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Ten-year resistance training background modulates somatosensory P3 cognitive brain response in older men: a magnetoencephalograpy study

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Abstract:

The brain electrophysiological component P3, associated with good cognitive abilities, deteriorates during healthy aging. Both cognitive functions and P3 component amplitude respond positively to exercise, but the effects of resistance training on P3 are much less studied. Short-term resistance training interventions in older adults indicate modulation towards larger P3 amplitude, but this association has not been studied with a longitudinal study design. We investigated magnetoencephalographically recorded P3 (P3m) in a unique study design of nine aged men (mean age 77.7 y) with quasi-supervised resistance training background over a 10-year period and eight controls of similar age (mean age 77.5 y) with no training background. We elicited P3m utilizing lower limb electrical stimulation, as the resistance training program was mostly directed to lower limbs. Somatosensory oddball paradigm was performed with the right foot's fourth toe as standard (90 %) and hallux as deviant (10 %). Participants were asked to respond to deviants with a button press using their left index finger. Topographic maps showed bilateral temporoparietal activation for P3m in both groups. No amplitude differences were found in active P3m regions between groups. However, the groups differed in hemispheric activity of P3m. The exercise group showed stronger activation in the right frontotemporal and parietal sensor-groups compared to the left sensor-groups, and the control group showed stronger activation in right frontotemporal sensor-group compared to left. The control group showed shorter P3m latency in the right temporal sensor-group than the exercise group, but the latencies in other sensor-groups were similar. In aging, the brain utilizes compensatory areas to perform cognitive tasks. Our results suggest modulation in topographic distribution of P3m activity in aging men with long-term resistance training background compared to their controls. This might arise from a difference in age-related compensatory mechanisms in P3m generation.

Keywords: P3m, electrical stimulation, strength training, exercise, magnetoencephalography, aging

1. Introduction

In normal aging, the brain undergoes both structural and functional changes, leading to a decline in cognitive performance in late life (Beheshti, Maikusa, & Matsuda, 2019; Harada, Natelson Love, & Triebel, 2013). Cognitive abilities such as memory, processing speed, attention, and executive functions, are among those subjected to age-related deterioration, especially after the age of 60 (Harada et al., 2013; Reuter-Lorenz & Park, 2010). Event-related potential P3 (previously called P300) is a widely studied brain electrophysiological component as a measure of cognitive function. Specific brain processes behind P3 generation remain elusive and it likely originates from several overlapping cognitive processes. P3 is linked to attentional processes, memory, and executive function, and it is reliably elicited with an oddball paradigm demanding conscious detection of random target stimuli (Polich, 2007; van Dinteren, Arns, Jongsma, & Kessels, 2014). P3 is also sensitive to the effects of aging. Reduced P3 amplitude, altered topographic distribution of brain activity, and longer P3 latency are reported to occur in older individuals compared to young (Polich, 1996; van Dinteren et al., 2014). Thus, it serves as a useful tool to study age-related deterioration in brain function.

So far, P3 has been mostly studied with electroencephalography (EEG). It is reliably detected as a centroparietal cortical electrophysiological component, a positive waveform, approximately 300 ms after the target stimulus onset. P3 represents complex brain functions involving target detection, memory, and decision-making. Recognizing individual sources has proven difficult, and it is considered to originate from many independent sources and their broad and deep connections in the brain (Polich & Kok, 1995; Polich & Criado, 2006). Studies using EEG and magnetoencephalography (MEG) methodologies have detected bilateral temporoparietal, medial temporal and frontal sources for somatosensory P3 (Rezaie et al., 2011; Tarkka, Micheloyannis, & Stokic, 1996; Valeriani, Fraioli, Ranghi, & Giaquinto, 2001). Furthermore, lesions in the temporoparietal junction have been shown to markedly reduce P3 for both lower and upper limb somatosensory stimulation (Yamaguchi & Knight, 1991; Yamaguchi & Knight, 1992).

During aging, physical activity is an important lifestyle element to maintain physical and cognitive health (Hamer, Lavoie, & Bacon, 2014; Harada et al., 2013; Northey, Cherbuin, Pumpa, Smee, & Rattray, 2018). Research also indicates a strong connection between exercise and higher P3 amplitude in the aging brain. Yet, most P3 research has focused on

aerobic exercise, fitness, and physical activity background (Kao et al., 2019; Pontifex, Hillman, & Polich, 2009; Strömmer et al., 2017). Resistance training is a promoted exercise method for older adults, as it maintains functional capacity and good quality of life (Fragala et al., 2019; Ihalainen et al., 2019; Kell, Bell, & Quinney, 2001; Walker et al., 2014). It has also been demonstrated to improve cognitive functions during aging (Northey et al., 2018). Studies have investigated whether improvement in cognitive function can be observed also in P3 characteristics. Özkaya et al. (2005) reported higher P3 amplitudes in older individuals after a 9-week resistance training intervention, and Tsai et al. (2015) reported diminished amplitude in non-training controls but not in resistance-trained individuals after 12 months of training (mean age 75.8 and 70.9 y, respectively). Resistance training interventions could help to attenuate age-related deterioration seen in P3 component. However, there is insufficient evidence to conclude whether this effect is seen after years of resistance training. Furthermore, short-term interventions may provide multiple other beneficial aspects for brain and cognition, such as learning new skills and social activity, compared to years of training. As cognitive decline in healthy aging develops slowly, and it seems that longer training interventions have shown more consistent results in improved cognition compared to shorter interventions (Sáez de Asteasu et al., 2017), it is yet to be shown whether long-term resistance training consistently effects P3 characteristics.

In the present study, we examined magnetically recorded P3 (P3m) elicited with lower limb stimulation, a unique quasi-experimental study design in healthy older men. We have tracked the resistance training and strength performance of (presently) ~77-year-old men over ten years along with controls of similar age who have no regular training background. We chose lower limb stimulation as our target because of the critical role of lower limbs in an individual's functional capacity and independence, and the resistance training program included exercises targeting lower limb muscles. We hypothesized that there would be modulation in P3m towards larger amplitudes in older men with a long-term resistance training background.

2. Materials and Methods

2.1. Participants

Participants were 17 male volunteers; age range from 74 to 82 years. The exercise group consisted of nine men aged 77.7 ± 2.1 y, and the control group of eight men aged 77.5 ± 2.5 y (Figure 1). This study was performed as a sub-study of a larger SARCOPENIA-project, started as a randomized trial in 2007 in the Faculty of Sport and Health Sciences, University of Jyväskylä (Ahtiainen et al., 2015).

