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ORIGINAL ARTICLE

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The effects of an exercise intervention on neuroelectric activity and executive function in children with overweight/obesity: The ActiveBrains randomized controlled trial

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Abstract

Objective: To investigate whether a 20-week aerobic and resistance exercise program induces changes in brain current density underlying working memory and inhibitory control in children with overweight/obesity.

Methods: A total of 67 children (10.00 ± 1.10 years) were randomized into an exercise or control group. Electroencephalography (EEG)-based current density ($\mu A/mm^2$) was estimated using standardized low-resolution brain electromagnetic tomography (sLORETA) during a working memory task (Delayed non-matched-to-sample task, DNMS) and inhibitory control task (Modified flanker task, MFT). In DNMS, participants had to memorize four stimuli (*Pokemons*) and then select between two of them, one of which had not been previously shown. In MFT, participants had to indicate whether the centered cow (i.e., target) of five faced the right or left.

Results: The exercise group had significantly greater increases in brain activation in comparison with the control group during the encoding phase of DNMS,

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particularly during retention of second stimuli in temporal and frontal areas (peak t = from 3.4 to 3.8, cluster size [k] = from 11 to 39), during the retention of the third stimuli in frontal areas (peak t = from 3.7 to 3.9, k = from 15 to 26), and during the retention of the fourth stimuli in temporal and occipital areas (peak t = from 2.7 to 4.3, k = from 13 to 101). In MFT, the exercise group presented a lower current density change in the middle frontal gyrus (peak $t = -4.1$, $k = 5$). No significant change was observed between groups for behavioral performance ($p \geq 0.05$).

Conclusion: A 20-week exercise program modulates brain activity which might provide a positive influence on working memory and inhibitory control in children with overweight/obesity.

KEYWORDS

brain activity, brain function, cognitive function, cognitive performance, physical activity, youth

1 | INTRODUCTION

Childhood is considered a critical period for cognitive and neural development.[1,2] In this context, one highly prevalent exposure that negatively alters brain health is obesity, as it has been associated with detectable structural brain abnormalities underlying executive function.[3,4] Executive function constitutes supervisory control of higher cognitive processes that enable forethought and goal-directed actions.[5] Specifically, executive function refers to specific cognitive domains including working memory (i.e., ability to briefly store and manipulate information), inhibitory control (i.e., ability to suppress irrelevant information and maintain focus), and cognitive flexibility (i.e., ability to shift attention when appropriate) that are vital to success in school and in life. A meta-analysis supported the existence of broad executive function deficits, including working memory and inhibitory control in children with overweight/obesity.[6] Indeed, having an obesity condition is clearly associated with a reduced capacity to modulate and control the executive function networks, therefore, predisposing individuals to gain overweight.[7] This could be explained in that much of our behavior is determined by an interaction between the impulsive system and the executive control system.[6] Thus, children who show lower levels of executive control may be more susceptible to obesity-related behaviors (e.g., increased intake of fatty foods due to impulsive behaviors and loss of control). Accordingly, there exists a fundamental neurobiological principle that affirms that biological events in the brain, although sometimes small, are amenable to modification by environmental factors.[8,9] This indicates the importance of understanding how environmental factors such as physical activity (PA) may influence brain health, particularly in children with overweight/obesity.

The recent, rapid development of neuroelectric and other neuroimaging techniques has favored the advance of research on the understanding of the neural foundations of PA-induced benefits to brain health.[10] Brain activity changes identified by functional magnetic resonance imaging (fMRI) and resulting from exercise interventions have been observed in children of normal weight[11] and with overweight or obesity.[12,13] Electroencephalography (EEG) and, more specifically, event-related brain potentials (ERP) (e.g., P3 component which is a positive-going, stimulus-locked potential peaking occurring approximately 300 to 800 ms following stimulus onset) have been among the most prominent approaches to study exercise effects on brain function.[14,15] In general, this body of evidence has shown that children participating in exercise programs exhibit larger amplitude[16–19] and shorter latency[16] P3-ERP components. Subsequently, substantial effects of exercise have been observed during tasks that measure higher-order executive functions, which are considered vital to success in school,[20] and include working memory and inhibitory control. However, it should be noted that a consensus has not been reached in the literature as some studies have observed null effects of exercise on cognitive outcomes.[12,21–23]

The vast majority of research addressing exercise effects on brain function in children has used an ERP approach.[14,15,24] Despite the excellent temporal resolution of this measurement technique in milliseconds, a fundamental limitation of this approach is the inverse problem; that is, the measure is challenged in localizing activated brain regions by scalp-recorded EEG activity.[25]

Alternatively, fMRI has a far superior spatial resolution capability than EEG, but is inherently slower (i.e., on the scale of seconds) and the low temporal resolution of this measurement may mask temporally separated processes into a single, more wide-spread spatially distributed activity.[26] In the last decade, EEG source localization algorithms have emerged as an alternative approach that inherit the high temporal resolution of EEG and additionally generate an estimation (i.e., current source density) of the brain activity with greater spatial sensitivity.[27] Specifically, standardized low-resolution brain electromagnetic tomography (sLORETA) has become an accepted EEG-based tool for the reliable detection of temporal–spatial brain activity involving simple, economical, and noninvasive use.[28] Thus, to better understand modulations in brain activity induced by exercise, we used an EEG-based brain source analysis to take advantage of its unique characteristic of spatially estimating brain activation underlying higher-level cognitive function (e.g., working memory and inhibitory control) during a specific time frame in which these processes occur (i.e., the millisecond range). By using sLORETA, the present study adds spatial sensitivity over previous EEG-based and ERP-based studies by detecting regional brain locations and networks that are influenced by exercise, while also providing a very-high temporal resolution over previous fMRI studies by detecting, on the order of a millisecond, in which cognitive processes (e.g., encoding, maintenance or retrieval processes during working memory operations) the effects of exercise (if any) occur. Therefore, this approach combines both an improved spatial resolution with a very-high temporal resolution, which may enhance the understanding of where and when the effects of exercise occur in brain function during cognitive operations.

To the best of our knowledge, there is only one study in children of normal weight that has used EEG-based sLORETA brain source localization to investigate the acute effects of moderate exercise on current source density.[29] However, no previous studies have investigated the long-term effects of exercise on current source density underlying working memory and inhibitory control operations in children with overweight/obesity. Furthermore, aerobic exercise (i.e., use of oxygen to meet energy demands during exercise via aerobic metabolism) has been the most predominant type of exercise in studies assessing the effects of exercise on brain activity,[15,24] with no information to date about the effects of other types of exercise such as the resistance training (i.e., the goal is to strengthen muscles via physical effort to overcome bodily or external loads). Previous examinations into the implications of muscular strength for health[30] indicated that higher levels of muscular strength are associated with a variety of health benefits such as decreased adiposity,[31] improved metabolic control,[32,33] and reduced insulin resistance,[34] which may consequently be beneficial for cognition, especially in children with obesity.[35] Furthermore, resistance exercise targeting improvements in muscular fitness may be beneficial for brain and cognitive processes[36] given that skeletal muscle serves as an endocrine organ influencing brain metabolism through cytokines and peptides that are produced and released by muscle contractions.[37] As such, the international PA guidelines suggest that exercise in children should be mostly aerobic, yet muscle- and bone-strengthening activities should be performed at least three times per week to maximize the health benefits in this age group.[38] Therefore, the aim of the present study was to investigate whether a 20-week exercise program combining aerobic and resistance training, based on meeting PA recommendations,[38] induces significant changes from pre- to post-intervention in spatial–temporal brain current source density while performing tasks of working memory and inhibitory control in children with overweight/obesity. Following previous evidence, we hypothesized that a 20-week exercise program will induce significant changes in brain current source density underlying working memory and inhibitory control as well as produce a significant improvement in behavioral performance in children with overweight/obesity.

