (0.015)	0.027 (0.013)	0.40	0.530	1.14	0.293
L IFG	0.022 (0.020)	0.030 (0.012)				
R Caudate	0.021 (0.019)	-0.006 (0.013)	1.25	0.271	5.75	0.022
L Caudate	0.018 (0.020)	0.015 (0.015)				
R Putamen	0.041 (0.019)	-0.0007 (0.014)	4.50	0.041	1.21	0.279
L Putamen	0.052 (0.023)	-0.001 (0.015)				

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.dcn.2019.100664>.

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