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ORIGINAL RESEARCH

Effects of computerized cognitive training as add-on treatment to stimulants in ADHD: a pilot fMRI study

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Abstract
The neurofunctional effects of Cognitive training (CT) are poorly understood. Our main objective was to assess fMRI brain activation patterns in children with ADHD who received CT as an add-on treatment to stimulant medication. We included twenty children with ADHD from a clinical trial of stimulant medication and CT (10 in medication + CT and 10 in medication + non-active training). Between-group differences were assessed in performance and in brain activation during 3 fMRI paradigms of working memory (N-back: 0-back, 1-back, 2-back, 3-back), sustained attention (Sustained Attention Task - SAT: 2 s, 5 s and 8 s delays) and inhibitory control (Go/No-Go). We found significant group x time x condition interactions in working memory (WM) and sustained attention on brain activation. In N-back, decreases were observed in the BOLD signal change from baseline to endpoint with increasing WM load in the right insula, right putamen, left thalamus and left pallidum in the CT compared to the non-active group; in SAT - increases in the BOLD signal change from baseline to endpoint with increasing delays were observed in bilateral precuneus, right insula, bilateral associative visual cortex and angular gyrus, right middle temporal, precentral, postcentral, superior frontal and middle frontal gyri in the CT compared to the non-active group. CT in ADHD was associated with changes in activation in task-relevant parietal and striato-limbic regions of sustained attention and working memory. Changes in brain activity may precede behavioral performance modifications in working memory and sustained attention, but not in inhibitory control.

Keywords ADHD · Methylphenidate · Cognitive training · fMRI · Neuroimage

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is one of the most common neuropsychiatric disorders of childhood and adolescence (Buitelaar and Medori 2010) with an estimated prevalence of around 5% (Polanczyk et al. 2007). It is characterized by age-inappropriate symptoms of inattention, impulsivity and hyperactivity, resulting in several impairments to the individuals and their families (American Psychiatric Association 2013), as well as substantial economic impact to society (Maia et al. 2016).

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There is evidence suggesting an association between ADHD and several neurocognitive deficits mainly on executive functions such as working memory, attention and inhibitory control (Coghill et al. 2014). fMRI studies have furthermore shown that ADHD patients have underactivation in task-relevant frontal, striatal and parietal regions during performance of these tasks (Hart et al. 2013; Norman et al. 2016; Rubia 2018). These deficits may lead, as the nuclear symptoms of ADHD, to important impairments to the patient's functioning, especially in academic performance (Bikic et al. 2017).

Cognitive training (CT) is a non-pharmacological approach that could cover both clinical symptoms and the co-existent neurocognitive deficits, becoming an alternative tool to treat the disorder. It usually consists of a computer-delivered intervention of several game-like activities that is aimed to improve cognitive functions (Bikic et al. 2017) through strengthening of brain networks underlying these functions (Cortese et al. 2015). There is evidence that CT improves cognitive function, including enhancements on WM performance (Chacko et al. 2013; Gray et al. 2012; Green et al. 2012). The effects of CT on reducing ADHD symptoms are more controversial and a recent meta-analysis concluded that the effects of cognitive training on ADHD symptoms is only significant for unblinded raters; the effects were substantially reduced when considering probably blinded raters or when an active control arm was used, showing the need for more studies on this topic using more rigorous designs (Cortese et al. 2015). However, CT approaches targeting several cognitive functions relevant to ADHD have been shown to be more promising (Cortese et al. 2015).

Another way to assess if cognitive training could be an effective approach for ADHD would be demonstrating that this training leads to changes in brain activity. It has been demonstrated that WM training, for instance, can alter brain function, including increase in WM-related brain activity in several frontal, parietal and temporal lobe regions in ADHD patients (Stevens et al. 2016). Moreover, a fMRI study using a motor inhibition task to assess the benefits of a CT program targeting several cognitive domains observed increased brain activation after the training in the left orbitofrontal, right middle temporal, left superior frontal and right inferior frontal cortices. During another paradigm – an attention task - the same study found increased activity in the right superior posterior cerebellum post treatment (Hoekzema et al. 2010). Despite these promising few studies, the functional correlates of changes in brain activity following CT compared to a non-active control condition remains largely understudied. Those studies could provide clues on the mechanisms by which cognitive training changes brain function in ADHD patients.

In this fMRI study, we tested the effects of a CT program that targets several brain cognitive functions at the same time (i.e. sustained and selective attention, working memory, inhibitory control, cognitive flexibility and category formation) in ADHD children and adolescents. For this purpose, we selected three fMRI tasks – a Sustained Attention Task (SAT), a working memory task (N-back) and a motor inhibition task (Go/No-Go) - that encompass important cognitive domains related to ADHD and trained with the CT program. These tasks are consistently associated with reduced activation in ADHD patients relative to healthy controls in inferior and dorsolateral prefrontal, striato-thalamic and parietal regions (Chantiluke et al. 2015; Christakou et al. 2013; Norman et al. 2017; Smith et al. 2006). We hypothesized that CT would modulate activity in neural structures targeted by the fMRI-paradigms, in particular the dorsolateral prefrontal cortex (DLPFC) for WM and SAT, the inferior frontal cortex (IFC) for inhibition and parietal regions for all 3 tasks, and that CT would lead to better performance during the neuropsychological tasks.

Materials and methods

Study design and participants

The study was approved by the Ethics and Research Committee of the Hospital de Clínicas de Porto Alegre (HCPA) – (CAAE 25048913.8.0000.5327) and was registered in the Clinical Trials database (NCT02184598). A parent written informed consent and child assent were obtained before the initial assessment. No monetary compensation was offered to the patients for participating in the study.

