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1 **THE LOCAL PROPERTIES OF BOLD SIGNAL FLUCTUATIONS AT REST MONITOR**
2 **INHIBITORY CONTROL TRAINING IN ADOLESCENTS.**

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23

24 **HIGHLIGHTS**

25 • ReHo and fALFF signals differentially predict Cool and Hot IC in adolescents.

26 • Cool and Hot IC efficiency did not improve after IC training.

27 • ReHo and fALFF signals in subcortical areas changed after IC training.

28 • ReHo and fALFF signal changes precede behavioural changes.

29

30 **ABSTRACT**

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

45

46 **Keywords:** Inhibitory control, Training, Adolescence, IFG, ACC, Striatum

47

48 1. INTRODUCTION

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

58 Several studies have shown that the ability to solve a conflict in affectively neutral contexts
59 (also referred to as ‘Cool’ IC, Aïte et al., 2018; Prencipe et al., 2011) develops linearly from childhood
60 to adulthood in close relation to the protracted maturation of the prefrontal cortex (PFC, Gogtay et al.,
61 2004; Luna et al., 2010, 2015). Indeed, IC relies on the activation of a number of PFC sub-regions (see
62 recent fMRI meta-analyses: Criaud & Boulinguez, 2013; Simmonds et al., 2008; Swick et al., 2011),
63 namely, the dorsolateral PFC, the ventrolateral PFC, the inferior frontal cortex (IFG), especially in the
64 right hemisphere, the anterior part of the insula, and the anterior cingulate cortex (ACC). IC also elicits
65 activation in other brain regions, such as the parietal cortex (Criaud & Boulinguez, 2013), the sub-
66 thalamic nucleus (Aron & Poldrack, 2006; Aron et al., 2016) and the striatum (i.e., caudate nucleus and
67 putamen) (Beste et al., 2018). Striatal regions, classically involved in learning (Seger, 2006, 2008; Seger
68 & Cincotta, 2005, 2006), are also involved in IC partly because of their structural and functional
69 connectivity to the PFC (Beste et al., 2018).

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

84 cognitive control that would plateau in mid-adolescence rather than continuing to increase until early
85 adulthood.

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

88 Previous studies on typically developed children used IC training of medium duration (5 to 10
89 h over several weeks) and child friendly versions of the Stop Signal or the Go-NoGo tasks. Some studies
90 reported no transfer, namely, IC training induced improvements on the trained tasks but not on the non-
91 trained tasks (Thorell et al., 2009), while other studies detected a transfer, namely, an increased
92 performance after IC training in not only the trained tasks but also the non-trained tasks (non-trained
93 tasks involving either other executive functions such as working memory and task switching (Zhao et
94 al., 2018) or abstract reasoning abilities (Liu, Zhu et al., 2015)). Of note, the results showed that such
95 transfers on non-trained tasks had short-lived effects, i.e., they did not persist and were no longer evident
96 6 months after the IC training (Zhao et al., 2018). IC training in children was also associated with brain
97 changes. Using EEG, Liu, Zhu et al. (2015) found, particularly in girls, a specific effect on the N2
98 component, a classical neuro-functional index of IC (Daurignac et al., 2006; Jonkman et al., 2007).

99 In adults, previous studies showed that IC training of short (i.e., 1 h) to medium duration (i.e.,
100 5 to 10 h over several weeks) - based on the Stop Signal, Go-NoGo, Stroop or Simon tasks - led to
101 increased performance either in the trained task only (Berkman et al., 2014; Manuel et al., 2013;
102 Talanow & Ettinger, 2018; Zhao et al., 2018) or also in non-trained tasks, involving IC abilities (Millner
103 et al., 2012) or decision-making processes (Verbruggen et al., 2012). Such IC training in adults also led
104 to functional brain changes in regions of the IC network (Berkman et al., 2014; Chavan et al., 2015;
105 Manuel et al., 2013; Spierer et al., 2013) and parietal cortices (Manuel et al., 2010). Furthermore,
106 behavioural changes in a trained task, i.e., the Stop Signal Task (SST), were found to be related to
107 activity changes in the right IFG (Berkman et al., 2014). No transfer of such a non-affective training
108 task to a non-trained affective task (emotion regulation task) was observed at the behavioural level
109 (Beauchamp et al., 2016). However, brain activation changes, in regions associated with training on the
110 SST (Berkman et al., 2014), during the execution of an emotion regulation task, appear to be the result
111 of an SST-based IC training (Beauchamp et al., 2016), suggesting that the brain is subject to fast plastic
112 changes. Brain changes following IC training are not limited to changes (either increases or decreases)
113 in local activity but also to changes in long-distance functional connectivity during IC tasks (Hu et al.,
114 2017). In addition to studying the effects of IC training on functional connectivity during an IC task,
115 resting-state fMRI (rs-fMRI) studies also reported the effects of IC training on functional connectivity
116 at rest (Cao et al., 2016).