Initially, a total of 35 men took part in a one-year supervised intervention study. Participants were recruited with an advertisement in the local newspaper and all volunteers went through detailed medical screening. All participants aged ~ 70 years, who passed the physical examination were included in the original study. Exclusion criteria were cardiovascular and pulmonary diseases, malfunctions of the thyroid gland, diabetes, obesity (body mass index ≥ 30), or any other disease or medications that may have precluded the ability to perform the exercise training and testing, and participation in systematic physical training in the previous year. After the baseline measurements, researchers performed block randomization by a random number generator to three resistance training groups, which differed only by muscle biopsy procedures in the measurements, and one control group (3:1 for exercise and control, but 1:1:1:1 for each original group). Twenty-six participants were randomly selected to the exercise groups with identical resistance training intervention and nine to the non-exercising control group.

The exercise group first participated in one-year supervised resistance training (two times a week for six months and then three times a week for six months) in the University gym. Exercises included leg press, squat, and knee extension and flexion for lower limb muscles, and four to five exercises targeting the other main muscles of the body. The training was first performed with light loads, seven to eight exercises at 40–60% of one repetition maximum (1RM) with three 10–20RM sets and short rest periods in between. After one month the loads were increased progressively up to 60–80% of the 1RM in three to five sets (8–12RM per sets) to increase muscle mass. After three months, 9 to 10 exercises were performed and the training program also included higher loads, 70–90% of the 1RM, with a longer recovery time, using 5–10RM sets to optimize gains in maximal strength. In the training program, two sets were also performed with lower loads (40–50% of the 1RM with 8–12 repetitions) and higher movement velocities to improve muscle power (Ahtiainen et al., 2015). After the first year, participants in the exercise group continued voluntary resistance training ~2 x week, without any supervision. The present control participants continued their normal daily

routines without resistance training. Participants were followed up with strength measurements after the first and second years of voluntary training, and later after four and seven years. Participants kept a training diary during the year with supervised training and completed questionnaires for each follow-up measurement. During the first year, one participant from the exercise group died and three participants were not willing to continue with the study program. Two participants from the exercise group and one participant from the control group declined to participate in follow-up measurements. In addition, two participants from the control group moved to another region, one was not reached, and one was deceased. One participant in the exercise group did not continue resistance training after the first-year intervention and transferred voluntarily to the control group.

After ten years, 24 men participated in the follow-up measurements and were invited to the present sub-study. Six participants from the exercise group and one participant from the control group were excluded from MEG registration due to a diagnosis of neurological or psychiatric disease, such as Parkinson's or Alzheimer's disease or depression. From the exercise group, one participant was not measured due to tooth fillings, one for musculoskeletal issues preventing from participating in the MEG measurement, and one participant was not reached.

From the 14 participants taking part in the MEG recordings, 10 participants were part of the original exercise group and had continued self-directed resistance training until the 10-year follow-up. Mean ± SD training adherence for the first year was 93 ± 8 % and participants reported 2.2 ± 0.4 resistance training sessions per week during the subsequent follow-up. One participant was later excluded from the exercise group for inadequate MEG data (n=9). The control group of the present study consisted of four original participants and four recent recruits (n=8) (Figure 1). The inclusion criteria for the new recruits were; age 72 to 80 years, no background in resistance training or other regular moderate or vigorous exercise training, no neurological or psychiatric diseases or medications affecting the nervous system, or disease that prevents normal exercise training or daily activities, and no pacemaker or metal implants preventing the MEG registration. All original participants except one resistance trained and one control subject reported carrying-out endurance-type physical activities during the 10-year period, e.g., skiing, swimming, and walking. Participants in the exercise group reported remaining healthy for the follow-up period and being able to continue resistance training. One participant reported musculoskeletal disease that did not affect the

exercise training. All control participants reported health-related changes during the follow-up period that did not prevent participating in MEG recordings. All recordings and analyses were performed blinded to the participants' group status.

The study protocol was approved by the Ethics Committee of the University of Jyväskylä, Jyväskylä, Finland, 10.4.2017. Written consent was obtained from all participants, and the study was conducted according to the principles of the Declaration of Helsinki. Funding was provided by the Faculty of Sport and Health Sciences, University of Jyväskylä, Jyväskylä, Finland and MEG registrations and facilities by Jyväskylä Centre for Interdisciplinary Brain Research (CIBR), University of Jyväskylä, Jyväskylä, Finland.

2.2. Task and stimulation procedure

We performed a somatosensory oddball task utilizing electrical stimulation (DeMeTec SCG30, DeMeTec GmbH, Langgöns, Germany) delivered to the fourth toe and hallux of the right foot. Two non-magnetic ring electrodes, built in-house, were placed proximally and distally on each toe (Figure 2) with 1 cm inter-electrode distance. Five-hundred monophasic square-wave current pulse stimuli of 0.2 ms duration were delivered with an interstimulus interval of 1000 ms. Standard stimuli (90 %) were delivered to the fourth toe and deviant stimuli (10 %) to hallux. Stimulation intensity was set individually at 120-150 % of the sensory threshold to a comfortable level with clear sensation without any pain and adjusted separately for each toe. Participants were instructed to attend to stimuli and react to each deviant stimulus in the hallux by pressing a button in a response box with their left index finger. All participants reported being right-handed.

2.3. MEG recording

Somatosensory evoked field recordings were conducted with 306 sensor magnetoencephalography equipment (Elekta Neuromag®, Triux™, Stockholm, Sweden) in a magnetically shielded room with a bandpass of 0.1–330 Hz and a sampling rate of 1000 Hz. Eye movements and blinks were recorded with electro-oculogram (EOG). To register head shape and position, five continuous current head position indicator (HPI) coils were placed on the scalp. Head shapes were registered with a 3D digitizer (Fastrak®, Polhemus, Vermont, USA) in addition to the nasion and preauricular points, along with circa 100 additional points around the scalp and nose. In MEG, participants were asked to sit still, with hands resting on the table (the left hand ready on the response box) and gaze fixed forward on a black dot

approximately 1.5 meters in front of them. They were advised to avoid blinking during the recordings. The head position was continuously monitored through the recording. The data were stored for offline analysis.