2 | METHODS

2.1 | Design and participants

The ActiveBrains project was a two-group randomized controlled trial (RCT) carried out in children with overweight/obesity with the aim of analyzing the effects of a 20-week aerobic and resistance exercise program on brain health, including brain structure and function, cognition and academic performance, and on physical and mental health outcomes (http://profith.ugr.es/activebrains).[39,40] Details of the ActiveBrains project and the CONSORT (Consolidated Standards of Reporting Trials) checklist have been previously described.[39,40] The present study analyzed brain function and executive function outcomes, while the exercise effects on primary outcomes can be found elshewhere.[41] All data were collected at pre- and post-intervention from November 2014 through June 2016.

Eligibility screening was performed over 115 children, and finally, 112 were accepted in the study after meeting inclusion/exclusion criteria (Figure 1). Of these 112, 3 children chose not to continue and therefore randomization was applied over 109 children who were allocated to an exercise group, which participated in the exercise program, or a wait-list control group. The implementation of wait-list control group strategy has been done in previous

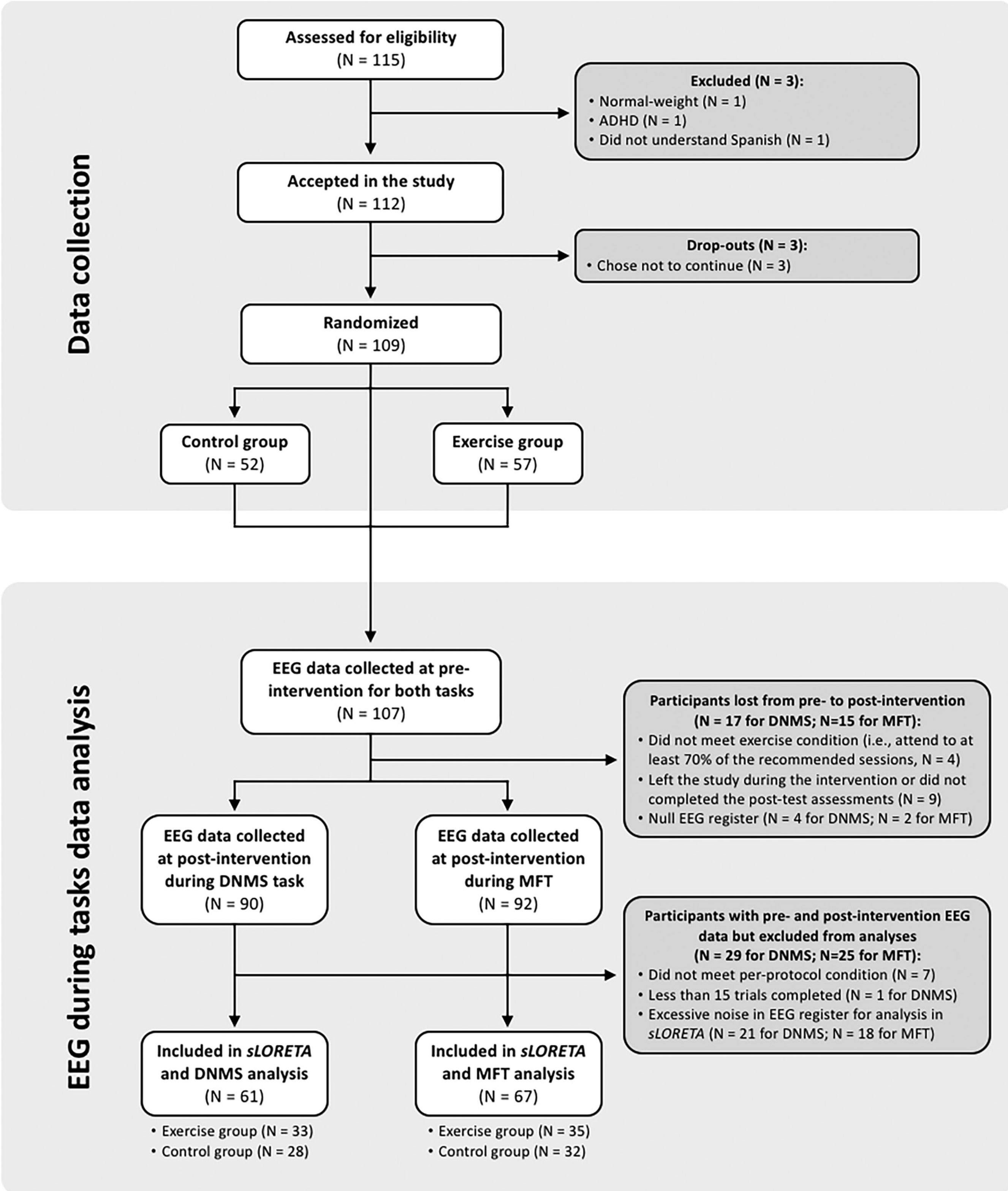


FIGURE 1 CONSORT flow chart describing the study sample selection for the analysis. ADHD, Attention-Deficit Hyperactivity Disorder; DNMS, Delayed-non-matched to sample task; EEG, Electroencephalography; MFT, Modified flanker task; sLORETA, Standardized low-resolution brain electromagnetic tomography.

research.[11,42] Following this strategy, participants of the wait-list group also receive the exercise program once the whole project has been completed. A computer random number generator in SPSS software for Windows (version 25.0; Armonk, NY, USA) was used to perform participants' simple random allocation into the exercise or the control group. In this context, a "blinded" researcher (FBO) not involved in the assessments nor exercise program was responsible of the randomization. Equal probability of being allocated to either of the two groups (ratio 1:1) was warranted. For the reduction of the risk of bias, the following actions were carried out: (1) the person that conducted computer random generation was not involved in the assessments; (2) the randomization was performed immediately after the pre-intervention assessments; and (3) the people in charge of the exercise program did not take part in the assessments or randomization processes.

For the present study, EEG data were collected during a delayed non-match-to-sample (DNMS) task (i.e., working memory) and a modified flanker task (MFT) (i.e., inhibitory control). Of the 109 randomized children, 107 successfully completed the EEG and task performance assessments at pre-intervention (Figure 1). At post-intervention, EEG data during DNMS task were collected for 90 children and EEG data during MFT for 92 children. Participants were included in analyses only if they had valid EEG data (i.e., good quality of EEG register) and valid cognitive tasks data (i.e., more than 20 trials completed) for both pre- and post-intervention assessments, as well as whether they met the per-protocol criteria (see next section). Therefore, of the 90 (DNMS) and 92 (MFT) children with pre- and post-intervention EEG data, 7 were excluded from analyses due to not meeting the per-protocol criteria (i.e. attending to at least 70% of the 3 recommended sessions/week), 1 was excluded due to having less than 20 trials completed for the DNMS task, and 21 (DNMS) and 18 (MFT) were excluded due to having an excessive noise of pre- or post-intervention EEG register after visual inspection. Accordingly, for analyses, a total of 61 children (exercise group, $n=33$; control group, $n=28$) and 67 children (exercise group, $n=35$; control group, $n=32$) were included in analyses for working memory and inhibitory control tasks, respectively. An exploratory analysis was performed to determine whether significant baseline differences for the demographics and cognitive variables existed between the included and excluded participants of the present study. No significant differences were observed ($p>0.05$; Table S1).