117 Recent brain imaging studies also showed that (i) local properties of BOLD signal oscillations
118 at rest, namely, the Regional Homogeneity (ReHo, Jiang & Zuo, 2016; Zang et al., 2004) and the

119 fractional Amplitude of Low Frequency Fluctuations (fALFF, Zou et al., 2008) of the spatio-temporal
120 coherence and amplitude of the local BOLD fluctuations, can serve as non-invasive proxies of brain
121 metabolism (Aiello et al., 2015); and (ii) individual differences in these BOLD fluctuations at rest are
122 related to individual differences in Cool IC efficiency in adults (Liu, Chen et al., 2015 for ReHo and Hu
123 et al., 2014 for fALFF).

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

139

140 2. MATERIALS AND METHODS

141

142 2.1. Participants

143 Sixty healthy adolescents, aged 16 to 17 years old (**mean age 16.78 ± 0.49 y.o.**, 21 males), were recruited
144 from high schools in Paris (France), **coming** from high-income families (mean **income / month:** 4375€
145 ± 1100 €). The recruited participants were all of the regular age for their grade. Participants were
146 randomly assigned to two different trainings: the Inhibitory Control (IC) group ($n = 32$, 16.85 ± 0.53
147 y.o, 11 males) and the Active Control (AC) group ($n = 28$, 16.71 ± 0.44 y.o, 10 males; for more
148 information, see the ‘Training procedure’). A computerized algorithm (randoweb) was used to ensure a
149 balanced **male to female** ratio between the two training groups. Eight participants were discarded from
150 the **training** analyses because they did not reach the minimum number of 15 training sessions and thus
151 (i) did not have sufficient training (i.e., at least 15 sessions of 15 min), which means a minimum of 3 h
152 45 **min**) and / or (ii) **stopped** the training too early before the post-training session. Therefore, the sample
153 for these training analyses included 52 participants (IC: $n = 28$, 16.83 ± 0.53 y.o, 8 males; AC: $n = 24$,
154 16.72 ± 0.44 y.o, 7 males). **The participants in the AC and the IC groups completed an average of 24.21**

155 ± 1.72 ([20 - 26]) and 24.96 ± 2.10 ([21 - 33]) training sessions, respectively. There was no performance
156 difference at baseline (pre-training session) between the groups for the Cognitive Stroop Task (AC:
157 86.56 ± 88.45 vs. IC: 61.95 ± 89.55 , $F(1,50) = 0.987$, $p = .325$, $\eta^2_p = 0.019$) or for the emotional version
158 of the Stroop task (AC: 62.61 ± 123.81 vs. IC: 49.94 ± 80.10 , $F(1,50) = 0.197$, $p = .659$, $\eta^2_p = 0.004$).
159 All participants were right-handed, as determined by the Edinburgh Handedness Inventory (Oldfield,
160 1971), born full-term, had normal or corrected-to-normal vision, had no history of neurological disease,
161 and had no cerebral abnormalities. Parents or legal guardians gave written consent, and all adolescents
162 agreed to participate. All participants were tested in accordance with the national and international
163 norms that govern the use of human research participants. This study was approved by a national ethics
164 committee (IRB 2015-A00811-48).

165

166 2.2. Experimental procedure

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

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

190

191 2.2.1. Training sessions

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

197 Since (i) IC is a multidimensional construct (Diamond, 2013) and (ii) transfer effects can be
198 potentially larger when the same cognitive function is trained with different tasks (Buschkuehl et al.,
199 2012; Green & Bavelier, 2008), IC training included two tasks involving interference control (*Colour-*
200 *Word Stroop task / Cool Stroop task*) and response inhibition (*Stop Signal Task*).