The current fMRI study is part of a randomized controlled clinical trial (RCT) comparing the effects of an add-on cognitive training program versus a non-active training on ADHD core symptoms and neuropsychological performance. Participants were recruited from the Attention-Deficit/Hyperactivity Disorder Outpatient Program – ProDAH (located at the University hospital [HCPA] of the Federal University of Rio Grande do Sul, Porto Alegre, Brazil) and from public and private schools in the same city. A total of 53 participants were randomized to one of the two groups using a minimization method and following the guidelines of the Cochrane Risk of Bias Tool for Randomized Controlled Trials (Higgins et al. 2011), resulting in 29 subjects in the CT group and 24 individuals in the non-active group. There was a loss of $n = 8$ participants – five belonging to CT group – due to logistical problems (difficulty in maintain access to face-to-face sessions). Not all subjects enrolled in the RCT took part of the neuroimaging study. After randomization for the RCT, the families of children enrolled in the active group were consecutively invited to take part of the imaging study if they did not have formal contra-indication for MRI up to the number of 10 participants. For each one from the active group included in the imaging study, we selected the next one enrolled from the control group with similar demographic and clinical characteristics up to the number of 10 participants. A total of 20

ADHD subjects, of both genders, all medicated with stimulants (at least 4 weeks of the same type and dosage of stimulant treatment before start of the intervention), aged 9 to 13 years old, with an IQ ≥ 80 were included.

The inclusion criteria for the current study were as follows: age 6–13 years; diagnosis of ADHD according to the DSM-IV criteria; current use of a stable dose of stimulants; residual symptoms of inattention despite the maximum dose of stimulants; fluency in Portuguese; and a computer and internet access at home or school. Participants were excluded if they had a non-stabilized comorbid psychiatric condition requiring any additional treatment; an estimated IQ score lower than 80; any change in the dose of stimulant treatment, or the inclusion of any other medication and/or psychosocial treatment in order to control ADHD symptoms during the protocol. Additional exclusion criteria were MRI-specific contraindications (e.g. metal implants, phobia).

Treatment

The Computerized cognitive training program (ACTIVATE™) is composed of six different games, designed to address different neuropsychological domains such as speed processing, sustained, selective and divided attention, visual-spatial working memory, category formation, cognitive flexibility and inhibitory control. The program starts at a basic level, going through gradual and more complex levels of the tasks and adapting the degree of difficulty according to the participant's performance during the task. Throughout the sessions, participants perform several different cognitive tasks like completing patterns, assigning objects into categories, holding sequences in working memory, responding to some stimuli but not others (motor and interference inhibition), and task-switching. More information about ACTIVATE™ can be found in our published protocol (Rosa et al. 2017) or at the c8sciences website (http://www.c8sciences.com/about /games/).

For the non-active intervention, we created an online platform with educational issues composed by videos and questions related to school content. Each package was stratified according to age groups (6–7, 8–9, 10–11, 12-13y) and school grade. The material was related to general knowledge, Brazilian-Portuguese grammar, history and geography. More information can be found in our published protocol (Rosa et al. 2017), and the content of this platform is available in a video at www.youtube.com/watch?v=dAv6Y83BDqc, where subtitles in English can be triggered at the bottom of the video as indicated. By implementing this approach, we aimed to include a potential benefit for the subjects assigned to the control group (such as school reinforcement) without directly stimulating cognitive functions. Similarly, we choose to use this model of control group for constructing a rigorous study design - the use of waiting list, e.g., could fail to control for unspecific effects of the intervention.

Both interventions had online access and were composed by 48 sessions of 30 min duration each. The proposed protocol length was four sessions per week, always under supervision of the parents (at home) or a tutor (at school). We considered the completion of at least 85% of the sessions as an adequate implementation of the Computerized Cognitive Training (CCT) program.

fMRI tasks

All subjects were submitted to a practice task prior to the fMRI scan in a mock scanner, in order to get accustomed to the scanning environment and to be trained in the fMRI tasks, avoiding unsuccessful scans.

fMRI task - sustained attention task: this is an event-related parametric vigilance task with 3 different difficulty loads of sustained attention (Christakou et al. 2013; Murphy et al. 2014; Norman et al. 2017). In the 10 min 48 s sustained attention task, participants were asked to respond as quickly as possible to the appearance of a visual timer via a right-hand button response within 1 s. The visual stimuli appear either after a short, predictable consecutive delays of 0.5 s, in series of 3–5 stimuli (240 in total: 20 blocks of 5, 20 blocks of 4 and 20 blocks of 3 consecutive stimuli) or after an unpredictable time delays of 2, 5 or 8 s (20 delays of 2 s; 19 delays of 5 s and 20 delays of 8 s), pseudo-randomly interspersed into the blocks of 3–5 delays of 0.5 s. The long, infrequent, unpredictable delays place a higher load on sustained attention/vigilance, whereas the short, predictable 0.5 s delays are typically anticipated placing a higher demand on sensorimotor synchronization. Please, see Fig. 1 for additional information.

fMRI task - WM task (n-back): the block design 9 min 58 s WM task consists of four load factors ("0-back" to "3-back") (Chantiluke et al. 2015; Cubillo et al. 2014). It requires participants to respond on every trial by indicating the letter shown "n" trials earlier. During 1-back, 2-back and 3-back conditions, subjects are presented with series of letters (A-Z) (1 s duration, inter-trial interval = 2 s) and must respond with their right thumb using a button box whenever the letter presented is the same as one, two or three before it, respectively (e.g. 3-back: N/M/L/H/M). This task requires simultaneous storage and processing of the material presented. The 0-back condition served as control condition, when subjects must respond to each "X" that appears on the screen. The task consists of 12 randomized blocks (3 blocks of each N-back condition). Before each block, written instructions are shown to inform which condition is next. In each of the WM blocks of 45 s duration (1 s stimuli +2 s interstimulus interval -ISI) only one WM condition is presented and contains 15 stimuli: 3

targets and 12 non-targets. Each condition is presented 3 times. Performance data were recorded during scanning. Please, see Fig. 1 for additional information.