The Human Research Ethics Committee of the University of Granada approved the ActiveBrains project. Registration was performed in ClinicalTrials.gov (identifier: NCT02295072).

2.2 | Physical exercise program

The physical exercise program lasted 20 weeks. This program was designed based on the international PA guidelines valid at the time the study was being carried out (http://www.health.gov/paguidelines/).[41] According to the PA guidelines, young people should perform at least an average of 60 min/day of aerobic PA as well as muscle- and bone-strengthening exercises should be incorporated at least 3 days/week to obtain health benefits.[38] Participants were offered five sessions/week from Monday to Friday with a session's duration of 90 min. Following the guidelines, the minimum attendance rate was set at three times/week, although they were advised to attend all five sessions/week. For the present study, the final sample of 67 children with overweight/obesity (10.00 ± 1.10 years; 61.2% boys) included in analyses met the per-protocol criteria of: (i) having completed the pre- and post-intervention EEG and both tasks assessments, and (ii) having attended at least 70% of the required three sessions/week (the exercise group).

The exercise program was based on physical multi-games to favor adherence to the program. The intervention was designed to be ecologically valid. That is, the intervention was designed to engage children in how they would normally play. To that end, it did not isolate aerobic or strength activities, rather it combined multiple exercise modes along with social interactions involving collaboration, competition, etc. The 90-min session was structured as follows: (1) a warm-up (5–10 min), (2) an aerobic-based part with 4–5 moderate-to-vigorous intensity multi-games (60 min), (3) a resistance-based part with muscle- and bone-strengthening activities (20 min), and (4) a cool-down part (5–10 min).

The target intensity of the exercise intervention was monitored and controlled individually in all children and in every session of the ActiveBrains program. Every child had their own heart rate monitor (POLAR RS300X, Polar Electro Oy Inc.), programmed individually based on their maximum heart rate achieved during a maximal incremental test, which is described elsewhere.[39,40] Target intensity and progress were registered daily and checked weekly by trained personnel, mainly to identify whether any child was training at a lower intensity than intended and also to adapt the intensity according to the specific progress of each participant. This allowed the physical trainers to increase motivation and adapt the intensity of the games when needed. This was done for both the aerobic and resistance components of the program. A description of the characteristics of the program's intensity can be found elsewhere.[40]

2.3 | Control group

The control group participants were requested to maintain their usual lifestyle and activities. A pamphlet with information on nutritional and PA guidelines was given to this group. An ad hoc question was administered to the control group at post-intervention to check whether they had generally maintained their usual lifestyle or not: "*Did you make any major change in your physical/sport activity participation during the intervention period?*" From these data, we detected that one of the children in the control group was enrolled in a swimming club with a heavy training load and competitions. We therefore decided to exclude this one participant from the main analyses. Based on the wait-list strategy explained above, children belonging to the control group participated in the exercise program once the whole project had been completed.

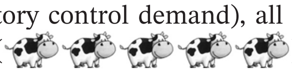
2.4 | Measurements

A complete measurement session consisted of an EEG recording during two different executive function tasks (i.e., DNMS and MFT) that lasted 85–90 min of total duration. The protocol for each child undergoing the measurement was divided into four phases. First, the EEG electrode cap was fit to child's head and electrodes filled with electrode gel for around 20 min. Second, the first executive function task (e.g., DNMS) was conducted. Third, after finishing the first task, evaluators checked the EEG data while the participant rested for approximately 10 min. Fourth, the second task (e.g., MFT) was conducted. The order of the cognitive tasks was counterbalanced across participants. All assessments were conducted by the same trained experimenters. Both tasks were presented centrally on a blue background on a computer screen using E-Prime software (Psychology Software Tools).

2.4.1 | Delayed non-matched-to-sample task

A version of the DNMS computerized task modified for children was used during EEG recordings to assess working memory.[43] A full description of the task and its protocol has been provided elsewhere.[44,45] Briefly, a trial had three different phases: encoding phase with the presentation and retention of stimuli (from −9000 to −4000 ms), the maintenance phase (0 ms), and the retrieval phase (0 to 1800 ms). Participants were asked to retain four stimuli that appeared sequentially during the encoding phase that lasted 5000 ms. Then, they were asked to maintain these stimuli memorized for 4000 ms, and finally, they were asked to select between two different stimuli (*Pokemon* cartoons) which one had not been shown during the encoding phase. The task was comprised of a total of 16 practice trials plus 140 experimental trials, of which 100 trials belonged to the high working memory load condition (i.e., more cognitively demanding) and 40 belonged to the low working memory load condition (i.e., less cognitively demanding). The main difference between these two conditions was that in the low load the four stimuli presented during the encoding phase were all the same, while in the high low load they were all different from each other. The 140 experimental trials were presented across four blocks of 35 trials in a randomized order, with a 3–5 min rest between blocks. Duration of the task, including instructions prior to task performance, practice trials, and rest between experimental blocks, ranged from 45 to 50 min. For the present study, mean reaction time (RT) (s) and response accuracy (%) were registered. RT was computed from accurate response trials only.

2.4.2 | Modified flanker task

A version of the Eriksen flanker task modified for children was used to assess inhibitory control.[46] Thus, a trial presented five cows focally presented at a 1.2° visual angle each, and participants had to indicate using a computer mouse, with their dominant hand, whether the centered cow target (i.e., 1.2 cm tall cow) was directed to the right or the left. Participants were instructed to first focus on a central fixation cross ("+") for 1250 ms, and once it disappeared, a target was presented that afforded the individual a response window of up to 1700 ms to provide a response. The inter-trial interval (ITI) ranged from 3682 to 6158 ms (average ITI = 4875 ms). There were two different trial types depending on the directions faced by the flanking nontarget stimuli (i.e., four identical cows). For the congruent condition (i.e., lower inhibitory control demand), all cows faced the same direction (). For the incongruent condition (i.e., higher inhibitory control demand), the targeted cow was positioned in an opposite direction with respect to the flankered cows (). The task was comprised of a total of 12 practice trials plus 144 experimental trials (72 per condition) presented randomly across three blocks of 48 trials each. The number of trials is similar to previously modified flanker tasks administered to children that also included EEG.[7,42] Total duration of the task ranged from 20 to 25 min including instructions, practice, and rest between blocks. Measures of mean RT (s) and response accuracy (%) were collected. RT was computed from accurate response trials only.

2.4.3 | Neuroelectric activity recording

A 64-channel Active Two BioSemi EEG system (24-bit resolution, BioSemi) was used to assess neuroelectric activity. We based on the International 10–10 system for EEG montage. Further details of this recording can be found in previous research.[45] In brief, stimulus-locked epochs were formed from −10 000 to 2000 ms focusing on the retrieval phase of the DNMS task. For the MFT task, a window from −100.0 prior to 1700 ms was conformed after stimulus onset. Baseline correction was applied using the −100.0 to 0 ms pre-stimulus period.