201 In the *Colour-Word Stroop task*, participants were instructed to identify the ink colour (e.g.,
202 blue) of a printed word denoting a colour by pressing one of the four colour buttons (i.e., blue, green,
203 yellow, red) on the tactile tablet. The word colour and the ink colour could be either congruent (e.g.,
204 “blue” written in blue) or incongruent (e.g., “blue” written in red). In addition, we designed control
205 items (i.e., colour word written in black) in which participants were instructed to determine the colour
206 denoted by the word. Control items were intended to force participants to encode the colour of the word
207 throughout the training sessions. Words were presented on the centre of the screen in a 24-pt Bold Arial
208 Font. The level of difficulty increased in the congruent and incongruent Stroop items as the stimulus
209 onset asynchrony (SOA) decreased between the presentation of the word (written in light grey) and the
210 colouring of this word in one of the four ink colours (blue, yellow, green or red, see, e.g., Appelbaum
211 et al., 2014). At the beginning of the training, the SOA was set at 450 ms (Level 1) and decreased by 50
212 ms intervals at each level of task difficulty (up to an SOA of 100 ms in Level 8). At each level,
213 participants performed 13 control, 13 congruent, and 13 incongruent Stroop items.

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

223 The AC training consisted of knowledge- and vocabulary-based tasks of increasing difficulty
224 (see Jaeggi et al., 2011). In each task, 4-choice trivia-like questions were presented, and participants
225 were asked to answer by pressing one of the four answers presented on the screen. A maximum of 30 s

226 was allowed for participants to answer each question. An online pre-test, administered to more than
227 1600 adolescents, was used to categorize the questions into 8 difficulty levels for each task. Ten
228 questions were finally chosen for each difficulty level.

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

238 To determine whether the adolescents progressed in the IC and AC training groups, we ran
239 separate t-tests on the average level of difficulty reached by the participants in the first and last sessions.
240 We found a significant difference between the two sessions in the AC group (first session: 2.26 ± 0.22 ,
241 last session: 6.44 ± 0.40 ; $t(26) = -12.71$, $p < .001$, $d = 2.45$) and in the IC group (first session: 2.33
242 ± 0.13 , last session: 5.08 ± 0.20 ; $t(31) = -14.05$, $p < .001$, $d = 2.48$). Importantly, participants made
243 progress from the first to the last training session in both the AC and the IC training groups.

244

245 **2.2.2.Evaluation of Cool and Hot inhibitory control**

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

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

256 In the *Emotional Stroop task*, four black-and-white photographic images depicting happy,
257 angry, sad, and fearful faces (two males and two females), taken from the *NimStim* set of facial
258 expressions (Tottenham et al., 2009), were combined with four words naming the corresponding
259 emotions (e.g., happiness, anger, sadness and fear) to create four congruent items (e.g., the fearful face
260 with “fear” written underneath) and 12 incongruent items (e.g., the fearful face with “anger” written
261 underneath). The faces with the word written underneath were presented in the centre of the screen on

262 a grey background (RGB code 135;135;135). The participants were instructed to indicate the emotion
263 of the facial expressions while ignoring the word written underneath.

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

293 294 **2.3. MRI acquisition**

295 Functional MRI data were acquired at the CIREN facility using a 3T MRI scanner (GE, DISCOVERY
296 MR750 3T MR System, United States). We acquired anatomical MRI data using a high-resolution 3-D
297 T1-weighted gradient sequence (field of view = 256 mm, slice thickness = 1 mm, matrix size = 256 x

298 256 mm, resolution = 1 mm³, flip angle = 11°, repetition time = 8.2 ms, echo time = 3.2 ms, inversion
299 time = 400 ms) and an rs-fMRI using a T2*-weighted echo-planar imaging (EPI) sequence (field of
300 view = 192 mm, slice thickness = 3 mm, 42 slices, matrix size = 64 x 64 mm, resolution = 3 x 3 x 3
301 mm³, flip angle = 90°, repetition time = 2000 ms, echo time = 23 ms). During the rs-fMRI sequence, the
302 participants were asked to lay still with their eyes closed, but not to fall asleep, instead to try to think of
303 nothing at all, and in the case of a sticky thought, to think of a starry sky.

304

305 **2.4. MRI analysis**

306

307 **2.4.1. Preprocessing of rs-fMRI data**

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

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

- 320 1. Slice time corrected for interleaved acquisition.
- 321 2. Realigned to correct for head movement by coregistering all the subsequent volumes to the first
322 time point.
- 323 3. Repaired if necessary, using ArtRepair, for volumes with movements (rapid motion threshold
324 > 0.5 mm / TR) using linear interpolation from the nearest unrepaired scans.
- 325 4. Spatially normalized. To normalize functional images, each participant's T1-weighted images
326 were coregistered to the mean functional images and were subsequently segmented into grey
327 matter (GM), white matter (WM), and cerebrospinal fluid (CSF). The parameters obtained from
328 the segmentation were used to normalize each participant's functional images onto the Montreal
329 Neurological Institute (MNI) space.