2.4. Data analysis

For preprocessing of data, temporal signal space separation (tSSS) (Taulu & Simola, 2006) with Maxfilter software (Elekta Neuromag®, Stockholm, Sweden) was utilized to reduce external artifacts and detect bad channels. The head position was transferred to mean coordinates for (maximum change of 2 cm) participants to enable group averaging and sensor-space analysis. After this, data were analyzed offline with Brainstorm software (version 29/3/2019). The data were bandpass filtered at 0.1-40 Hz. Eye blinks were detected from EOG traces. For some participants, we detected blinks exceeding the absolute value of the filtered signal at least six times the standard deviation (SD) due to excessive blinking. Detected eye blinks were removed utilizing signal-space projection (SSP) (Uusitalo & Ilmoniemi, 1997). Raw data were manually inspected, and segments with artifacts from muscle tension were removed. Data were segmented to epochs from -100 to 450 ms in relation to the stimulus onset, with a baseline correction of -100 to -1 ms. A stimulation delay of 3 ms, identified from stimulus artifacts, was corrected. Deviant epochs and an equivalent number of standard epochs preceding a deviant were averaged separately for each subject. The maximum allowed reaction time for deviant identification was 0.999 s, and only those deviants correctly identified with a button press within this time limit were taken into analysis. The minimum number of accepted deviants per individual was 29, and the average number obtained for all participants was 43. One participant from the exercise group was excluded from the analysis for not having enough accepted epochs.

2.5. Group source analysis

First, all gradiometers and magnetometers were used for source analysis. As we had no individual MRI images, each participant's head shape was aligned to a default anatomy template ICBM152. Noise covariance analysis was calculated utilizing empty room measurements recorded before each participant's research visit. The source model was performed with overlapping spheres and averaged epochs were used to generate minimum norm estimate current density maps in Brainstorm software. Current density maps were normalized with Z-score transformation and finally spatially smoothed. Based on previous P3

studies (Tarkka & Stokic, 1998; Yamaguchi & Knight, 1992), regions of interest (ROIs) were investigated with Brainstorm scout function.

Grand average source maps were created by extracting current source density maps with absolute values and creating grand average source maps for each group. Grand average source maps were used to detect ROIs with maximum amplitude between 320-390 ms for the exercise group and the control group. Scouts with 40 vertices were created at the source with maximum amplitude for each group, and a matching one was created in the contralateral hemisphere. These were investigated for each participant using group average scout waveform peak as the temporal cue, resulting in different latencies of the peak amplitudes (324-330 ms for the exercise group, 382-388 ms for the control group). A maximum amplitude using the group-determined time window was detected in each participant's scout waveform to explore common activations and hemisphere differences.

2.6. Sensor-level analysis

Second, for single sensor analysis, only gradiometers were included in the analysis as they best represent the brain activity below a specific sensor. Each 102 gradiometer pair signals were combined by calculating their root sum square (RSS; $\text{sqrt}(\text{grad2}^2 + \text{grad3}^2)$) to control for the sign of the amplitude (Figure 2). A similar method has been utilized previously (Kida et al., 2007; Onishi et al., 2013). The obtained gradiometer pair signals were used to locate the sensor with maximum amplitude from each participant between 320-390 ms, and peak amplitude and latency were measured. We also detected average amplitude within 320-390 ms time-period in order to measure average activation in typical P3 time-window because this activity involves larger processes and possibly deeper brain areas.

2.7. Sensor-group analysis

Third, information from topographic maps and gradiometer pair RSS waveforms with maximum activation was used to create sensor-groups from gradiometer pairs to detect activity from a broader area of cortex. As the magnetic fields showed bilateral temporal activity already around 200-260 ms time-window, we measured both early deviant detection (M200) and P3m. Sensor-groups were formed for fronto-temporal (P3m), temporal (M200, P3m), and parietal (P3m) cortices similarly for both hemispheres, according to topographic maps. We used a time-window of 200-260 ms, detected from the grand average waveforms, for M200 response and the previously determined time-window 320-390 ms for P3m. M200

was detected from temporal sensor-groups, and peak amplitudes and latencies were recorded. For P3m, we detected peak amplitudes, peak latencies, and average amplitudes, measured from temporal, frontotemporal, and parietal sensor-groups.

2.8. Statistical analysis

Statistical analysis was performed with Brainstorm software and IBM SPSS Statistics Version 24 (Armonk, NY, USA). The normality of the data was tested with the Shapiro-Wilk test. All between-group comparisons were tested with independent samples t-test for normally distributed data and Mann-Whitney U test for the non-normal data. Normally distributed data are presented as means and standard deviations and non-normally distributed data as medians and interquartile ranges. P3m and M200 analysis in sensor-groups was performed using linear mixed model (group, hemisphere, group*hemisphere). One major outlier exceeding upper fence (Q3 + (1.5 * IQR)) was detected in P3m average amplitude difference scores in left and right temporal sensor-groups. Therefore, we performed an additional analysis, excluding the outlier, as a sensitivity analysis for this variable. Between-group differences in latencies were tested with Mann-Whitney U test for non-normally distributed data. P-values (2-tailed) are presented as exact and the statistical significance threshold was set to <.05.

3. Results

3.1. Group characteristics

The groups were similar in their age, height, and weight. No between-group differences in reaction time or target hits were observed (mean 91 ± 4 % for the exercise group and 83 ± 5 % for the control group). All mean values are shown in Table 1.

Table 1. Characteristics of the participants presented as mean ± SD or median (IQR). Differences tested with independent samples t-test[a] or Mann-Whitney U test[b].

	Exercise (n=9)	**Control (n=8)**	**T-value[a] / U[b]**	**P-value**
Age (y)	77.7 ± 2.1	77.5 ± 2.5	0.150[a]	.882
Height (cm)	174.0 ± 3.6	173.3 ± 8.4	0.234[a]	.820

Weight (kg)	80.1 ± 10.6	78.3 ± 8.9	0.366[a]	.720
Reaction-time (ms)	577 ± 90	528 ± 64	1.292[a]	.216
Target hit (n)	48.0 (42.0-50.0)	42.5 (35.0-47.5)	19.0[b]	.114

*=p<.05

3.2. Group source localization

Figure 3 shows minimum norm estimate source maps for exercise and control groups and grand averaged waveforms from central scouts selected for each group. The maximum activation in the P3m time-window was detected in parietal areas of the cortex. Median amplitude Z-score was 1.78 (1.22-2.41) in the left scout and 1.92 (1.37-6.19) in the right scout for the exercise group and 2.45 (1.28-4.67) in the left scout and 1.33 (0.35-1.82) in the right scout for the control group. Detected sources did not reveal group differences (left scout U[n9,n8]=43.0, p=.541 and right scout U[n9,n8]=18.0, p=.093) or significant differences in the activation between hemispheres (exercise group Z=-1.599, p=.110 and control group Z=0.980, p=.327).

3.3. Sensor-level analysis

The grand average waveforms obtained from all planar gradiometers are shown in Figure 2 for the exercise and control groups separately. In single sensor analysis, peak amplitudes were similar in both groups (U[n9,n8]=30.0, p=.606). Peak amplitude was 89.8 (67.3-98.8) fT/cm in the exercise group and 70.8 (49.4-101.1) fT/cm in the control group. Average amplitudes over the period of 320-390 ms were also similar between groups (59.5 (52.5-76.9) fT/cm for the exercise group and 52.3 (25.3-80.8), U[n9,n8]=29.0, p=.541) fT/cm for the control group. Peak latency was 352 (346-388) ms in the exercise group and 349 (327-392) ms in the control group (U[n9,n8]=28.0, p=.481).