fMRI task - Go/No-Go (GNG) task: the event-related 8 min 32 s Go/No-Go task consists of frequent arrows (160 stimuli, 76.9%, with 500 ms duration) pointing to either the left or right direction (Go signals) that appear in the screen with a mean interstimulus interval of 1.8 s (jittered 1.6 s / 1.8 s / 2 s). Infrequently, arrows pointing up (24 stimuli, 11.5%, with 500 ms duration) (No-Go signals) or arrows slanted to the right or left with a 45° angle (24 stimuli, 11.5%, with 500 ms duration) (oddballs signals) appear. A button response had to be selectively executed to Go or oddball stimuli or inhibited to No-Go signals. The oddball trials control for the low frequency of the No-Go trials and thus the oddball attentional capture effect (Rubia et al. 2006; Smith et al. 2006). Please, see Fig. 1 for additional information.

fMRI data acquisition

Neuroimaging data was collected on a GE HDxt 3 T scanner using an eight-channel radio-frequency (RF) head coil. At the beginning of each scanning session, a single, high resolution T1-weighted [TE (echo time) = 2.18 ms, TR (repetition time) = 6.1 ms, flip angle = 11°, number of excitations (NEX) = 1, slice thickness = 1 mm, FOV (field of view) = 256 mm, resolution = 256 × 256, 196 slices] anatomic image was collected. A total of three fMRI runs were conducted. All runs were collected using a single-shot, gradient-echo planar pulse BOLD sequence [TE = 30 ms, TR = 2000 ms, flip angle = 90°, FOV = 220 mm, matrix size = 64 × 64]. Twenty-nine interleaved, sagittal 3.6 mm thick slices with a 0.3 mm gap were selected to provide whole-brain coverage (in plane resolution: 3.44 × 3.44 mm^2). For each paradigm, there were a total of 256, 299, 324 volumes collected for the Go/No-Go, N-Back and Sustained Attention Task, respectively. The first