330 These functional images were then processed as follows:

- 331 5. Resampled to a voxel size of 3 x 3 x 3 mm³.

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

340

341 2.4.2. Estimation of ReHo and fALFF signals

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

350 The regional spontaneous activity was also examined using the complementary ALFF measure
351 (Biswal et al., 1995). ALFF reflects the intensity of regional spontaneous brain activity (Zou et al., 2008)
352 and is particularly sensitive to physiological noise. The fractional Amplitude of Low Frequency
353 Fluctuations (fALFF) — defined as the total signal amplitude within the low-frequency range (0.01 -
354 0.1 Hz) divided by the total signal amplitude of the entire detectable frequency range (i.e., 0.01 - 0.25
355 Hz; Song et al., 2011) — was therefore used as it improves the sensitivity and specificity in detecting
356 spontaneous brain activities (Zou et al., 2008).

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

361

362 2.5. Statistical analysis

363 To confirm that ReHo and fALFF signals were associated with IC efficiency (Hu et al., 2014;
364 Liu, Chen et al., 2015; Tian et al., 2012), we conducted univariate linear models with Stroop interference
365 scores as the co-variable and brain hemispheres (i.e., "right" vs. "left") as the within-factor. Both the
366 Colour-Word Stroop task (Cool IC) and the Emotional Stroop task (Hot IC) were analysed. Data from

367 participants in both the AC and IC training groups were pooled into a common sample as was done in
368 the pre-test session; participants had not yet followed any training.

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

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

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

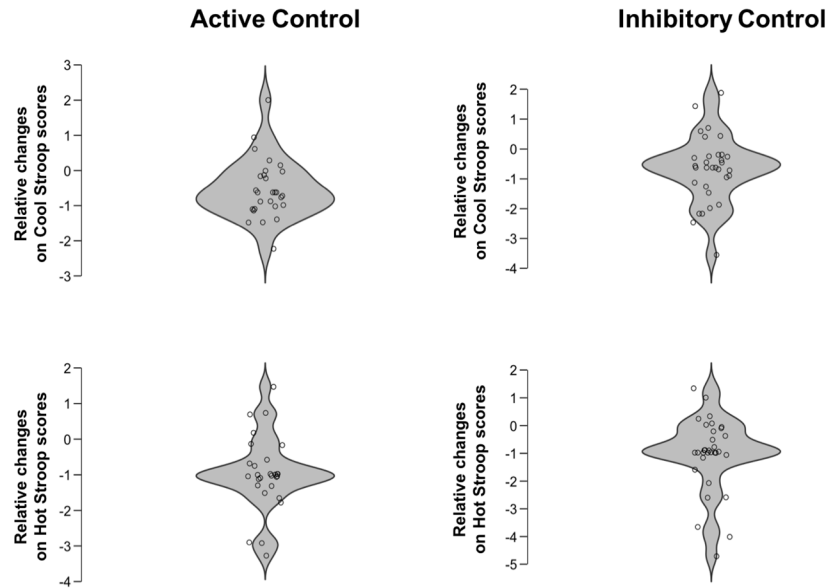
387

388 3. RESULTS

389

390 3.1. Behavioural analyses

391 The analysis of the cognitive changes after training, tested by comparing the relative changes after
392 training for both Cool and Hot Stroop scores between the AC and IC groups, did not reveal significant
393 group-specific training effects for the Cool Stroop ($F(1,50) = 0.379$, $p = .541$, $\eta^2_p = 0.008$) or for the
394 Hot Stroop ($F(1,50) = 0.214$, $p = .645$, $\eta^2_p = 0.004$) scores (see Figure 1 and Supplementary Material).
395