2.4.4 | Brain source analysis

We used sLORETA software to localize and identify neuroelectric activity.[28] Validity of sLORETA has been tested against fMRI confirming that this technique can be used to estimate brain current source density ($\mu A/mm^2$) and the brain areas underneath.[28,47] This software allows the representation of brain activity from the spatial–temporal perspective.[26] First, we submitted the overall averaged amplitude (μV) of each working memory load condition (i.e., low and high) and each inhibitory control condition (i.e., congruent and incongruent) for every participant at pre- and post-intervention to sLORETA. Second, we computed the current density time course of each of the 6239 voxels of the sLORETA brain map provided by the Montreal Neurological Institute (MNI). Finally, individual voxels' raw sLORETA values were allocated to their corresponding Brodmann areas (BA) and the brain activity at each voxel was computed as the squared standardized magnitude of the estimated current source density ($\mu A/mm^2$).

2.5 | Statistical analysis

Characteristics of the study sample are presented as means and standard deviations (SD), or percentages, when appropriate. Two analyses were performed in the present study to test the effects of the 20-week ActiveBrains program: (i) on working memory and inhibitory control performance, and (ii) on the current source density estimated during these tasks.

2.5.1 | Effects of the ActiveBrains program on working memory and inhibitory control performance

The effects of the ActiveBrains exercise program on the outcomes (i.e., RT and response accuracy) for each task (i.e., DNMS and MFT) and each condition of the task (i.e., high and low working memory; incongruent and congruent inhibitory control) were tested with analysis of covariance (ANCOVA). This analysis was formed using post-intervention outcomes as dependent variables, group as fixed factor, and pre-intervention outcomes as covariates. Winsorization was performed with those raw values that needed it to avoid extreme values.[48] The *z*-scores for each cognitive outcome (i.e., RT and response accuracy) at post-intervention were computed by dividing the difference of the post-intervention raw value of each participant from the pre-intervention mean by the pre-intervention SD (i.e., [post-intervention individual raw value − pre-intervention mean]/pre-intervention SD). This computation of *z*-score outcomes has been previously used in important RCTs focused also on cognitive outcomes.[48] The computation of *z*-scores has two main advantages: (1) by proving standardized estimates it allows the comparison between outcomes of different nature; (2) an interpretation of *z*-score of change as effect size (0.2, 0.5, and 0.8 considered as small, medium, and large effect sizes, respectively),[49] that is, how many SD the outcome at post-intervention changes from pre-intervention.[48] All the statistical procedures were performed using the SPSS software for Mac (version 20.0, IBM Corporation). A significance difference level of $p < 0.05$ was set.

2.5.2 | Effects of the ActiveBrains program on current source density

The effects of the ActiveBrains program on current source density during DNMS and MFT tasks were tested with an independent group analysis using sLORETA software. Through this test, the post- and the pre-intervention current source densities in the exercise group were compared to those of the control group. Therefore, this test allowed analysis of which group had a greater change in the current source density from pre- to post-intervention. For this purpose, sLORETA estimations of current source densities of every participant in the exercise and control groups were submitted individually for each task condition to a mass-univariate *t* test (5000 random samples). This test controls for multiple comparisons correction by using an approximation to the permutation analysis based on the empirical single-threshold of the *t*-max statistic.[50,51]

3 | RESULTS

3.1 | Effects of the ActiveBrains program on working memory and inhibitory control

Table 1 shows the pre-intervention characteristics of the study sample. Table S2 presents the effects of the ActiveBrains program on raw and *z*-score post-intervention working memory and inhibitory control outcomes after

TABLE 1 Descriptive baseline characteristics of the study sample.

	All		Exercise group		Control group	
	N	Mean ± SD	*N*	Mean ± SD	*N*	Mean ± SD
Sex						
Girls (*n* %)	26	38.8%	11	31.4%	15	46.9%
Boys (*n* %)	41	61.2%	24	68.6%	17	53.1%
Age (years)	67	10.00 ± 1.10	35	9.95 ± 1.14	32	10.05 ± 1.08
Body mass index (kg/m^2)	67	26.58 ± 3.59	35	27.05 ± 4.10	32	26.06 ± 2.88
Wave of participation						
First (*n* %)	9	13.4%	6	17.1%	3	9.4%
Second (*n* %)	22	32.8%	11	31.4%	11	34.4%
Third (*n* %)	36	53.7%	18	51.4%	18	56.3%
Working memory	61		33		28	
Low working memory load						
Mean reaction time (ms)[a]		897.17 ± 153.52		890.56 ± 150.83		904.95 ± 159.05
Response accuracy (%)		81.35 ± 13.65		82.88 ± 12.63		79.55 ± 14.80
High working memory load						
Mean reaction time (ms)[a]		885.86 ± 153.54		873.44 ± 150.36		900.49 ± 158.70
Response accuracy (%)		68.22 ± 13.55		70.35 ± 13.07		65.71 ± 13.90
Inhibitory control	67		35		32	
Congruent condition						
Mean reaction time (ms)[a]		803.13 ± 122.39		810.56 ± 120.24		795.00 ± 126.12
Response accuracy (%)		93.82 ± 6.85		94.68 ± 6.13		92.88 ± 7.55
Incongruent condition						
Mean reaction time (ms)[a]		852.26 ± 144.49		852.25 ± 149.68		852.26 ± 140.98
Response accuracy (%)		85.92 ± 19.15		86.90 ± 18.20		84.85 ± 20.37

Note: Values are expressed as means ± standard deviations (SD), unless otherwise indicated.

Working memory was measured by the delayed non-match-to-sample task. Inhibitory control was measured by the modified flanker task.

[a]Higher values indicate lower performance.

adjustment for pre-intervention values. Overall, the post-*minus* pre-intervention change between groups was non-significant for both DNMS and MFT tasks ($p \geq 0.484$).

3.2 | Effects of ActiveBrains program on current source density

Table 2, Figures 2 and 3 present the brain regions for each hemisphere (left, L and right, R) and time frames (TFs) showing the post- *minus* pre-intervention change in current source density between exercise and control groups during the performance of the working memory DNMS task. In the high working memory load condition, the exercise group, with respect to the control group, showed a higher current source density from pre- to post-intervention in four different TFs during the encoding phase of the task. In the TF from *−6547 to −6516 ms* (i.e., the time after the presentation of the second stimuli), the current source density change was observed in five BAs (i.e., RBA13, 22, 31, 40, and 41) with peak *t* values ranging from 3.4 to 3.8 and cluster size (*k*) ranging from 11 to 39. In the TF from *−6027 to −6008 ms* (i.e., the time before the presentation of the third stimuli), the current source density change was observed in three BAs, particularly in bilateral BA9 (peak $t = 3.9$, $k = 23$ for LBA9; peak $t = 3.7$, $k = 15$ for RBA9) and in LBA8 (peak $t = 3.8$, $k = 26$). In the TF from *−4090 to −4074 ms* (i.e., the time during the presentation of the last working memory stimuli), the current source density change between groups was observed in four BAs (i.e., LBA18, 22, 30, and 37) with peak *t* values ranging from 3.5 to 4.3 and cluster size ranging from 13 to 18. In the TF from *−4027 to −3988 ms* (i.e., time between the presentation of the last stimuli and the preparation for the maintenance phase), the current source density change between groups was observed in seven BAs (RBA11, 13, 20, 22, 38, 41, and 47) with peak *t* values ranging from 2.7 to 3.2 and cluster size ranging from 14 to 101.

