Long-term physical activity modulates brain processing of somatosensory stimuli: Evidence from young male twins

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A B S T R A C T
Leisure-time physical activity is a key contributor to physical and mental health. Yet the role of physical activity in modulating cortical function is poorly known. We investigated whether preconceptual sensory brain functions are associated with the level of physical activity. Physical activity history (3-yr-LTME), physiological measures and somatosensory mismatch response (sMMR) in EEG were recorded in 32 young healthy twins. In all participants, 3-yr-LTME correlated negatively with body fat%, r = −0.77 and positively with VO2max, r = 0.82. The fat% and VO2max differed between 15 physically active and 17 inactive participants. Trend toward larger sMMR was seen in inactive compared to active participants. This finding was significant in a pairwise comparison of 9 monozygotic twin pairs discordant for physical activity. Larger sMMR reflecting stronger synchronous neural activity may reveal diminished gating of preconceptive somatosensory information in physically inactive healthy young men compared to the active ones possibly rendering them more vulnerable to somatosensory disturbances from their surroundings.

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1. Introduction
Physical activity has been demonstrated to be beneficial to human cognitive performance in cross-sectional and interventional studies, still neither the exact cognitive and executive functions nor the neural mechanisms responsible for improved cognitive performance are unequivocally identified (Voelcker-Rehage & Niemann, 2013). For instance, the cardiovascular functional response to vigorous long-term physical activity has been extensively studied while far less is known about the effects of physical activity on brain function in healthy adults. The previously detected association between good cardiovascular fitness and cognition in humans has implied that the improvements in cognitive task performance may typically be related to prefrontal cortex and other cortical structures (Hillman, Erickson, & Kramer, 2008) as opposed to subcortical structures. Most studies searching for associations between factors of physical fitness and cognition concentrate on elderly people (Voelcker-Rehage & Niemann, 2013; Erickson et al., 2011). This is conceivable because of the strong societal interest in many countries to search for the prerequisites of the late-life independence. Yet aging and diseases lead to mobility limitations, which may not be easily recognized and may still influence results, when studying relationships between physical fitness and cognition (Wilkie, Peat, Thomas, & Croft, 2006). The connections between physical exercise and cognitive function especially in the elderly have recently been carefully reviewed (Voelcker-Rehage & Niemann, 2013). Most of these studies apply cognitively delivered responses to various tasks such as button presses or answers in questionnaires but the underlying brain functions are inadequately known.

Sensitive assessments of the changes in cortical function can be performed using EEG-based techniques such as evoked potentials (EP). The mismatch negativity (MMN), a well-defined component of the auditory evoked potential, is generated by a cortical automatic change-detection process. MMN is extensively studied in auditory modality where it is elicited by any discernible auditory change when the ongoing auditory input is found to differ from the preceding auditory stimulus (Näättänen, Paavilainen, Rinne, &
Alho, 2007). Auditory MMN is generated by both temporal cortices and the frontal cortex (Näätänen & Kähkönen, 2009). Less frequently studied somatosensory mismatch response (sMMR) is a corresponding change detection mechanism while the brain is processing somatosensory ascending information (Akatsuka et al., 2005; Kekoni et al., 1997). Characteristics of sMMR are sparsely studied, however, both early and late components to sensory stimulus deviance have been identified (Restuccia et al., 2009) and we recently detected differences between young and elderly adults (Strömmer, Tarkka, & Astikainen, 2014). The automatic change detection of the somatosensory stimulus likely occurs, at least in part, in the SI and SII sensory representation areas of the stimulated body part. Various types of stimuli can elicit sMMR including electrical and vibratory stimuli (Akatsuka, Wasaka, Nakata, Kida, & Kakigi, 2007; Spackman, Boyd, & Towell, 2007), and in all stimulus types violations to previous stimulus array need to be presented. Regardless of the stimulus mode deviance detection is present in the somatosensory system in healthy individuals.