396

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

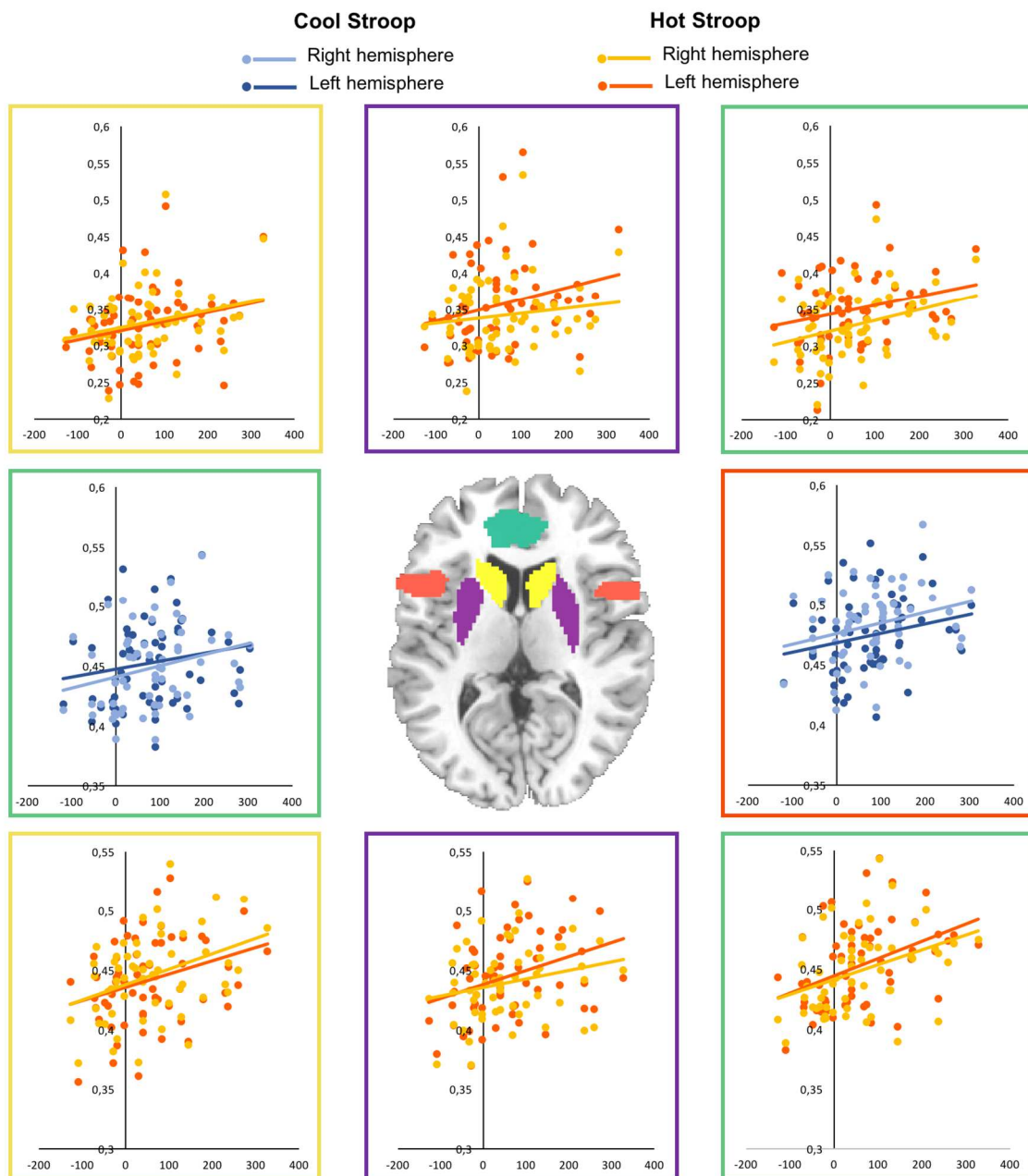
402

403 3.2. ReHo / fALFF and IC efficiency

404 Univariate linear model analyses revealed the main effects of the Cool Stroop score on the fALFF
 405 signal, with positive associations between the Cool Stroop score and the fALFF signals in bilateral ACC
 406 ($F(1,45) = 6.16, p = .017, \eta^2_p = 0.12$) and IFG ($F(1,45) = 8.01, p = .0069, \eta^2_p = 0.15$) (see Figure 2).
 407 There was no significant association between the Cool Stroop score and the ReHo signals.

408 Regarding Hot IC, analyses revealed the main effects of the Hot Stroop score on the ReHo signal
 409 with positive associations between the Hot Stroop score and the ReHo signals in the bilateral caudate
 410 nucleus ($F(1,45) = 4.25, p = .045, \eta^2_p = 0.08$), putamen ($F(1,45) = 4.19, p = .047, \eta^2_p = 0.08$) and ACC
 411 ($F(1,45) = 6.45, p = .015, \eta^2_p = 0.12$) (Figure 2). Similar results were observed for fALFF, with positive
 412 associations in the bilateral caudate nucleus ($F(1,45) = 7.95, p = .0071, \eta^2_p = 0.15$) putamen ($F(1,45) =$
 413 $8.16, p = .0065, \eta^2_p = 0.15$) and ACC ($F(1,45) = 10.77, p = .0020, \eta^2_p = 0.19$) (Figure 2). For both ReHo
 414 and fALFF, analyses also revealed an interaction between the Hot Stroop interference score and
 415 hemisphere within the putamen (ReHo: $F(1, 45) = 5.05, p = .030, \eta^2_p = 0.10$; fALFF: $F(1,45) = 8.56, p$
 416 $= .0054, \eta^2_p = 0.16$), showing stronger associations between ReHo / fALFF signals and interference
 417 score within the left rather than the right hemisphere (Figure 2).