3.4. Sensor-group M200 analysis

There were no differences in M200 amplitudes between groups or hemispheres (p=.678 and p=.051, respectively) and groups were similar in hemispheric differences (p=.305). Peak amplitude in exercise group was 40.2 (CI 30.1 – 50.2) ft/cm in the left temporal region and 37.4 (CI 27.3 – 47.4) ft/cm in the right temporal region, and in the control group 43.6 (CI 32.9 – 54.2) in the left temporal region and 34.4 (CI 23.7 – 45.1) ft/cm in the right temporal region. Latencies were also similar for groups and hemispheres (p=.888 and p=.611

respectively) and groups did not differ in hemispheric differences (p=.299). M200 latency in exercise group was 227.0 (CI 214.0 – 240.0) ms in left temporal region and 240.4 (CI 227.5 – 253.4) ms in right temporal region, and in the control group 238.3 (CI 224.5 – 252.0) ms in the left temporal region and 241.8 (CI 228.0 – 255.5) ms in the right temporal region.

3.5. Sensor-group P3m analysis

There were no differences in P3m peak amplitudes or average amplitudes between groups in the detected sensor-groups (p=.298, p=.393 and p=.731 for peak amplitudes and p=.219, p=.349 and p=.513 for average amplitudes in frontotemporal, parietal, and temporal sensor-groups, respectively). However, there was a difference in hemispheric activity in peak amplitude and average amplitude in frontotemporal sensor-groups (p=.043 and p=.008, respectively). The exercise group had stronger P3m peak amplitude and average amplitude in right hemisphere, as the control group in left hemisphere (p=.005 and p=.001 for group*hemisphere effect in peak amplitude and average amplitude, respectively). There was also a significant group difference in hemispheric activity in parietal sensor-groups. The exercise group showed stronger P3m amplitudes in right parietal sensor-group (p=.013 and p=.019 for peak amplitude and average amplitude, respectively). The control group had similar amplitudes in left and right parietal sensor-groups (p=.432 and p=.425 for hemispheric effect in peak amplitude and average amplitude, respectively). Peak amplitudes and average amplitudes were similar between hemispheres for both groups in temporal sensor-groups (p=.790 and p=.483 for hemisphere effect and p=.926 and p=.418 for group*hemisphere effect for peak amplitude and average amplitude, respectively). Because of one outlier in hemispheric difference scores in temporal average amplitudes, a sensitivity analysis was performed without the outlier, showing no difference between groups or hemispheres (p=.316 for hemisphere effect and p=.901 for group*hemisphere effect). Mean peak and average amplitudes are presented in table 2.

Table 2. Sensor-group characteristics for P3m peak amplitude and average amplitude (fT/cm) presented as means and 95% confidence intervals (CI), tested with linear mixed model, for group, hemisphere, and group*hemisphere effect.

Sensor-group	**Exercise, n=9 (95 % CI)**	**Control, n=8 (95 % CI)**
Peak amplitudes		
Left frontotemporal	35.7 (22.5, 48.9)	50.1 (36.1, 64.1)

Right frontotemporal	48.0 (34.8, 61.2)	38.1 (24.1, 52.1)
Left parietal	38.5 (24.8, 52.2)	48.2 (33.8, 62.9)
Right parietal	52.9 (39.2, 66.6)	44.5 (30.0, 59.0)
Left temporal	46.0 (34.9, 57.0)	43.7 (32.1, 55.5)
Right temporal	47.6 (36.5, 58.6)	44.9 (33.1, 56.6
Average amplitudes		
Left frontotemporal	25.1 (13.3, 36.8)	43.2 (30.9, 55.7)
Right frontotemporal	38.2 (26.5, 49.9)	27.8 (15.4, 40.2)
Left parietal	27.8 (15.1, 40.4)	38.6 (25.1, 52.0)
Right parietal	42.7 (30.0, 55.3)	34.1 (20.7, 47.6)
Left temporal	36.2 (25.8, 46.6)	35.5 (24.5, 46.6)
Right temporal	37.8 (27.4, 48.2)	32.9 (22.9, 44.0)

The control group showed shorter latency in the right temporal sensor-group than the exercise group (U[n9,n8]=15.5, p=.046). Peak latency was 360 (335-382) ms for the exercise group and 321 (320-365) ms in the control group. Latency was similar in left temporal sensor group (U[n9,n8]=37.5, p=.888) for exercise and control groups (381 (334-387) ms and 363 (335-390) ms, respectively). Latencies were similar in frontotemporal (U[n9,n8]=41.0, p=.673 and U[n9,n8]=24.0, p=.277 for left and right hemisphere, respectively) and parietal sensor-groups (U[n9,n8]=44.0, p=.481 and U[n9,n8]=30.0, p=.606 for left and right hemisphere, respectively) between groups. Peak latencies were 341 (322-390) ms and 353 (330-371) ms for the exercise group and 381 (330-389) ms and 326 (321-390) ms for the control group in left and right frontotemporal sensor-groups, respectively. In parietal sensor-groups, peak latencies were 360 (328-387) ms and 344 (326-382) ms in the exercise group and 382 (358-386) ms and 336 (320-386) ms in the control group for left and right, respectively. Grand averaged RSS waveforms for both groups are shown in Figure 4.

4. Discussion

In our groups of long-term resistance-trained older men and their controls, demographic characteristics were similar, and groups showed no differences in reaction times or their ability to perform target hits. For all participants, averaged deviant epochs revealed bilateral P3m activity in the typical P3 window. In contrast to our hypothesis, we did not find

significant differences in P3m amplitudes between groups. However, we found a difference between groups in hemispheric activity of the P3m in frontotemporal and parietal sensor-groups. The exercise group showed stronger activation in the right hemisphere in frontal and parietal regions in a time-window of 320-390 ms compared to the left hemisphere. The control group showed a stronger activation in the left frontotemporal sensor-group compared to the right frontotemporal sensor-group. The control group also showed shorter latency in the right temporal sensor-group than the exercise group.

As topographic maps showed bilateral temporal activation before P3m activity, already in the time window of 200-260 ms, we analyzed M200 activity in temporal sensor-groups. There is evidence that the early detection of deviant somatosensory stimuli is modified by both aging and exercise background, studied with non-attended somatosensory paradigms (Hautasaari et al., 2017; Strömmer, Tarkka, & Astikainen, 2014; Strömmer et al., 2017; Tarkka et al., 2016). Our study revealed no differences between the exercise and control groups in M200 amplitudes or latencies. Our stimulus detection task was performed attended with an active oddball paradigm, which is not directly comparable to the previous studies with a non-attended oddball paradigm. No studies to our knowledge have investigated the effects of resistance training on automatic deviant detection, either attended or non-attended.