Increased physical activity is known to modulate corticospinal neural function in addition to changes in muscle biochemistry and cardiovascular function (Carroll, Selvanayagam, Riek, & Semmler, 2011). We selected a cohort of young twin males to see whether dissimilarities in physical activity, when chronic diseases are uncommon and medications or possible prodromal phases are not yet present, are associated with modulation in brain electrophysiology. Our specific aim was to investigate whether the processing of precognitive somatosensory input is associated with long-term physical activity in young healthy men. We chose monozygotic twin pairs discordant for physical activity to adjust for known and unknown confounders of the association between physical activity and somatosensory brain processing. First we confirmed that our subjects differed in physical activity history. It is conceivable that the ascending information from the body is enhanced during physical exercise and thus we hypothesized that differences in sMMR may exist between those who habitually exercise and those who do not.

2. Methods

2.1. Subjects

Participants of the present study, a segment of FITFATTWIN study, were 32 healthy males (15 active and 17 inactive), specifically 16 monozygotic pairs, among whom 9 pairs were discordant for leisure-time physical activity during past 3 years (active and inactive co-twin, see detailed criterion for discordance (Rottensteiner et al., 2015). The remaining 7 pairs were divided into active and inactive individuals according to the same criteria however, both members of the twin pair were either active or inactive. Participants for the FITFATTWIN study were initially identified from the FinnTwin16Cohort, which is a population based, longitudinal study of Finnish twins born between October 1974 and December 1979 (Kaprio, Pulkkinnen, & Rose, 2002). Selection of the twin pairs to the present study was performed on the basis of the data on the web-based questionnaire, telephone interview, interview at the laboratory and medical examination at the laboratory. More details of the selection procedure can be found in (Rottensteiner et al., 2015). The participants of the present study participated in comprehensive two day FITFATTWIN clinical study measurements.

All experimental procedures and study protocols were approved by the Ethical Review Board for Human Research of the Central Finland Health Care District (9/29/2011) and the study was conducted in accordance with the Declaration of Helsinki. All participants volunteered and provided a written informed consent.

2.2. Physical activity estimation and physiological measures

In this study physical activity levels and pairwise discordance was based on structured retrospective physical activity interview (Kujala, Kaprio, Sarna, & Koskenvuo, 1998; Waller, Kaprio, & Kujala, 2008; Leskinen et al., 2009) covering leisure-time physical activity, including commuting activity, at one-year intervals over the past six years. The leisure-time physical activity volume was quantified as a leisure-time MET index. The leisure-time physical activity was calculated as frequency (per month) × duration (min) × intensity (MET) and commuting activity as frequency as five times per week × duration (min) × intensity of 4 METs, and were expressed as the sum-score of MET hours/day (MET index). The mean leisure-time MET index during the past three years (3-yr-LTMET index as MET hours/day) was calculated and used as a criterion to assess leisure-time physical activity level. The difference between the active vs. inactive participants in leisure-time physical activity for the past 3 years was ≥1 METH/day. The most common types of leisure-time physical activity reported were jogging and walking.

Weight, height and waist circumference (midway between the spina iliaca superior and the lower rib margin) were measured, body mass index (BMI) was calculated, maximal oxygen uptake (VO2max) was measured by a maximal exercise test using a bicycle ergometer, and the whole body composition was determined after an overnight fast using dual-energy X-ray absorptiometry (DXA Prodigy; GE Lunar Corp., Madison, Wisconsin), for more details (Rottensteiner et al., 2015). BMI, waist circumference, fat% and VO2max were retained for further analysis.

2.3. Somatosensory mismatch response recording

sMMR was elicited by precognitive location deviance detection. Somato-sensory stimuli were delivered through flexible metal ring electrodes (stimulating cathode around the proximal phalanx and anode around the distal phalanx) to the left index and little fingers (Digitimer Ltd., model DS7A, Welwyn Garden City, UK). Conductive paste was used to reduce impedance. First, standard stimuli were delivered to the index finger and deviant stimuli to the little finger. Second, standard stimuli were delivered to the little finger and deviant stimuli to the index finger. Each stimulus duration was 200 μs and the stimulus intensity was set twice the individual sensory threshold. In each condition, 1000 stimuli were delivered, 10% of them were deviants delivered in a random order. The interstimulus interval (ISI) was 600 ms. Participants listened to a radio play paying no attention to the electrical stimuli. After testing they were asked several questions of the play to ensure they had listened to it. Both twins were recorded on the same day. Continuous EEG was recorded with 128-channel sensor net (Electrical Geodesics, Inc., Portland, Oregon) and analyzed using average reference. The sampling rate was 1000 Hz using 0.1–400 Hz filters.