418



419

420 Figure 2: **Correlations between ReHo / fALFF signals and Inhibitory Control (IC) efficiency**

421 **assessed with the Cognitive Stroop Task (Cool IC) and the Emotional Stroop task (Hot IC).**

422 Regions of Interest (ROI), represented on an axial slice (middle panel), were derived from the standard

423 AAL2 atlas and colour coded as follows: caudate nucleus in yellow, putamen in purple, ACC in green,

424 and IFG in orange. Graphs on the top of the figure correspond to the ReHo signal, and graphs in the

425 middle and bottom correspond to the fALFF signal. Blue lines / dots on the graphs are used for Cool

426 Stroop data and orange lines / dots for Hot Stroop data. Box colours are as described above, with the

427 dispersion graph ReHo / fALFF versus interference score of Cool / Hot Stroop task codes for the

428 analysed ROI. Dark and light lines / dots represent data from the left and right hemispheres, respectively.

429

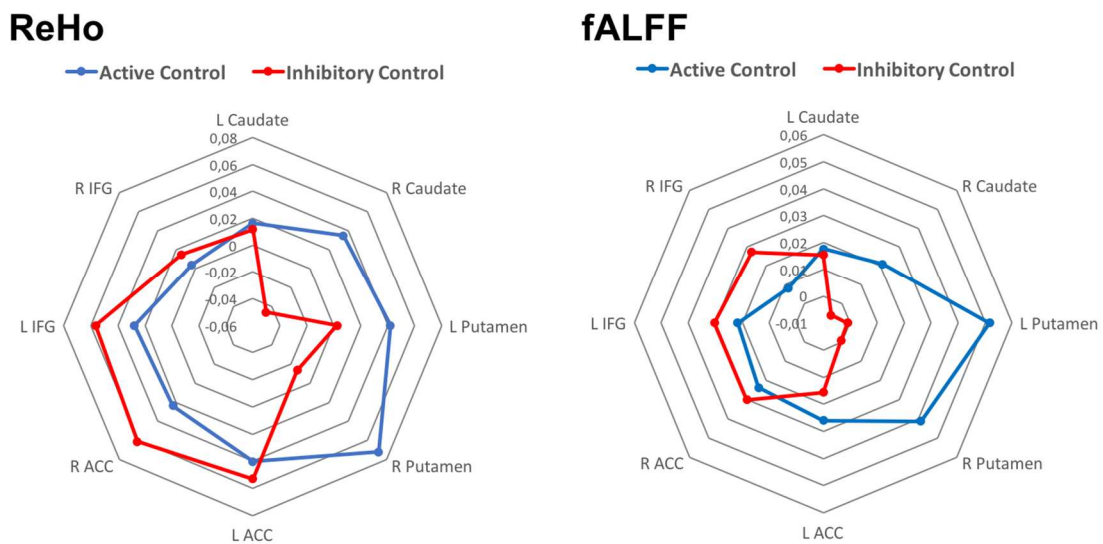
430

431 **3.3. ReHo and fALFF sensitivity to IC training**

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

443 The multivariate analysis on the whole pattern of relative changes after training indicated a
444 significant main group effect for ReHo ($F(8, 30) = 2.77, p = .02, \eta^2_p = 0.42$) and fALFF ($F(8, 30) =$
445 $2.45, p = .03, \eta^2_p = 0.39$) (Figure 3), showing that ReHo and fALFF change patterns differed between
446 the IC and AC groups.

447



448

449 **Figure 3: Global patterns of the relative changes of ReHo and fALFF after training.** The radar
450 graphs represent relative changes in the ReHo signal (left panel) and the fALFF signal (right panel) in
451 the subcortical (caudate nucleus, putamen) and cortical (ACC, IFG) regions of the IC network in the
452 Inhibitory Control (in red) and Active Control (in blue) training groups.

453

454

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 (0.028)	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)				

455

456

Table 1: Relative changes in ReHo after training in the Active Control (AC) and Inhibitory Control

457

groups (IC). Data for the AC and IC training groups are represented as the means \pm standard errors.