P3 response is well accepted as a marker of cognitive processing in the brain, and P3 amplitude varies in healthy, experimental, and pathological conditions (Hedges et al., 2016; Polich, 1997; Seer, Lange, Georgiev, Jahanshahi, & Kopp, 2016). Aging is one of the major factors affecting P3 amplitude (van Dinteren et al., 2014), and the effects of various forms of physical exercise on P3 during aging have been investigated. Both aerobic exercise and resistance training have enhanced P3 amplitude in intervention studies (Kao et al., 2019; Özkaya et al., 2005; Tsai et al., 2015). Long-term (3-year) aerobic exercise has resulted in larger P3 amplitudes, similarly to years of higher self-reported physical activity background (Kao et al., 2019). However, studies with long-term exercise training are scarce, and the effects of long-term resistance-training have not been investigated previously. Long-term training effects provide beneficial information compared to those achieved in the short-term, as interventions always provide other sudden beneficial attributes as well, such as social activity and learning features, in addition to exercise. Also, self-reported physical activity may contain reporting bias, and a physically active lifestyle may as itself be a result of a better cognitive function in older adults. Our participants were unique in their different

exercise backgrounds for ten years, during which time the exercise group had carried out a weekly resistance training schedule. Despite the long-term resistance training background, we did not detect amplitude enhancement in our trained participants. The enhancement of P3 amplitude in shorter intervention studies could have partly resulted from learning features and other novelty factors that do not apply in a long-term follow-up while the training continues. In our groups, there might also be other factors, such as other physical activity habits or education background and leisure-time activities, with cognitive training benefits that we were not aware of, and which may influence the P3m amplitude (Gajewski & Falkenstein, 2018). The large inter-individual variability in P3m amplitudes in the control group could support this explanation, and why we did not detect significant differences.

In our study, we detected bilateral P3m in both groups in accordance with earlier detected somatosensory P3 sources (Tarkka et al., 1996; Valeriani et al., 2001). We observed a difference in the distribution of P3m activity in topographic and source maps and, therefore, also performed a hemispheric analysis. The exercise group showed higher activation in the right parietal and frontotemporal regions, analyzed with sensor-groups, compared to the left parietal and frontotemporal regions. For controls, the left hemisphere had stronger activity in frontotemporal region compared to the right. In somatosensory P3 sources, this type of lateralization has not been reported in earlier studies, to our knowledge (Tarkka et al., 1996; Valeriani et al., 2001). However, Valeriani et al. (2001) reported an additional unilateral frontal source for P3, contralateral to stimulation, with a slightly different dipole modelling technique than in similar studies. In P3 studies with auditory stimulation, pronounced amplitude in the right hemisphere, however, is a more common finding (Gilmore et al 2009; Frodl et al., 2000). This is theorized to stem from right hemispheric network that is associated with working memory, sustained attention, and target detection. It is possible that in our study, the MEG technique reveals lateralization more sensitively than earlier EEG recordings in the somatosensory domain. It may be hypothesized that our exercise group was able to utilize right hemispheric network in the stimulus detection task more efficiently.

Another explanation for group differences might arise from age-related changes in brain function. Aged individuals are overall reported to use additional brain regions to implement the same cognitive tasks as young (Reuter-Lorenz & Park, 2010). Regarding the P3 component, a typical observation to occur during aging is frontal compensation (Van Dinteren et al., 2017). P3 is considered to arise from many independent sources and their

complex connections. In P3 generation, hemispheres may also have individual roles, as hemispheric specialization is a well-known principle in both sensory and cognitive processing (Banich, 2009; Tang, Riley, & Constantinidis, 2017). Cabeza et al. (2002) have introduced a theoretic model called "hemispheric asymmetry reduction in older adults" (HAROLD) as a part of the compensatory mechanism theory occurring in the aging brain. The model arises from the evidence that different cognitive functions seem to be less lateralized in older adults than in young adults. That has been suggested to reflect compensatory processes and dedifferentiation processes, which refer to the regional loss of specialization in the brain. Our results indicate lateralization in both groups in generation of somatosensory P3m. Our exercise group seemed to be able to activate the right hemisphere, ipsilateral to stimulation, more effectively than the left hemisphere, and the controls had stronger activity on the left hemisphere. With our participants, it is unclear whether the lateralization is associated with better or poorer performance, as we did not detect significant differences in reaction times and target hits. We do not have information on our participants' cognitive performance; thus, we cannot discuss whether the asymmetry is associated with high cognitive function. Without detailed information of our participants' cognitive status, the origins for the detected differences in brain function are not entirely clear. However, our results might suggest stronger right hemisphere activation arising from working memory and attentional processes (Gilmore et al. 2009). Both of our groups of aged individuals may utilize compensatory brain mechanisms for the deviant detection task, but perhaps there are differences in this development. Further studies with young and old individuals would be necessary to further confirm this.

In P3m latency analysis with sensor-groups, the control group revealed shorter latencies in the right temporal region than the exercise group. Shorter P3 latencies are found to increases with age in late adulthood and correlate with better cognitive performance (Pelosi et al., 1992; van Dinteren et al., 2014). In young individuals, physical activity has resulted in shorter P3 latency, but in the aging population, the results vary considerably (Kao et al., 2019). No studies have found a connection between resistance training and P3 latency modulation in aging individuals. Shorter latency may indicate faster processing of the target stimulus in the control group. However, in our sensor-group RSS values, the peak of the waveform may not properly describe the real latency of the P3 as there are multiple sensors and processes that affect the amplitude peak of the wave. Therefore, the peak value may not represent the real latency of the P3m phenomenon. Furthermore, the difference in P3m

latency was not visible in other regions with stronger P3m amplitude and therefore we cannot make strong conclusion of this difference.

The major strength of our study is the unique study design of an exercise group with a long-term, ten-year resistance training background and the otherwise very similar non-training control group.

5. Limitations

Our study has some limitations. Our participants were part of a larger, ten-year project where various exclusion criteria were applied, and thus our final sample size was rather small. Our MEG measurements were a later addition to the on-going project, which is the reason that we have no data recorded at the start of the intervention period. Furthermore, we were not able to perform formal cognitive testing, however, the present participants were free of neurological or musculoskeletal diseases (see Methods). Four participants in the control group were new recruits, and therefore were not part of the original randomization. Also, they did not take part in the measurements at the beginning and during follow-up of the original study. This study was not an intention-to-treat trial and participants who developed neurological or psychiatric diseases were excluded from MEG recordings. Therefore, we cannot draw conclusions on possible effect of resistance training on brain pathologies and their development. Our results present an opening in the field and further research with complete cognitive testing and structural brain imaging would be necessary to fully understand the relationship between resistance training and cognitive aging.