The EEG data was bandpass filtered (in a range 0.1–25 Hz) and segmented to 500 ms epochs (100 ms pre-stimulus for baseline, 400 ms post-stimulus interval). Epochs containing artifacts were rejected, where epochs with high absolute amplitude potential shifts (at channels selected for further analysis) and eye-blink/movement artifacts (detected from the frontal, electro-oculographic channels) were selected for rejection. Noise-free epochs were baseline corrected and averaged to form the deviant wave form and the same amount of standard stimuli as the individual’s deviant stimuli to form the standard wave form for each individual. Standard stimuli selected for averaging were randomly picked from remaining subset excluding first 20 and last 20, to avoid adaptation and habituation effects. The minimum number of accepted deviants was 42 per participant to be included in the average and to further analyses (individual deviant mean 87, range 42–100). Then a difference wave form was calculated by
subtracting the standard wave form from the deviant wave form. The difference wave form, which isolates the response to stimulus deviance, was further analyzed for the sMMR in the data window from 85 ms to 300 ms. The current stimulating technique resembled to some extent somatosensory evoked potential, which is known to arrive first to the contralateral primary somatosensory cortex (SI) of the stimulated hand (Srisa-an, Lei, & Tarkka, 1996; Yamada, Shivapour, Wilkinson, & Kimura, 1982; Huttunen, Ahlfors, & Hari, 1992) and for this reason the first step of analysis was a hemispheric comparison. It was performed to specify the hemisphere to be analyzed more in detail. First, the analysis window was rectified and its area, integral, calculated. The integral values in the centroparietal areas were compared between the hemispheres. This comparison indicated that the major response located in the centroparietal somatosensory cortex. Then the rectified difference wave form was divided to early (85–180 ms) and late (180–300 ms) sMMR windows and within both windows maximum peak amplitudes and latencies were detected using automatic peak detection algorithm in five channels in the centroparietal somatosensory cortex (channels 93, 103, 104, 109, 110, locating in the close vicinity of right hand cortical representation area, see Fig. 1). For further group and pairwise comparisons integral values of the full window (85–300 ms) was used.

2.4 Statistical analyses

Data were analyzed using SPSS Statistics 20.0 (IBM, Amonk, NY, USA) and Stata 12.0 (Stata, College Station, TX, USA). In individual-based analyses the differences between inactive and active groups were analyzed with adjusted Wald test by taking into account clustered observations of twins within pairs (Williams, 2000). When calculating individual-based correlations they were performed with Pearson’s correlation coefficient, and the statistical significance of the association was tested using a linear regression model where the within-pair dependency of monozygotic twin individuals was accounted for. Pairwise analyses between the members of physical activity discordant twin pairs were performed with two-sided paired-sample t-test. Significance values were corrected for multiple comparisons using Benjamini–Hochberg False Discovery Rate calculation (Benjamini & Hochberg, 1995). Significance level was p < 0.05.

3. Results

3.1 Subject characteristics

Since the participants were first classified to active (n = 15) and inactive (n = 17) individuals to answer the question of the role of physical activity/inactivity in somatosensory precognitive brain processing, the past 3-yr-LTMET indexes indeed differed significantly between groups. Furthermore, the active group had significantly lower body fat%, however, neither the body weight, BMI, nor waist circumference differed between the groups (see Table 1). The mean BMI of both groups was normal (BMI < 25 kg/m²). Also the 3-yr-LTMET index correlated negatively with body fat%, r = −0.77 (p = 0.01) and positively with VO₂max, r = 0.82 (p = 0.01).