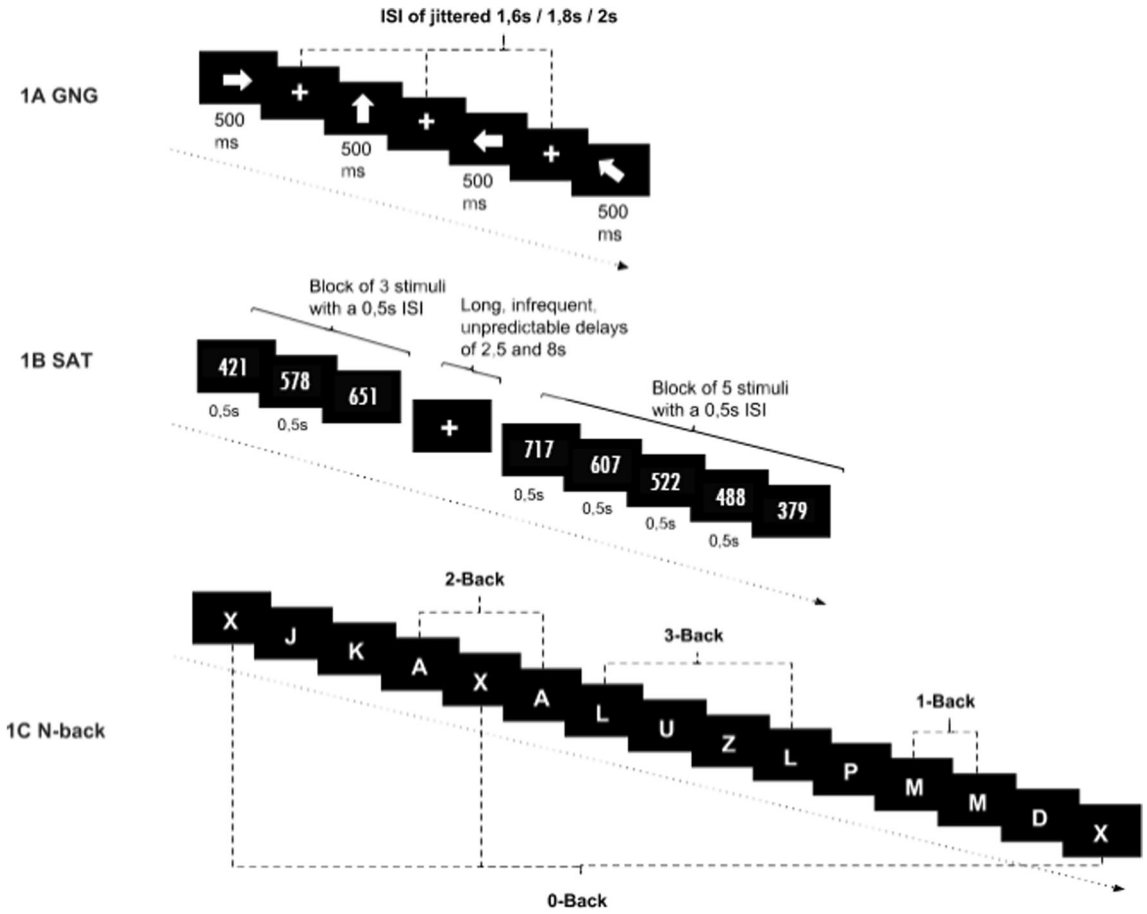

Fig. 1 Schematic representations of fMRI tasks. 1A - Go/No-Go (GNG). Participants had to press the left or right button according to the direction of the arrows displayed on the screen (Go signals). When the arrows pointed up (No-Go signals) the participants were not supposed to respond. During the oddball arrows, slightly slanted arrows pointing either to the left or to the right appeared and the subjects were told to respond as they would to a "go" prompt. 1B - Sustained attention task (SAT). Participants are required to press the button as soon as possible when it appears a timer on the screen. The timer appears after either predictable short delays of 0.5 s in blocks of 3–5 stimuli or after unpredictable long delays of 2,5,8 s, pseudo-randomly interspersed into the blocks of 0.5 s. 1C - N-back. Each trial had 15 stimuli - 3 of them are targets and the other 12 are random letters. The figure shows 8 stimuli. The "n-back" letters where participants should respond are indicated by dotted paths

three volumes were subsequently eliminated to account for T1 equilibrium effects.

fMRI preprocessing

All preprocessing and statistical analyses were carried out in the Analysis of Functional NeuroImages (AFNI) toolbox (R W Cox 1996) assessed by a blinded evaluator. Preprocessing was performed using the afni_proc.py function which included slice-time and motion correction. The motion corrected fMRI images were co-registered to the individual's anatomical images (T1). The T1 images were segmented into the gray matter, white matter and cerebrospinal fluid, as well as spatially normalized using a nonlinear registration to a standard space – Haskins Pediatric Template (Molfese et al. 2015). Using the same registration parameters for the T1 image, fMRI images were registered to the template space and then smoothed using a 6 mm FWHM Gaussian filter. Censoring was performed on time-points that had functional imaging outliers above 0.15 (Cox 2002).

Statistical imaging data analysis

Due to the high number of statistical tests performed with the neuroimaging data, at the voxel level, a multiple comparison correction approach is necessary. Within AFNI's 3dClustSim function (Cox et al. 2017), residuals from the multiple regression analysis were used to calculate the spatial smoothness of these data through an autocorrelation function. Ten thousand permutations of random data blurred with the smoothing estimates were computed to calculate the necessary thresholds for correction for multiple comparisons. Neuroimaging results were considered statistically significant for the adjusted p value ($\alpha < 0.05$), using a threshold of $p < 0.005$ and minimum cluster size of 2430 μL for Go/No-Go test and 2376 μL for N-Back and SAT.

Go/No-Go Task: Using multiple regression, the hemodynamic response function was fitted for each of the five conditions; go-left, go-left-up, go-right, go-right-up, and up. The go-left and go-right conditions were labeled as Go conditions, the go-right-up and go-left-up were labeled as Oddball conditions, and the Up was labeled as the No-Go condition. With an Analysis of Variance (ANOVA), the within subject interaction of time (baseline and endpoint) and condition (No-Go and Oddball) was calculated. A between subject interaction was also calculated comparing groups (active x non-active group).
N-Back Task: In the N-back task each of the Working Memory Loads (WML) was fitted to a hemodynamic response function, including the N-0 back, N-1 back, N-2 back and N-3 back conditions. The N-0 back condition was modeled as a baseline condition and hence not used in the ANOVA. The contrast 0-back vs. each condition was then used as the main dependent variable of the analysis to test for time, group, condition and time x group x condition interactions in the model.
Sustained Attention Task: For the sustained attention task, the hemodynamic response function was fitted for each of the Inter Stimulus Intervals (ISI) (0.5, 2.0, 5.0 and 8.0 s). The 0.5 ISI was modeled as the baseline condition. The interaction between Group x Time x ISI was calculated in a 2x2x3 (Group x Time X 3 long delays) ANOVA.

Performance data analysis

Performance data were analyzed using mixed design ANOVA. In all analyses, we tested the effects of group (between-subject variable; 2 levels), time (within-subject variable; 2 levels) and time by group interactions as independent variables for all the models tested in the study. In SAT another within subject variable was added, delay (3 levels), as well interactions between delay, time and group; dependent variables were mean reaction time, intrasubject deviation of reaction time, omission and premature errors. In Go/No-Go the dependent variables were proportion of commission errors. In N-back another within subject variable was added, working memory load (3 levels), as well interactions between working memory load, time and group; dependent variables were percentage of correct responses.

Effect sizes were quantified using omega squared (ω^2). Interpretations for ω^2 have been suggested that values of 0.01, 0.06 and 0.14 represent small, medium and large effect sizes respectively (Kirk 1996).

Results

Demographic and clinical characteristics

The mean age for the total sample was 11.4 years (SD = 1.5) and 55% were male. Table 1 presents the demographic and clinical characteristics of the study sample. There were no significant group differences for age, gender, IQ, socioeconomic status (SES), ADHD subtype and comorbidities. The analysis was conducted with 19 subjects (10 cases and 9 controls) on the SAT paradigm; 18 subjects (10 cases and 8 controls) on the WM paradigm and 18 subjects on the GNG (9 cases and 9 controls). The images from one subject on SAT and two subjects on WM, all belonging to the non-active group, were lost due to excess of head-movement during the exam as well as two subjects on GNG each belonging to one of the groups.