TABLE 2 Brain regions and time frames (TF) showing post- *minus* pre-intervention differential change in current source density (μA/mm^2) between exercise and control groups during working memory and inhibitory control tasks.

BA	Hem	Brain region	*X*	*Y*	*Z*	Peak *t*	Cluster size
WORKING MEMORY							
Low load							
No significant effects of exercise program							
High load							
Encoding phase							
TF −6547 to −6516 ms							
13	R	Insula	35	−35	20	3.8	39
22	R	Superior temporal gyrus	50	−35	5	3.6	16
31	R	Cingulate gyrus	20	−45	25	3.5	11
40	R	Supramarginal gyrus	50	−50	20	3.4	19
41	R	Superior temporal gyrus	35	−35	15	3.8	22
TF −6027 to −6008 ms							
9	L	Medial frontal gyrus	−5	40	35	3.9	23
8	L	Superior frontal gyrus	−15	30	55	3.8	26
9	R	Medial frontal gyrus	0	40	35	3.7	15
TF −4090 to −4074 ms							
37	L	Fusiform gyrus	−55	−60	−20	3.5	17
30	L	Posterior cingulate	−10	−65	10	4.3	18
22	L	Superior temporal gyrus	−60	−45	5	3.7	13
18	L	Cuneus	−15	70	15	4.1	14
TF −4027 to −3988 ms							
11	R	Middle frontal gyrus	35	40	−20	2.7	24
13	R	Insula	35	15	15	3.2	101
20	R	Temporal Sub-gyral	40	−10	−25	2.7	18
22	R	Superior temporal gyrus	45	−20	0	2.9	14
38	R	Superior temporal gyrus	35	5	−15	2.8	32
41	R	Transverse temporal gyrus	40	−25	10	3.1	22
47	R	Inferior frontal gyrus	40	25	0	2.8	49
Maintenance phase							
No significant effects of exercise program							
Retrieval phase							
No significant effects of exercise program							
INHIBITORY CONTROL							
Congruent condition							
No significant effects of exercise program							
Incongruent condition							
TF 508 to 528 ms							
10	L	Middle frontal gyrus	−35	50	15	−4.1	5

Note: Independent group analysis was performed using standardized low-resolution brain electromagnetic tomography (sLORETA) software to test post- *minus* pre-intervention differential change between exercise and control groups (i.e., to test whether exercise group, post- *minus* pre-current source density = control group, post- *minus* pre-current source density). Therefore, a positive peak *t* (e.g., 3.8) means that the post- *minus* pre-current source density's change is greater for the exercise group than for the control group, whereas a negative peak *t* (e.g., −4.1) means that post- *minus* pre-current source density's change is lower for the exercise group than for the control group. Multiple comparison correction was performed using permutation analysis based on *t*-max threshold statistic. Anatomical coordinates (*X*, *Y*, *Z*) are given in Montreal Neurological Institute (MNI) Atlas space.

Working memory was measured by the delayed non-match-to-sample task. Inhibitory control was measured by the modified flanker task.

Abbreviations: BA, Brodmann areas; Hem, Hemisphere; L, Left; R, Right.

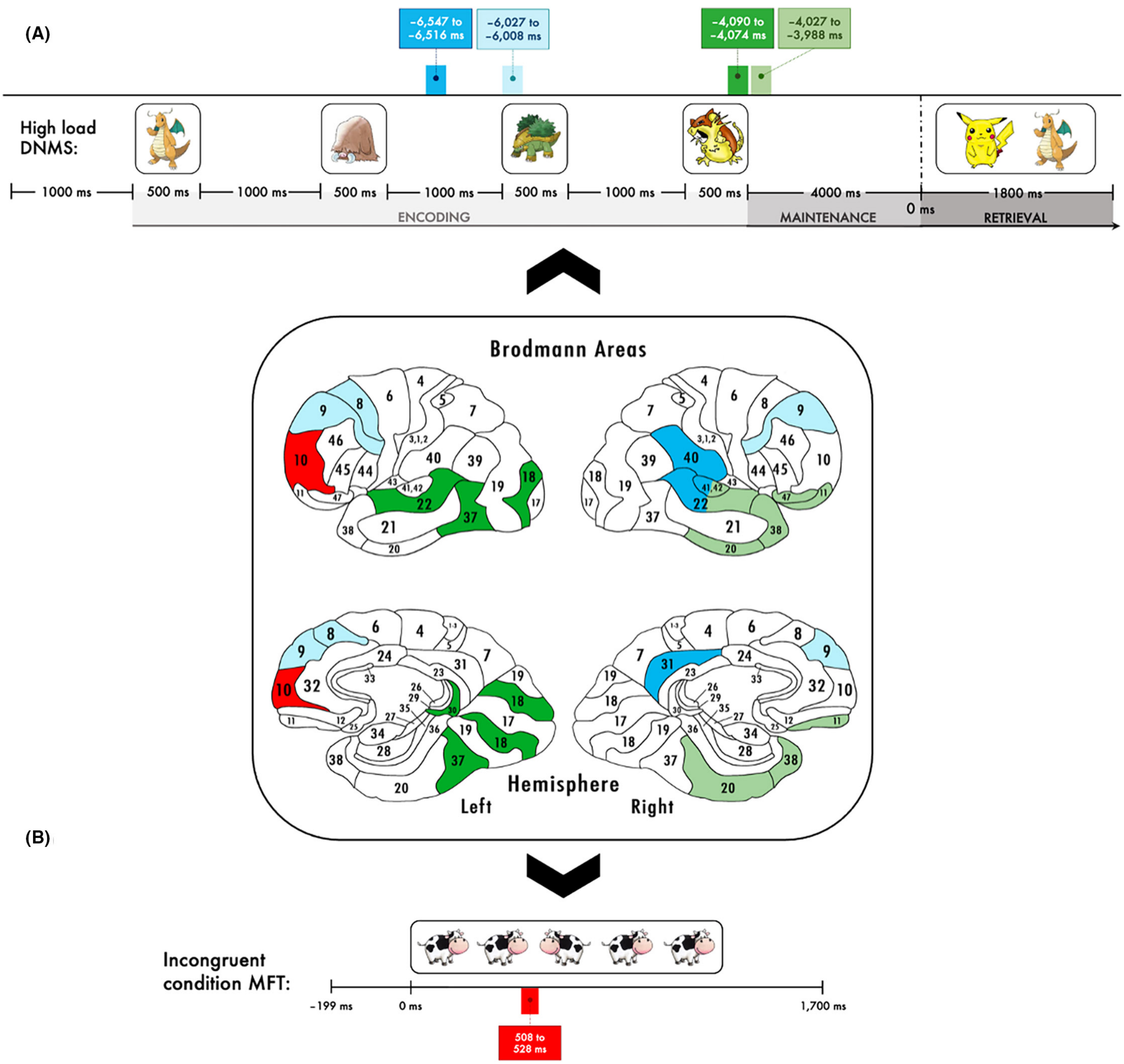
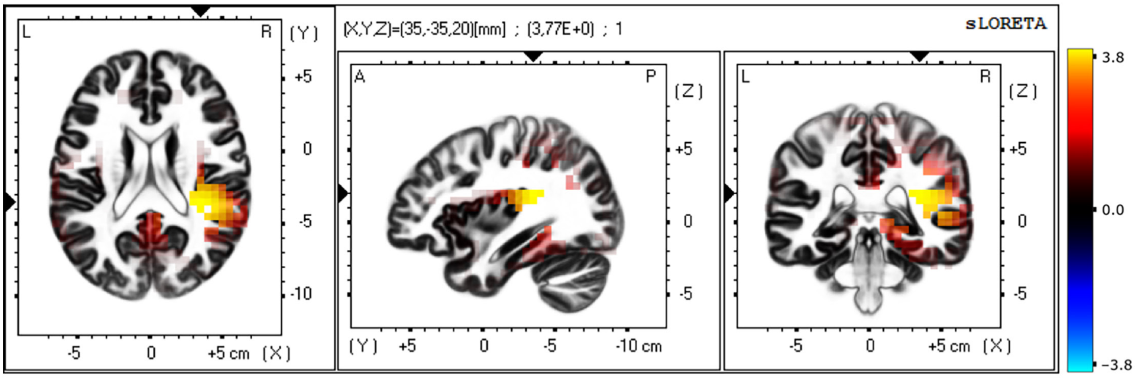