6. Conclusions

Ten-year resistance training background in older men did not lead to significant differences in P3m amplitude over their nonresistance-trained controls. However, we found stronger right hemisphere contributions in P3m generation in resistance-trained individuals and stronger left hemisphere contribution in their untrained controls. This finding suggests not entirely symmetrical P3m activation in the aging brain and possibly modulation in the age-related

compensatory mechanisms in the P3m generation due to long-term resistance training background.

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Conflict of interest

The authors have no conflict of interest to declare.

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Figure legends:

Fig.1: Flow chart describing the flow of the participants during the 10-year study process.

Fig.2: Grand average waveforms (root sum squared, RSS) recorded from planar gradiometers showing both standard and deviant conditions superimposed. The exercise group is presented above (A) and the control group below (B). Stimulation electrode ring placement in the right foot is shown below waveforms. For both groups, a selected gradiometer pair with strong activity in the time window of 320-390 ms is shown in the right panels (C, E). Right panels (D, F) show one gradiometer pair averaged to the button press, selected based on the strong activity from the right hemisphere in the primary motor cortex area (M1), demonstrating both the readiness field before movement onset and the motor-evoked field peaking after the button press.

Fig.3: Grand average minimum norm estimate -source maps for exercise and control groups at their maximum source amplitudes. Below are scout waveforms created from each group, showing temporal evolution in the central activation sources, separately for both hemispheres.

Fig.4: Grand average waveforms (±SD) in frontotemporal, parietal, and temporal sensor-groups for exercise and control groups, both hemispheres are shown in each graph. Grey shaded area demonstrates the analyzed time window in each sensor-group. Topographic maps show grand averages of both groups in planar gradiometer activity at 220 and 380 ms after stimulus onset. Black squares indicate the sensor-groups selected for analysis.

CRediT authorship contribution statement

Heidi Pesonen: Investigation, Formal analysis, Validation, Writing -original draft, Visualization. **Simon Walker:** Investigation, Resources, Writing - Review & Editing, Supervision, Project administration, Funding acquisition. **Juha P. Ahtiainen:** Resources, Writing - Review & Editing, Project administration, Funding acquisition. **Pekka Hautasaari:** Investigation, Writing - Review & Editing, Supervision. **Ina M. Tarkka:** Investigation, Writing - Review & Editing, Supervision, Project administration, Funding acquisition.

Highlights

- The connection between P3 amplitude and exercise training is well recognized
- P3m differed between hemispheres in exercise and control group
- Long-term effects of resistance training on P3 amplitude remain unclear

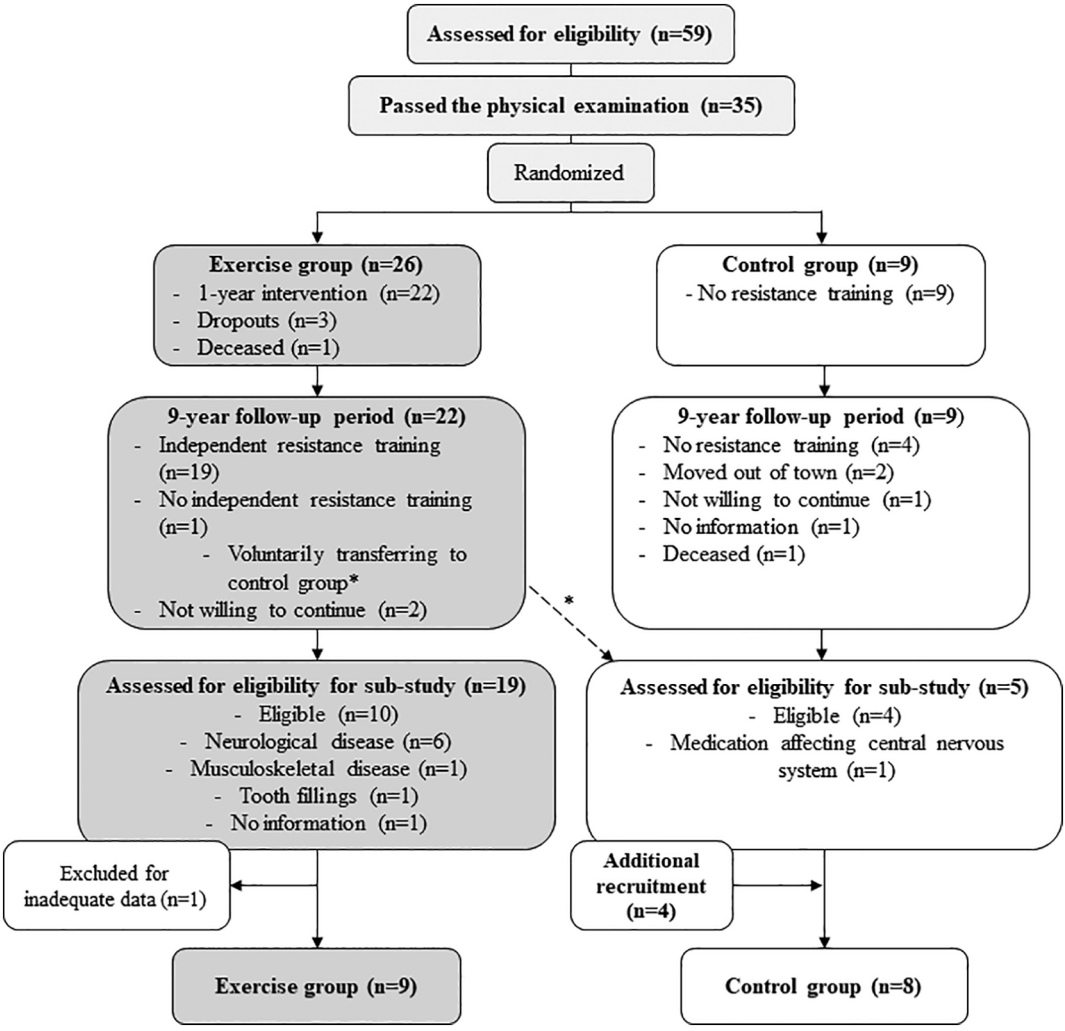
Assessed for eligibility (n=59)
Passed the physical examination (n=35)
Randomized
Exercise group (n=26)
- 1-year intervention (n=22)
- Dropouts (n=3)
- Deceased (n=1)
Control group (n=9)
- No resistance training (n=9)
9-year follow-up period (n=22)
- Independent resistance training (n=19)
- No independent resistance training (n=1)
- Voluntarily transferring to control group*
- Not willing to continue (n=2)
9-year follow-up period (n=9)
- No resistance training (n=4)
- Moved out of town (n=2)
- Not willing to continue (n=1)
- No information (n=1)
- Deceased (n=1)
*
Assessed for eligibility for sub-study (n=19)
- Eligible (n=10)
- Neurological disease (n=6)
- Musculoskeletal disease (n=1)
- Tooth fillings (n=1)
- No information (n=1)
Assessed for eligibility for sub-study (n=5)
- Eligible (n=4)
- Medication affecting central nervous system (n=1)
Excluded for inadequate data (n=1)
Additional recruitment (n=4)
Exercise group (n=9)
Control group (n=8)