Table 1 Demographic and clinical characteristics ($n = 20$)

		Group		p-value
		CT ($n = 10$)	Non-active group (n = 10)	
Gender, n (%)				
	Male	5 (50)	6 (60)	0.65
Age, m (SD)		10.9 (1.6)	11.9 (1.3)	0.14
IQ, m (SD)		99.15 (13.09)	100.55 (12.62)	0.81
Socio-economic level, n (%)				0.45
	A	3 (30)	3 (30)	
	B	4 (40)	6 (60)	
	C	3 (30)	1 (10)	
ADHD subtype, n (%)				0.65
	Inattentive	4 (40)	6 (60)	
	Combined	5 (50)	5 (50)	
Comorbidities (KSADS), n (%)				
	Anxiety	3 (30)	1 (10)	0.52
	Conduct disorder	1 (10)	0	0.3
	Oppositional Defiant Disorder	5 (50)	3 (30)	0.36
	Others (enuresis/Tic disorder /Tourrete)	4 (40)	2 (20)	0.32
Baseline SNAP scores, m (SD)				
Parents	Inattentive	1.65 (0.34)	1.82 (0.38)	0.31
	Total	1.36 (0.28)	1.51 (0.41)	0.33
Teachers	Inattentive	1.31 (0.41)	1.42 (0.62)	0.65
	Total	1.06 (0.45)	1.1 (0.56)	0.85

n, number of participants; *m*, mean; *SD*, standard deviation; *CT*, cognitive training

Behavioral performance data

Working memory performance

Across all participants, there was a WM load effect in mean accuracy ($F_{3,51} = 51.5$, $p < 0.001$), showing that accuracy decreased with increasing WM load (0-back = .94, 1-back = .79, 2-back = .60, 3-back = .47) and a main effect of time ($F_{1,17} = 4.81$, $p = 0.043$) showing an overall improvement in accuracy over time (baseline = .66, endpoint = .75), but neither a main effect of group, nor of two and three-way interactions with group and time were significant (all p values>0.05). See Table 2.

Inhibitory-based executive function performance

No significant time or time by group interactions emerged for commission errors (all p values >0.05). See Table 2.

Sustained attention

There was a significant delay-effect in accuracy, meaning that performance decreased with larger delays, except for 8 s delay, for which performance increased. We also detected a three-way interaction between time, group and delay, regarding mean reaction time. This meant that there was an improvement with treatment across time if compared to non-active treatment only in the 5 s delay. No other main effects or interactions were found to be significant (p-values >0.05). See Table 2.

Neuroimaging results

Working memory

There was a group x time x WM-load interaction effect in two clusters in the N-back task, 1) in the right insula and putamen (Brodmann Area – BA – 13), and 2) in left thalamus and pallidum ($p < 0.001$). (see Table 3). The interaction reflected decreases in the BOLD signal change from baseline to endpoint with increasing working memory load in the cognitive training group, which contrasted with patterns from the non-active group. See Figs. 2 and 3.

Sustained attention

We found four clusters of activation in SAT task presenting a time x group x ISI interaction, which include: 1) right precuneus, angular gyrus, middle temporal lobe and associative visual cortex (BA 19, 39); 2) right postcentral and

Table 2 Mixed-effects analysis of variance investigating the effects of time, group and their interactions for cognitive performance indicators

	ANOVA	*p*	ω^2
Working memory (N-back)			
Time	F(1,17) = 4.81	0.043	0.16
WM load (accuracy)	F(3,51) = 51.5	<.001	0.72
Time x group	F(1,17) = 0.91	0.35	0.05
WM load x group	F(3,51) = 1.19	0.32	0.003
Time x WM load x group	F(3,51) = 1.8	0.16	0.04
Inhibitory Control (GNG)			
Mean RT			
Time	F(1,17) = 3.77	0.07	0.12
Time x group	F(1,17) = 0.14	0.71	0
SD RT			
Time	F(1,17) = 1.57	0.22	0.03
Time x group	F(1,17) = 0.4	0.53	0
Accuracy			
Time	F(1,17) = 0.63	0.43	0
Time x group	F(1,17) = 0.13	0.72	0
Sustained Attention (SAT)			
Mean RT			
Time x group	F(1,18) = 0.32	0.57	0
Delay x group	F(3,54) = 1.24	0.3	0.006
Time x delay x group	F(3,54) = 3.04	0.037	0.09
SD RT			
Time x group	F(1,17) = 0.13	0.72	0
Time x delay x group	F(3,51) = 0.8	0.49	0
Accuracy			
Time x group	F(1,18) = 0.83	0.37	0
Delay	F(3,54) = 65.87	<.001	0.75
Delay x group	F(3,54) = 2.04	0.12	0.01
Time x delay x group	F(3,54) = 1.11	0.35	0.006

Mixed-effects analysis of variance investigating the effects of time, group (and task load) and their interactions with cognitive performance indicators (accuracy and reaction time). Effect sizes were quantified using omega squared (ω^2). Abbreviations: *RT*, reaction time; *SD*, standard deviation

precentral gyrus and right insula (BA 3, 6, 13); 3) right superior frontal and middle frontal gyrus (BA 8, 9) and 4) left precuneus, associative visual cortex and angular gyrus (BA 19, 39) ($p < 0.001$)(see Table 3). The interaction reflected increases in the BOLD signal change from baseline to endpoint with increasing delays in the cognitive training group, which contrasted with patterns from the non-active group. See Figs. 2 and 3.

Go/no-go

No cluster emerged from the analyses involving the task of inhibitory control.

Discussion

The purpose of this study was to assess differences in brain activity from pre to post-intervention between cognitive training and a non-active intervention in children with ADHD on stimulant treatment. To the best of our knowledge, this is the first fMRI study with a rigorous design comparing the effects of cognitive training as an add-on treatment to stimulants on brain activation in ADHD.

Regarding the brain activation patterns, during the sustained attention task, our cognitive training program resulted in greater activation relative to the control group with increasing levels of delay, reflecting sustained attention load, in several right hemispheric brain regions that are crucial for sustained attention such as dorsolateral prefrontal cortex, and inferior and superior parietal regions. These findings possibly indicate that the CT group activated more intensively right fronto-parietal brain areas that mediate sustained attention after the intervention.