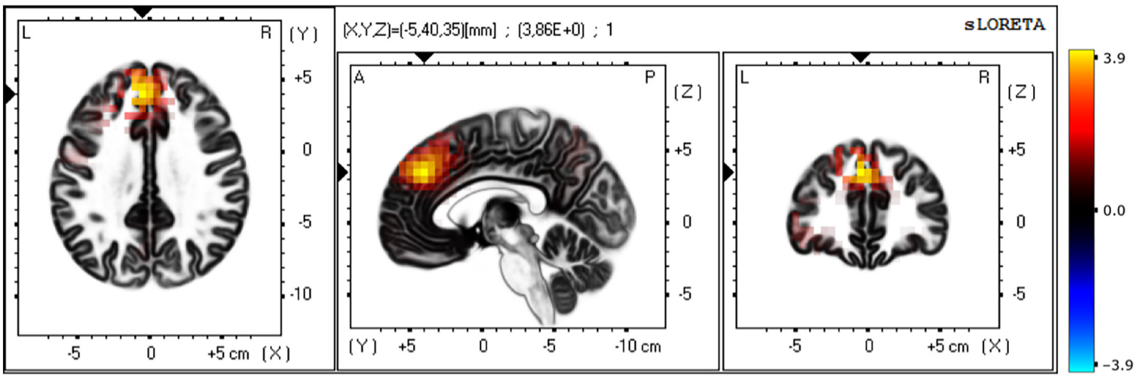
FIGURE 2 Graphical representation of Brodmann areas showing exercise-induced effects and times frames in which those effects occurred for (A) working memory (i.e., delayed non-matched-to-sample task, DNMS) and (B) inhibitory control (i.e., modified flanker task, MFT) tasks. Colors of Brodmann areas link to the colors of the times frames in which the exercise effects were found.

FIGURE 3 Brain areas and time frames (TFs) showing post- *minus* pre-intervention differential change in current source density (μA/mm^2) between exercise and control groups in the high load of the working memory task. Independent group analysis was performed using standardized low-resolution brain electromagnetic tomography (sLORETA) software to test post- *minus* pre-intervention differential change between exercise and control groups (i.e., to test whether exercise group, post- *minus* pre-current source density = control group, post- *minus* pre-current source density). The color bar represents peak *t* values (also shown between parenthesis following the coordinates), with red and yellow colors indicating that post- *minus* pre-current source density's change was greater for the exercise group than for the control group, and blue colors indicating that post- minus pre-current source density's change was lower for the exercise group than for the control group. Anatomical coordinates (*X*, *Y*, *Z*) are given in Montreal Neurological Institute (MNI) Atlas space. A, Anterior; L, Left; P, Posterior; R, Right. Working memory was measured by the delayed non-match-to sample task.