458

The main and interactive effects are derived from univariate linear models with group (“AC” vs. “IC”)

459

as the between-factor and brain hemisphere (“right” vs. “left”) as the within-factor. Analyses were

460

controlled for the age, sex, and high school of the participants.

461

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)				

462

463

Table 2: Relative changes in fALFF after training in the Active Control (AC) and Inhibitory

464

Control groups (IC). Data for the AC and IC training groups are represented as the means \pm standard

465

errors. The main and interactive effects are derived from univariate linear models with group (“AC” vs.

466

“IC”) as the between-factor and brain hemisphere (“right” vs. “left”) as the within-factor. Analyses were

467

controlled for the age, sex, and high school of the participants.

468

469 4. **DISCUSSION**

470 Consistent with the findings of previous studies in adults (Deng et al., 2016; Liu, Chen et al.,
471 2015; Takeuchi et al., 2015), we found that ReHo and fALFF signals were associated with IC efficiency
472 during adolescence. Importantly, we are the first to provide evidence that the relation between ReHo
473 and fALFF signals differ according to the type of IC tasks, namely, cognitive (Cool) or emotional (Hot)
474 Stroop tasks, in adolescents.

475 We found that the fALFF signal in the IFG and ACC, a non-invasive proxy of regional brain
476 metabolism (Aiello et al., 2015), was positively correlated with the Cool Stroop interference score.
477 Hence, a lower fALFF signal was associated with a higher IC efficiency in adolescents. In the current
478 study, neural activity at rest was investigated from the analysis of local properties of BOLD fluctuations,
479 complimenting previous studies on IC at adolescence, based on functional and structural connectivity.
480 Resting-state fMRI studies reported functional connectivity changes within the executive network,
481 encompassing the fronto-parietal and the cingulo-opercular networks, with decreased short-range
482 connections (correlations between close regions, i.e., ‘segregation’) and increased long-range
483 connections (correlations between distant regions, i.e., ‘integration’) during development (Fair et al.,
484 2007, 2009). Recently, a diffusion MRI study investigated the structural connectivity during
485 development and revealed that both modular segregation and network efficiency are associated with
486 enhanced executive performance and also mediate the improvement of executive functioning with age
487 (Baum et al. 2017; Satterthwaite et al., 2013). At the cellular level, the myelination process, which
488 enables more effective long-distance neural pathways, favours integration, whereas synaptic pruning
489 favours segregation (Fair et al., 2007, 2009).

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

498 ReHo and fALFF signals in subcortical (caudate nucleus and putamen) and cortical (ACC)
499 regions were positively correlated with the Hot Stroop interference score, showing that adolescents with
500 higher ReHo and fALFF signals within these brain regions of the IC network had lower IC efficiency.
501 These findings provide additional evidence for the role of the caudate nucleus and the putamen, sub-
502 regions of the striatum, in solving conflict in an affectively charged context (Chein et al., 2010; Hare et
503 al., 2005). We also found a stronger association between Hot IC efficiency and ReHo / fALFF signals
504 in the putamen in the left compared to the right hemisphere. This leftward asymmetry may be associated

505 with the hemisphere-specific maturational changes that occur during adolescence, with a greater
506 decrease of putamen volume in the left hemisphere compared to that of the right hemisphere (Dennison
507 et al., 2013). Hence, the putamen in the left hemisphere, by maturing earlier than the putamen in the
508 right hemisphere, might play a greater role in solving conflict in an emotional context during
509 adolescence. The association between performance in the Hot Stroop task and the ReHo and fALFF
510 signals within the dorsal part of the ACC suggests that the Hot Stroop task might also require conflict
511 detection and conflict resolution processes similar to those involved in affectively neutral contexts
512 (Botvinick, 2007, Simon et al., 2015).