Previous research with the same task showed that with increasing delays there is increased activation in healthy controls of a typical sustained attention network including dorsolateral prefrontal cortex (DLPFC) and right inferior prefrontal cortices, cingulate, supplementary motor area, parieto-temporal regions, cerebellum, basal ganglia, thalamus and hippocampus (Christakou et al. 2013; Murphy et al. 2014). Furthermore, dorsolateral prefrontal, striato-thalamic and parietal regions were underactivated in ADHD patients relative to healthy controls (Christakou et al. 2013). The findings of increased activation after the CT intervention in right fronto-parietal regions during sustained attention may hence potentially reflect a shift towards the norm, given that they have been found to be underactivated during the same task relative to healthy controls. The findings of upregulation of dorsolateral fronto-parietal regions after CT are also in line with and extend previous findings of increased activation in ADHD children after CT in task-relevant regions during other tasks. Thus, a fMRI study found that cognitive training that exercises working memory, cognitive flexibility, attention, planning and problem solving – in unmedicated ADHD children elicited increases in activity after cognitive training in the right superior posterior cerebellum during an attention paradigm and increased activity in orbitofrontal, superior and inferior frontal, and middle temporal cortices during an inhibition paradigm (Hoekzema et al. 2010). Interestingly, a fMRI study that investigated the effects of methylphenidate on brain activation in ADHD children during a sustained attention task found that medication, compared to placebo, enhanced activation in inferior frontal, premotor, inferior parietal and cingulate cortices as well as cerebellum and precuneus (Rubia et al. 2009). These findings suggest that cognitive training and psychostimulant medication might act on similar neural circuitry of sustained

Table 3 Clusters exhibiting the main interaction effect for Sustained Attention Task (SAT) and the Working Memory (WM) task

	Region	BA	Peak MNI coordinates			Cluster size (Voxels)	Cluster size (μL)	ANOVA (3-way)	p
			x	y	z				
SAT									
1	R Precuneus; R Angular and Middle Temporal Gyrus; R associative visual cortex	19; 39	34.5	−74.5	36.5	224	6048	F (1;17) = 16.9	<.001
2	R Postcentral Gyrus; R Precentral Gyrus; R Insula	3; 6; 13	37.5	−17.5	30.5	192	5184	F (1;17) = 12.27	<.001
3	R Superior Frontal Gyrus; R Middle Frontal Gyrus;	8; 9	28.5	27.5	51.5	190	5130	F (1;17) = 22.46	<.001
4	L Precuneus; L associative visual cortex; L Angular Gyrus	19; 39	−37.5	−74.5	36.5	109	2943	F (1;17) = 14.72	<.001
WM									
1	R insula; R Putamen	13	34.5	3.5	15.5	162	4374	F (1;16) = 8.82	<.001
2	L Thalamus; L Pallidum	–	−1.5	−14.5	3.5	112	3024	F (1;16) = 9.24	<.001

BA, Brodmann Area; *R*, right; *L*, left; Cluster numbers correspond to numbering in Figs. 2 and 3

attention. No other fMRI study has assessed the effects of pharmacological or non-pharmacological interventions on brain activation during a sustained attention task in ADHD individuals. The findings of enhanced activation in task-relevant fronto-parietal regions after the intervention in the CT compared to the control group hence suggests that complex training of a range of executive functions appear to improve the underlying fronto-parietal neurofunctional substrates of sustained attention in ADHD.

On the other hand, during the working memory paradigm, the CT group showed decreased activation during the 3-back condition in subcortical regions, including the insula and striato-thalamic regions. It is possible that participants, after the intervention, no longer needed to activate these brain areas to maintain cognitive performance even with the increase of WM load – demonstrating, perhaps, greater efficiency. On the other hand, insula and striato-thalamic regions are not key part of the WM network (Andre et al. 2015; Braunlich et al. 2015). The anterior insula in particular has been associated with increased saliency processing in ADHD and there is evidence for abnormal resting state connectivity of the salience network with the cognitive control and attention networks in ADHD (Cai et al. 2018). Although not considered classical default mode network (DMN) regions, posterior thalamus and striatum form part of the DMN in the automatic fMRI meta-analyses generated in the neurosynth database under the search term: "default network" (www.neurosynth.org) (Yarkoni et al. 2011). Furthermore, children and adolescents have an immature DMN, and a recent meta-analysis of the DMN in children includes the thalamus, striatum and posterior insula (Mak et al. 2017). The DMN is thought to reflect mind-wandering and has been shown to be less deactivated in ADHD children during cognitive tasks (Rubia 2018), in particular during the most difficult conditions of tasks of working memory or the same sustained attention task (Christakou et al. 2013; Cubillo et al. 2014). It is hence possible that the CT downregulated areas of saliency processing (insula) and/or insula-thalamic areas of the default mode network. A study that tested fMRI effects after a working memory intervention in ADHD adolescents, showed increased less recruitment of anterior insula, medial frontal gyrus, and inferior frontal gyrus with increasing WM load, but increased recruitment in several other regions including inferior/middle frontal gyri, superior/middle temporal gyri, anterior cingulate and inferior parietal cortex (Stevens et al. 2016). The upregulation findings in fronto-parietal regions are more in line with the upregulation findings we observed in the sustained attention task. It is possible that findings of upregulation or downregulation effects after CT may be task- or region-dependent. Unfortunately, we did not include a healthy control group in the study design which would have been helpful to establish whether the respective up and downregulation effects in the two tasks represented a shift towards the norm.