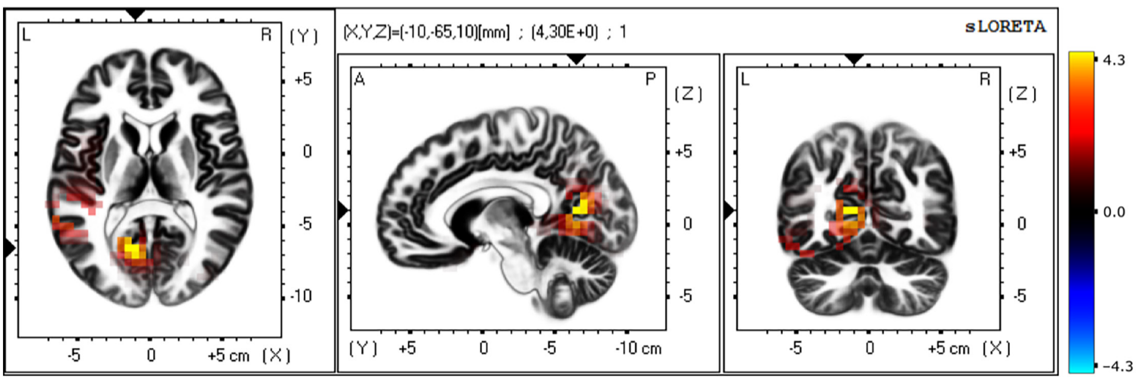
TF -6,547 to -6,516 ms



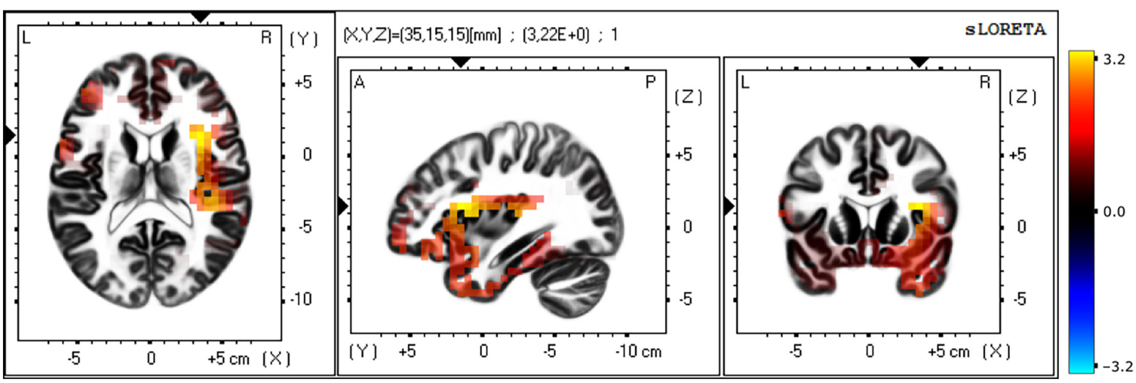
TF -6,027 to -6,008 ms



TF -4,090 to -4,074 ms



TF -4,027 to -3,988 ms



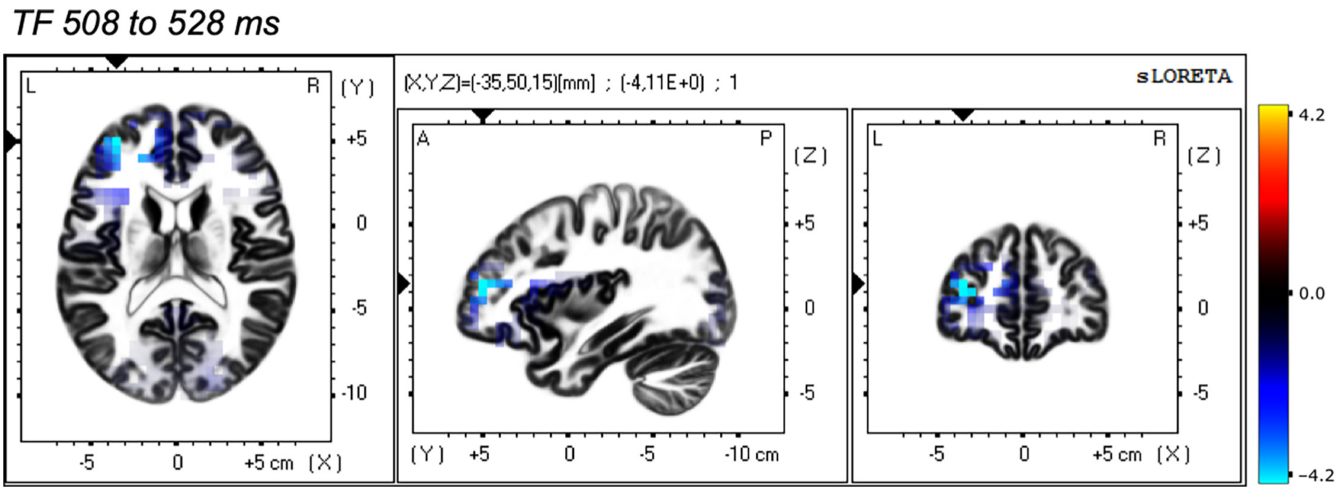


FIGURE 4 Brain areas and time frames (TFs) showing post- *minus* pre-intervention differential change in current source density (μA/mm^2) between exercise and control groups in the incongruent condition of the modified flanker task. Independent group analysis was performed using standardized low-resolution brain electromagnetic tomography (sLORETA) software to test post- *minus* pre-intervention differential change between exercise and control groups (i.e., to test whether exercise group, post- *minus* pre-current source density = control group, post- *minus* pre-current source density). The color bar represents peak *t* values (also shown between parenthesis following the coordinates), with red and yellow colors indicating that post- *minus* pre-current source density's change was greater for the exercise group than for the control group, and blue colors indicating that post- *minus* pre-current source density's change was lower for the exercise group than for the control group. Anatomical coordinates (*X*, *Y*, *Z*) are given in Montreal Neurological Institute (MNI) Atlas space. A, Anterior; L, Left; P, Posterior; R, Right. Inhibitory control was measured by the modified flanker task.

There was not a significant current source density differential change between groups in TFs of the maintenance and retrieval phases of the high load condition or in the low working memory load condition.

Table 2, Figures 2 and 4 present the brain regions for each hemisphere and TFs showing the post- *minus* pre-intervention differential change in current source density between exercise and control groups during the performance of the inhibitory control MFT. In the incongruent condition, only in the TF from *508 to 528 ms* (i.e., approximately the moment of information processing previous to the target response), the LBA10 showed a lower post- *minus* pre-intervention current source density incremental change in the exercise group with respect to the control group (peak $t = -4.1$, $k = 5$). No significant current source density change was observed in the congruent condition of the task.

4 | DISCUSSION

The present study, carried out in a sample of children with overweight/obesity, shows the effects of a long-term exercise program on brain activity underlying working memory and inhibitory control. While EEG-based studies of exercise generally use an ERP approach that lacks spatial resolution, this study included measures of brain source analysis that leverages the high temporal resolution of the EEG with higher spatial representation and affords a better understanding of the influence of exercise on brain function and cognition. We found that both the exercise and control groups improved task performance on working memory and inhibitory control tasks, with no differences observed between groups. Importantly, between-groups differences in current source density from pre- to post-intervention were seen even in the absence of task performance differences. In particular, children with overweight/obesity, who were randomly assigned to a 20-week exercise program had significantly greater increases in brain activation from pre- to post-intervention mainly in areas of the frontal and temporal lobes in the DNMS task. This finding was specifically observed during the encoding phase of the high working memory load condition of the DNMS relative to their peers in the control group. On the contrary, participants from the exercise group presented a lower current source density change from pre- to post-intervention in a single brain area (i.e., Middle frontal gyrus; LBA10) of the frontal lobe during the phase of information processing previous to the target answer of the incongruent condition of the inhibitory control task (i.e., MFT), in comparison with the control group. Together, these findings support previous research reporting that exercise effects may selectively influence brain function during tasks that are the most cognitively demanding.[17] Future studies should confirm or contrast our findings by utilizing brain source localization algorithms such as CLARA or SSLOFO that are more recent and deal with the inverse solution more accurately.

Recent meta-analyses have shown similar benefits to executive function from different modes of exercise: aerobic, resistance, and/or coordinative.[52–54] In the present RCT, both the aerobic and resistance training embedded a coordinative/motor component (i.e., including games based on playful balance, bilateral, hand–eye, and leg–arm coordination).[55] Thus, our exercise program was not specific to aerobic or resistance exercise, rather it had complex cognitive and social (i.e., games were mostly cooperative) components that cross the various exercise modes (as it is often the case with exercise in the real-world, that is, outside of the laboratory). Collectively, the neurobiological and neuropsychological adaptations in connection with aerobic and resistance exercises may explain the exercise-induced change on neuroelectric activity observed in this study.[53,56] Neurogenesis, angiogenesis, neural plasticity, and neurotransmitters have been presented as potential mechanisms that explain the beneficial effects of aerobic and resistance exercise on brain health.[36] For instance, resistance training serves to produce adaptations at a skeletal muscle level, which serves as an endocrine organ that influences brain metabolism through cytokines and peptides released by muscle contractions.[37] Future studies should investigate the separate underlying neurobiological mechanisms of different types of exercises on brain activity and executive function.

Our findings showing an equal improvement in behavioral performance (i.e., shorter RTs in working memory and inhibitory control tasks) for both the exercise and control groups and no differences between groups partially concur with those of previous RCTs carried out in children with overweight/obesity.[12,19] In those studies, both the children participating in 8-month[12] and 9-month[19] exercise programs and those from a control group showed an improvement in response accuracy from pre- to post-intervention in a flanker task that measured inhibitory control. Similar findings were observed in RCTs on children with normal-weight, wherein no significant differences in working memory or inhibitory control were observed between groups.[19,21,22,57] In contrast, the FITKids 9-month afterschool PA program, which included at least 70 min of moderate-to-vigorous PA per day, resulted in improvements in working memory,[58] and inhibitory control,[11,17,42] only for those normal-weight children belonging to the exercise group. However, other non-RCT studies obtained similar findings to ours as they showed no effects of exercise on working memory[59,60] and inhibitory control.[59,61] The inconsistency of findings across studies might be due to differences in the sample's characteristics (i.e., children with overweight/obesity versus normal weight peers), the design of the tasks used for assessing working memory (i.e., DNMS, Sternberg task,[58] Digit-span task,[59] or Random number generation task[60]), and inhibitory control (i.e., flanker task[11,12,17,19,42,57,61] or Stroop[59]), and/or different intervention characteristics (i.e., 9 months,[11,17,19,57,58] 8 months,[12] 6 months,[60] 3.5 months,[21] 2.5 months,[57] 2 years,[59] or 1.5 months[61]). Therefore, since an effect of the exercise program was only observed for brain function (i.e., current source density), this outcome may be more sensitive to exercise-induced changes than task performance measures. Behavioral measures may not be sensitive enough to detect differences between groups. However, as a result of an insufficient number of studies using experimental designs (i.e., RCTs) and the methodological differences between them, more well-designed RCTs are needed to draw conclusions about the effect of long-term exercise programs on working memory and inhibitory control.