513 In addition to the association observed between the ReHo and fALFF signals and the Cool and
514 Hot IC efficiencies at baseline, we also found IC training-related changes in these two measures of
515 BOLD signal fluctuations at rest in the sub-regions of the striatum (i.e., caudate nucleus and putamen),
516 key regions of the inhibitory control network (Beste et al., 2018; Grahn et al., 2008, Rubia et al., 2006)
517 but also involved more generally in learning (Seger, 2006, 2008; Seger & Cincotta, 2005, 2006). These
518 changes in striatal regions (i.e., the caudate nucleus and putamen) after a IC training are consistent with
519 previous studies reporting (i) an increased caudate activation in the Stop versus Go condition during an
520 SST task (Berkman et al., 2014) and (ii) fronto-basal changes by SST practice (Manuel et al., 2013;
521 Spierer et al., 2013). These results are thus in line with fMRI studies reporting activations within the
522 sub-thalamic nucleus (Aron & Poldrack, 2006; Aron et al., 2016) and the striatum (Beste et al., 2018)
523 during IC tasks. The involvement of the striatal regions in IC is partly due to their structural and
524 functional connectivity to the PFC (Beste et al., 2018). These ReHo and fALFF changes related to IC
525 training were also found to be hemisphere-dependent. This hemispheric specificity is in line with
526 previous studies in adolescents (Houdé et al., 2010; Rubia et al., 2006) and in adults (Garavan et al.,
527 1999), which reported a rightward hemispheric dominance for response inhibition. For instance, Rubia
528 et al. (2006) reported increased fronto-striatal activations, especially in the right caudate and putamen,
529 from adolescence to adulthood in motor and cognitive IC tasks. Moreover, a meta-analysis of functional
530 MRI studies in children and adolescents reported an age- and hemisphere-specific activation during
531 executive tasks, with a larger activation in the right than in the left anterior insular cortex (AIC, a region
532 involved in cognitive control; Bunge et al., 2002; Dosenbach et al., 2006) in adolescents but not in
533 children (Houdé et al., 2010). Taken together, these different studies support the notion that the IC neural
534 network is right-lateralized with an increasing lateralization with age (Houdé et al., 2010; Rubia et al.,
535 2006).

536 Given that a 5-week computerized IC training induced changes in brain function, assessed by
537 ReHo and fALFF signals at rest, we argue that such proxies of regional metabolism (Aiello et al., 2015)
538 could provide more sensitive markers of the potential effect of intensive and sustained cognitive training
539 compared to behavioural outcomes. This combination of brain changes associated with the lack of
540 behavioural changes after cognitive training was recently observed by Beauchamp et al. (2016), who
541 did not find behavioural changes but detected activation changes, during an emotion regulation task, in

542 the left IFG and supramarginal gyrus, after an SST-based IC training. **Notably**, unlike **the study by**
543 **Beauchamp et al. (2016)**, which investigated task-evoked BOLD signal changes, the present study
544 measured spontaneous BOLD signal **fluctuation** changes at rest. Such functional changes at rest may
545 reflect **the** consolidation of previous experience (Lewis et al., 2009), which in turn may lead to
546 behavioural changes in **the** near future. On the other hand, the lack of training-induced cognitive changes
547 may **have also resulted** from slight differences between the cognitive Stroop trained task and the
548 cognitive version of the Stroop task performed during the pre- and the post-training sessions. Indeed,
549 while improvements are often observed in the trained tasks, little or no transfer may be detected for non-
550 trained tasks even if **they are** very similar to the trained tasks (Green & Bavelier, 2008). Regarding the
551 emotional IC, the lack of performance increase in **the** Hot Stroop task after a Cool Stroop training is
552 consistent with **a** previous study reporting no transfer effect from a non-affective training task to a non-
553 trained affective task (Beauchamp et al., 2016). As already suggested by previous studies (Green &
554 Bavelier, 2008; Schmidt & Bjork, 1992), we may have to vary **the** task items to be learned and the
555 context in which they appear during the training phase to attempt to facilitate the transfer from the
556 trained task to non-trained tasks (e.g., Hot Stroop task). Indeed, **this** may force the participants to extract
557 general principles about the trained task and thus may ensure **that** the learned skills **are** reused.
558 Moreover, given that functional changes in the brain following IC training seem to precede behavioural
559 changes, we suspect that increasing the training dose by increasing the session duration and / or the
560 number of sessions (Beauchamp et al., 2016; Jolles & Crone, 2012; Kelly & Garavan, 2005) may
561 facilitate the training transfer and thus enable the detection of changes at the behavioural level.

562 The present study has several limitations that call for caution when interpreting the results. First,
563 despite the large sample size associated with a longitudinal design, the statistical effects are moderate.
564 Our findings should thus be taken with caution and replicated with a larger group of independent
565 samples. Future studies should investigate the effects of IC training at **both** the brain and behavioural
566 levels not only on adolescents but also on younger and older participants (i.e., children and young adults)
567 to determine whether the IC training-related ReHo and fALFF signal changes are training- or age-
568 specific. In addition to an immediate post-training effect, future work should also test **the** possible lasting
569 effects (e.g., 3- or 6-months follow-up sessions) of an IC training. **Furthermore**, developmental studies,
570 involving children, adolescents and adults should also investigate to **what** extent age can, or not,
571 modulate these effects (Zhao et al., 2018).

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

578

579

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584

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