Regarding the cognitive training effects on cognitive performance, in our study, we found improvement on SAT in the CT group only on the middle load difficulty condition, the 5 s delay. Between-group gains did not occur for both WM and GNG tasks. There are several studies demonstrating the effects of pharmacological and non-pharmacological approaches on cognitive functions during similar tasks with mixed results depending to the specific domain and measures used (Sonuga-Barke et al. 2014). A fMRI study that assessed the effects of a cognitive training targeting multiple neuropsychological domains in ADHD children, using an inhibition and attentional paradigm, indicated reductions in omission errors on an inhibition paradigm and reduction in incorrect targets and target omissions on a selective attention paradigm for participants in the CT group, albeit not Bonferroni-corrected (Hoekzema et al. 2010). Another fMRI study, using the same CT program in ADHD, found no significant differences in task-performance

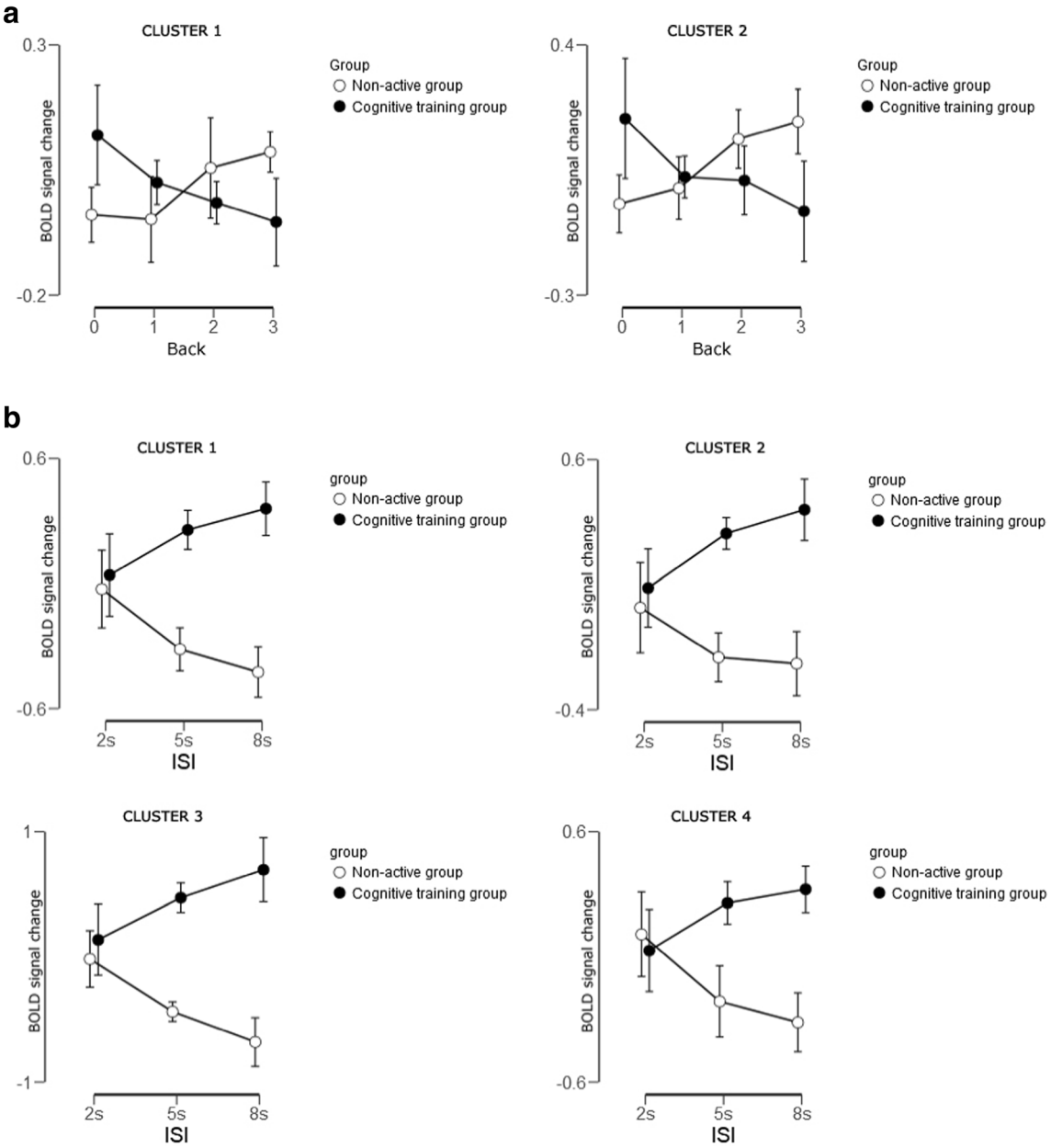

Fig. 2 Descriptive plots – 2A. Clusters of working memory activation (pre versus post intervention) showing that with increase in working memory load, during 3-back condition, the non-active group shows increased brain activation whereas the cognitive training CT group shows decrease in activation. 2B. Clusters of SAT activation (pre versus post intervention) showed that with increasing delay, the cognitive training group showed an increase in brain activation whereas the non-active group showed decreased activation. The following clusters are described detailly in Table 3

post-intervention during a task that assessed attention performance (Hoekzema et al. 2011). Our results are in agreement with another study that assessed the neuropsychological changes of a cognitive training program in ADHD using a GNG paradigm which found no significantly reaction times change after the intervention (Siniatchkin et al. 2012). Regarding non-pharmacological approaches, studies have shown some benefits on sustained attention performance (Bigorra et al. 2016; Johnstone et al. 2012; O'Connell et al. 2006) which is in line with our results. On tasks that assessed working memory, regarding cognitive training, there are studies that have shown some benefits of interventions targeting working memory plus inhibitory control (Johnstone et al. 2012) and working memory alone (Bigorra et al. 2016) on working memory measures. A recent study that assessed the effects of working memory training on brain function in ADHD adolescents found significant improvement on WM tests after the intervention (Stevens et al. 2016). To our knowledge there is no study that used exactly the same paradigms that we used to test the neuropsychological effect of CT.