To the best of our knowledge, there is no previous evidence analyzing the effects of a long-term exercise program on brain activity underlying working memory in children with overweight/obesity. The novel findings observed in the present study indicate that children with overweight/obesity from the exercise group had a significantly greater increase in brain activation from pre- to post-intervention during a high working memory load task than their peers from the control group. This activation occurred selectively in brain areas over the frontal and temporal lobes, and, to a lesser extent, in areas over the parietal and occipital lobes, during the encoding phase of the working memory task. More concretely, participants from the exercise group had a higher change in current source density during the time period where higher demands on working memory were necessary (i.e., retention of second, third, and fourth stimuli) and this change occurred across a broad range of brain areas. Taking into account that the previous neuroimaging literature has identified a broad network of brain areas (i.e., frontoparietal, motor, and cingulate networks) underlying working memory function,[62] one explanation of our findings may be that exercise benefits the functional interaction of a range of brain areas rather than a single system. Accordingly, differences in brain activation from pre- to post-intervention observed in areas such as the cuneus (i.e., BA18), responsible for processing visual information,[63] or the posterior cingulate (i.e., BA30), which plays a crucial role in the storage of visual objects during a delayed period,[64] suggest that exercise enhances the capacity to visually process and store information during the memory encoding—target interval in children with overweight/obesity. Further, exercise may also benefit access to storage information during working memory processes, as we observed in the maintenance phase. That is, an increment of current source density occurred in prefrontal areas including the middle and inferior frontal gyri (e.g., BA11 and BA47).[65] Collectively, these findings have been shown to be biologically plausible as exercise appears beneficial for brain function and cognition reflected in the exercise-induced brain plasticity, angiogenesis, and synaptogenesis in mammals.[66–68] Only a previous study analyzed the effect of a 14-week exercise intervention on fMRI-based brain activity during a spatial working memory task in a sample of normal-weight children and found no effects.[22] Discrepancies with our findings showing modulation of brain activity underlying working memory after an exercise program may be due to the different tasks used (i.e., DNMS vs. Spatial Span task) or that children with overweight/obesity may response differently to exercise.[60] Also, given the dose–response effects of exercise on brain function previously suggested,[24] it may be that the dose of PA in the study with normal-weight children (14 weeks) might have been too low to bring about positive effects.[22] Future RCTs addressing the long-term effects of exercise on the current source density underlying working memory are needed to confirm or contrast our findings.

A different brain activation pattern was observed during performance of the incongruent condition of the inhibitory control task. In this case, the exercise group showed a smaller increase of current source density from pre- to post-intervention in the frontal lobe, specifically the middle frontal gyrus (i.e., BA10), in comparison with the control group. Two previous RCTs, one in children with overweight/obesity[12] and another other in children of normal weight,[11] used fMRI to assess the activation pattern of brain areas during a flanker task following an exercise intervention. While the RCT in children with overweight/obesity showed that the exercise group had significantly higher increment of activation in the insula and superior temporal gyrus than the control group,[12] the RCT in children of normal weight showed that the exercise group decreased brain activation in the prefrontal cortex along with better task performance (i.e., greater efficiency of resources).[11] This decreased activation pattern partially concurs with our findings showing that children from the exercise group, in comparison with those from the control group, had a significantly smaller increase of current source density from pre- to post-intervention in the frontal lobe during the information processing phase previous to the target answer in the MFT. These findings may indicate more efficient brain function during performance of an executive function task from the perspective that less brain activation reflects more efficient brain functioning.[69,70] However, we did not observe between-groups differences in task performance, and, therefore, it is difficult to draw strong conclusions.

In our study, two different activation patterns were observed depending on the task. During the working memory task, the exercise group showed a higher increase in current source density from pre- to post-intervention in comparison with the control group, whereas during the inhibitory control task, the exercise group showed a lower increase in current source density. These differences in activation could be related to the different cognitive demands of each task. Whereas the DNMS task (i.e., working memory) had a longer duration of the pre-target phase including the encoding and maintenance phase prior to the retrieval phase, the MFT (i.e., inhibitory control) had a single target-response phase. Previous research has suggested that tasks such as the DNMS are more sensitive to sustained activation, which is maintained throughout performance of the task, whereas single target-response tasks are more sensitive to transient activation, which includes processing specifically involved in each trial of the task.[48] Accordingly, we speculate that sustained and transient current source density activation were differentially affected by exercise and therefore changes in current source density mainly reflected differences in task strategy between groups, rather than differences in task performance abilities.

The main limitations of the present study are that (i) the results are limited to a sample of children with overweight/obesity and comparison with peers of normal weight were not possible; (ii) it is unknown whether current source density alterations would persist after a period of detraining; (iii) the sample size included for analyses of the present study was relatively small ($N=67$), although it is among the largest compared to previous studies analyzing the long-term effects of exercise on activity of specific brain areas. However, the previous studies used fMRI, which is considered a more spatially precise measurement than brain activation derived from EEG recordings. In summary, the sample size and hence power is not an issue for all significant effects reported in this study; (iv) although several protocols were adopted to reduce the risk of bias in the evaluations (e.g. randomization after baseline assessment and physical trainers not involved in any evaluations), some of the project staff involved in the post-intervention evaluations were not fully blinded to the group allocation, which could add some bias to the measurements. However, since all of the outcomes of the present study were assessed by the same evaluators, we believe is unlikely that the conclusions of this study would largely change due to this limitation; (v) there was a high number of excluded participants due to having an excessive noise of pre- or post-intervention EEG register ($N=21$ for DNMS and $N=18$ for MFT). The present study includes also several strengths as follows: (i) To be the first study using a new approach of EEG analysis based on brain source analyses in relation to exercise effects; (ii) the inclusion of a working memory task together with an EEG measurement and the study of the effects of exercise on current source density changes during this task; and (iii) the general use of standardized and validated instruments.

5 | PERSPECTIVE

Our results add to the literature on the effects of exercise on brain health by providing support for the effects of a 20-week game-based exercise program on brain activity. Children from the exercise group, to a greater extent than those from the control group, significantly increased the current source density of a broad network of brain areas primarily in the frontal, temporal, and limbic areas during a working memory task. More specifically, these effects were observed during the encoding phase of the high load condition, suggesting that the long-term practice of exercise might enhance the capacity to visually process and store information during working memory processes. On the contrary, children belonging to the exercise group showed a significantly smaller increase in current source density of the frontal lobe during the information processing stream prior to the response during an inhibitory control task. Regardless, an aerobic and resistance exercise program modulates brain activity. However, no effects were observed in working memory and inhibitory control performance, and therefore, our findings showing the effect of exercise on brain activity must be viewed with caution. Finally, we suggest that exercise programs based on aerobic plus resistance training (mainly games), with 3–5 sessions per week, can induce brain activation changes, although further studies must test whether other types of exercise (e.g., including motor agility) or of longer duration can have a higher impact on executive function as well as brain activity.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Participants' consent to share the data was not obtain. Further, this was not included in the IRB protocol.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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