Figure 1

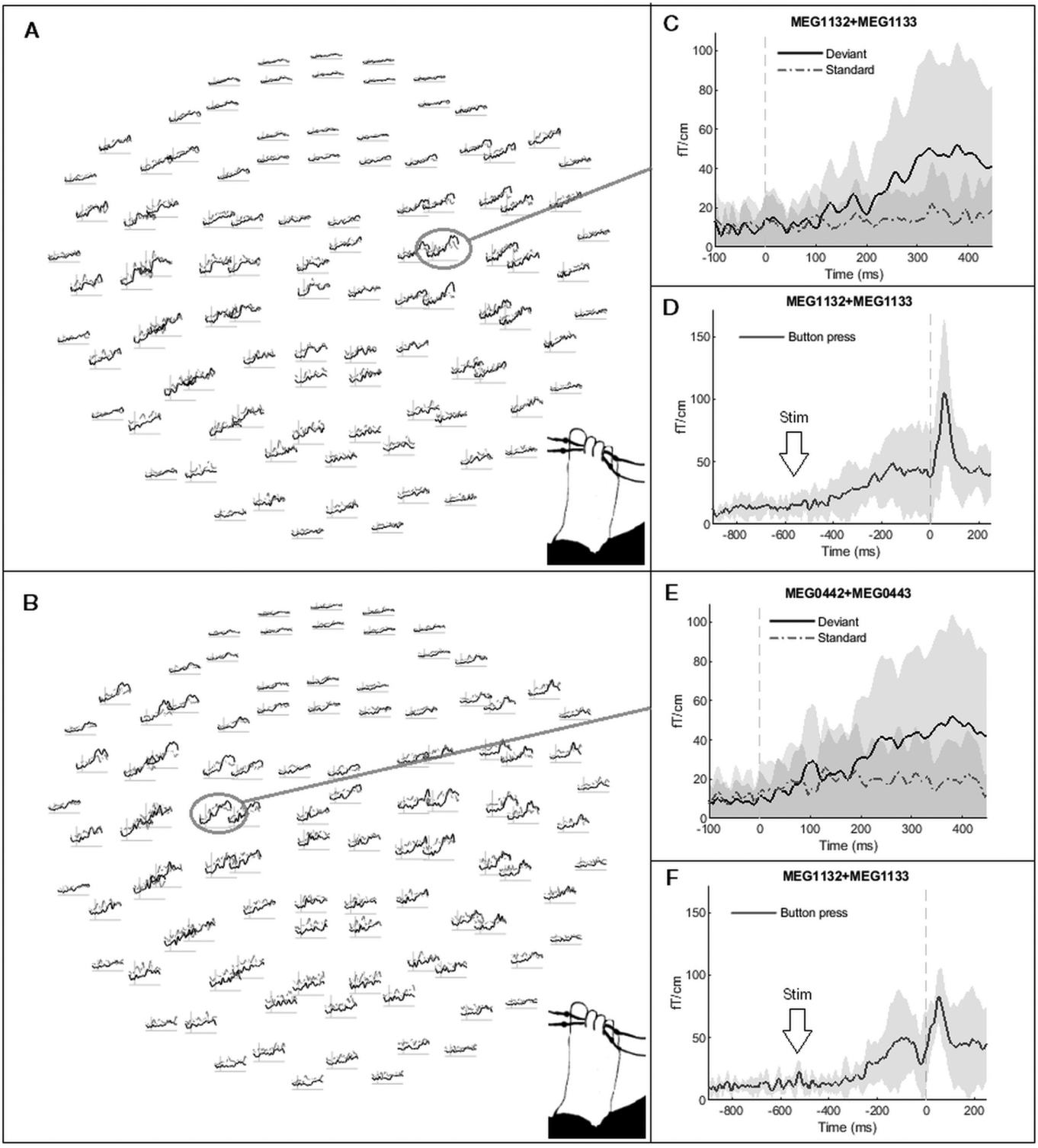
A
B
C
MEG1132+MEG1133
Deviant
Standard
fT/cm
Time (ms)
D
MEG1132+MEG1133
Button press
Stim
fT/cm
Time (ms)
E
MEG0442+MEG0443
Deviant
Standard
fT/cm
Time (ms)
F
MEG1132+MEG1133
Button press
Stim
fT/cm
Time (ms)