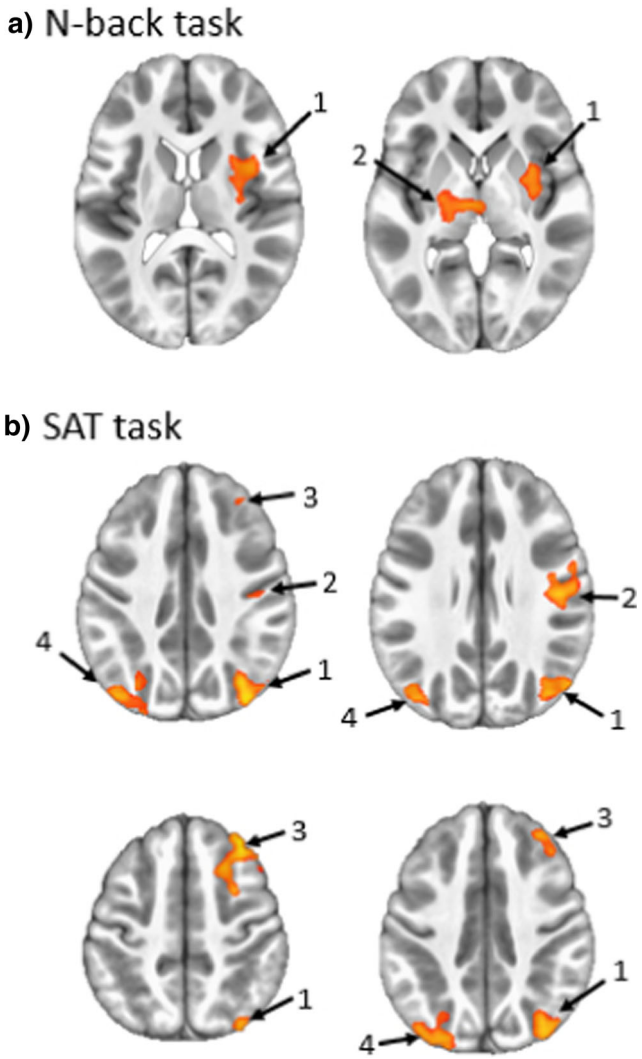

Fig. 3 Results from the main group comparisons. Axial sections showing the ANOVA between-group differences in brain activation between CT and non-active group A) During N-back task. Clusters denote areas with a significant group x time x WM-load interaction effect. B) During SAT task. Clusters denote areas with a time x group x ISI interaction. The figure shows brain regions in which the regions of interest consist of are listed in Table 3. The right side of the image corresponds to the right side of the brain. CT, cognitive training; SAT, sustained attention task; ISI, inter-stimulus interval

Our study has some strengths. The sample was derived from a larger study with a randomized controlled trial design that was never used in any add-on study for CT in ADHD. Our CT protocol was not restricted to one or two cognitive abilities, but targeted several cognitive domains. The patterns of activation derived from the neuroimages were assessed by a blinded evaluator. However, the results reported here should also be considered in the light of some limitations. The sample size was small and particularly underpowered to assess task performance changes and this could explain why we did not find substantial differences in task performance and limited findings on brain activation only in two of the fMRI tasks. Similarly, the difference found between groups only at 5 s delay in the SAT is more likely to reflect a spurious finding than a real effect due to the lack of a clear pattern of differentiated response between groups with the increase in demand.

Conclusion

To our knowledge, this is the first fMRI study to test neural effects of a cognitive training program acting as an add-on approach to stimulant treatment in ADHD. Our results extend previous findings that training cognitive functions in ADHD can alter brain function underlying the performance on related tasks than the trained ones. These brain modifications after CT may occur earlier and before neuropsychological changes take place. Studies with larger sample sizes are needed to replicate the findings, and to further elucidate the effects of cognitive training as an add-on strategy to improve brain function in ADHD children.

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Compliance with ethical standards

Conflict of interest Luis A. Rohde has received honoraria, has been on the speakers' bureau/advisory board and/or has acted as a consultant for Eli-Lilly, Medice, Novartis and Shire in the last three years. He receives authorship royalties from Oxford Press and ArtMed. He also received travel awards for taking part of the 2015 WFADHD and 2016 AACAP meetings from Shire. The ADHD and Juvenile Bipolar Disorder Outpatient Programs chaired by him received unrestricted educational and research support from the following pharmaceutical companies in the last three years: Janssen-Cilag, Novartis, and Shire. Dr. Carlos Renato Moreira-Maia has received financial research support from Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES) and Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq); development of educational materials for Libbs, Novartis and Pfizer; has received travel and accommodation support for a speaker training and participated in the development of a cell phone applicative for Shire; has received travel, accommodation and registration support to the fourth and fifth World Congress on ADHD from the World Federation of ADHD. Other authors do not have conflicts to declare. Dr. Schmitz has received financial support from Shire Laboratories to participate in international meetings. Katya Rubia has received grants for other projects from Shire and Lilly and speaker's honoraria from Shire, Lilly, Medice and Novartis.

Ethical approval The study was approved by the Ethics and Research Committee of the Hospital de Clínicas de Porto Alegre (HCPA) – (CAAE 25048913.8.0000.5327). All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in this study.

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