Figure 2

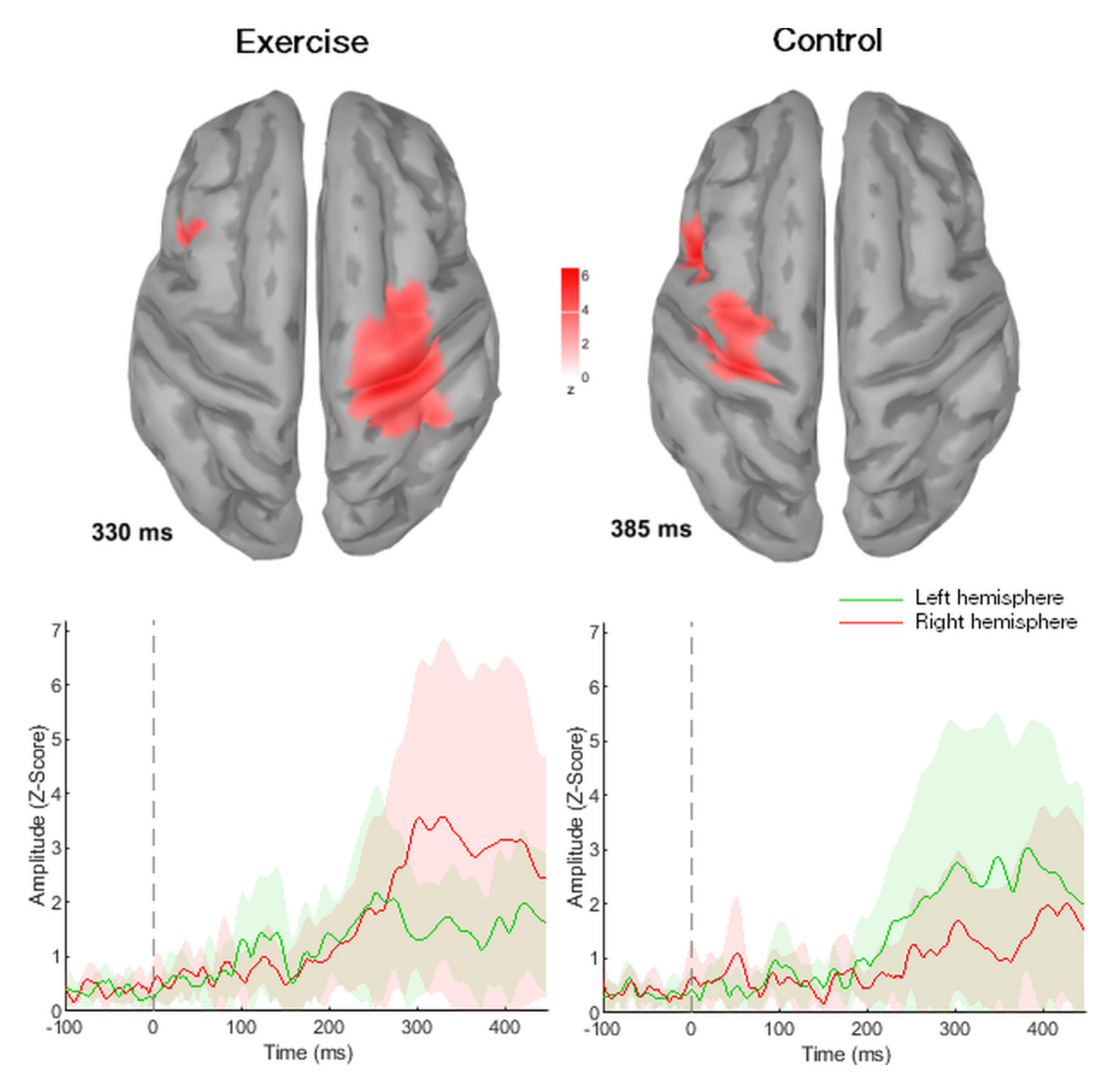
Exercise
Control
330 ms
385 ms
6
4
2
0
z
Left hemisphere
Right hemisphere
Amplitude (Z-Score)
Time (ms)
-100
0
100
200
300
400

Figure 3

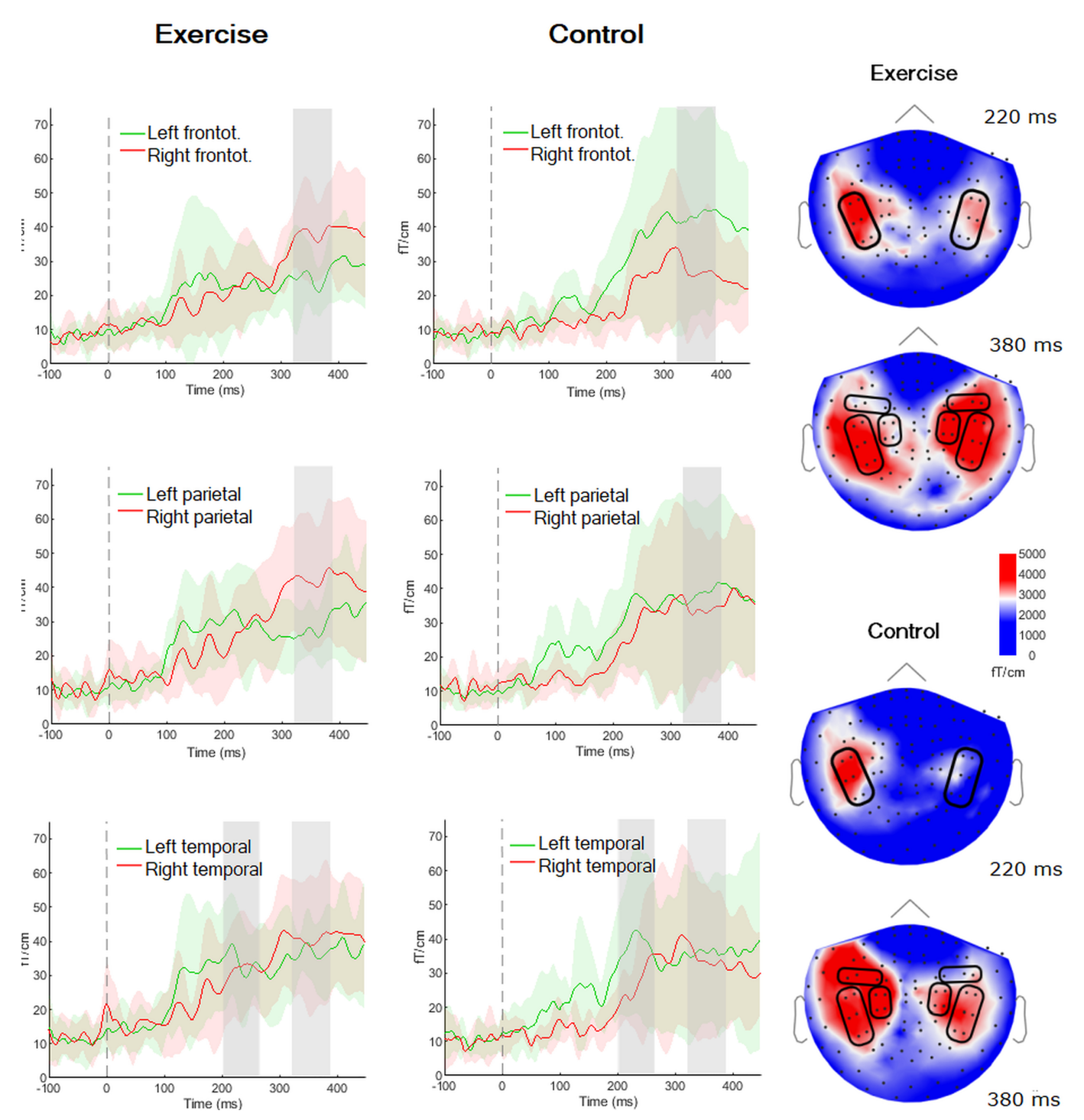
Exercise
Control
Left frontot.
Right frontot.
Left parietal
Right parietal
Left temporal
Right temporal
fT/cm
Time (ms)
Exercise
220 ms
380 ms
Control
220 ms
380 ms
5000
4000
3000
2000
1000
0
fT/cm

Figure 4