3.2 sMMR characteristics in the right and left hemispheres

The integrals of rectified difference wave forms of sMMR of the 85–300 ms window differed between the hemispheres in the corresponding electrode locations (channel, ch, 36; mean 0.21 µVs (SD ± 0.10) vs. ch 104; 0.26 µVs (±0.17); t = 11.5, df = 31, p = 0.001 and ch 29; 0.26 µVs (±0.13) vs. ch 110; 0.32 µVs (±0.16); t = 10.8, df = 31, p = 0.001) indicating that the above mentioned chs 104 and 110, in the somatosensory cortices (SI and SII) contralateral to the stimulated hand, registered larger somatosensory response. The electrode cap numbers in EGI electrode net correspond to International 10–20 System so that ch 36 corresponds to C3 in the left hemisphere and ch 104 corresponds to C4 in the right hemisphere and chs 93, 103, 109, and 110 are in the vicinity of C4 (see Fig. 1). Grand average wave forms (not rectified in the figure for illustration purposes) of all 32 subjects in ch 29 in the left hemisphere in the hand sensory area and in ch 110 in the right hemisphere hand sensory area are illustrated in Fig. 2. The standard, deviant and difference grand average wave forms are plotted and noted also how the difference wave form (black) shows two components (each shaded) for the right hemisphere. The recordings of the centroparietal cortex contralateral to the stimulated hand were analyzed in more detail in one full window and also divided into two windows, early and late, in active and inactive groups.

3.3 sMMR in five recording sites in the right hemisphere

Visual inspection of the sMMR difference wave forms led first to division of the analyzed window to early (85–180 ms) and late (180–300 ms) windows to separate the components. However, with the considerable interindividual variation and with the rather small number of observations no significant group differences were obtained in separate windows. Thus the analysis was further performed for the whole window (85–300 ms). It is noteworthy that a contamination from any P300-like component was unlikely since the stimulus reached cerebral cortex 25–30 later than in the auditory or visual studies driving the P300 toward 390 ms (Tarkka, Micheloyannis, & Stokic, 1996). Rectified integral values in all the
analyzed channels in the right hemisphere SI–SII area showed only a tendency toward significant difference in the amplitude of the sMMR between active and inactive individuals (Table 2). The peak latencies did not differ in any of the channels (Table 2). The difference wave forms of sMMR are illustrated in Fig. 3 (black solid line indicating active group, red dotted line indicating inactive group) where sMMR of the inactive group appears earlier with a larger amplitude in the contralateral somatosensory cortex of the stimulated hand.

3.4. Pairwise analysis of sMMR between monozygotic twins discordant for physical activity

Pairwise analysis was performed with the nine twin pairs among whom one twin was active and his co-twin was inactive in order to see if the suggestive tendency in the group-wise result was driven by the monozygotic pairs. Significant intrapair differences were observed in rectified integral values of the sMMR difference wave forms in four recording locations (Table 3). The intrapair differences were present in close-lying channels recording activity predominantly from the SI and SII cortical areas.
In the present study, the sMMR was reliably elicited using a relatively small location difference of mild electrical stimulation as deviant in young healthy humans. Our aim was to find out if this type of MMR can detect modulation in the cortical function and we showed that sMMR may be sensitive to physical activity status of healthy young adult men. sMMR was observed in the contralateral hemisphere of the stimulated hand, in the primary, SI, and in the secondary sensory, SII, the cortical sensory representation areas. sMMR has previously been divided into two varying components based on varying rationales and stimulation methods (Akatsuka et al., 2005; Restuccia et al., 2009; Spackman et al., 2007). Here we analyzed the complete precognitive window of 85–300 ms, which starts after the P60, which is a known middle latency somatosensory evoked potential (Srisa-an et al., 1996; Yamada et al., 1982) and our window ended before the cognitive P300 component, which is known to occur later (i.e., 390 ms) in the somatosensory modality than in the more commonly studied auditory modality (Tarkka et al., 1996). This window allowed us to detect enhanced, more intense, precognitive neural activation in SI and SII in the inactive healthy men than in the active ones as a response to violation to ongoing sensory input, which in the present case was a difference in stimulus location. It is probable that sMMR is composed of overlapping contributions from SI, SII and frontal cortex processes. However, the complex source configuration generating sMMR with
varying involvements of different cortical areas was not the target of the present study.

Physical activity is known to have many beneficial effects on the human body, e.g., cardiovascular system, endocrine system and skeletal muscle function enhance as a result of physical activity. Currently less is known about the effects of long-term physical activity on brain structure and function in healthy population. Associations between cardiovascular fitness and cognitive tests in humans have indicated advantages in the more fit persons in behavioral tasks which test attentional resources mainly in prefrontal and cortical structures however, it is important to remember that participants in most of those studies are over seventy years old (Voelcker-Rehage & Niemann, 2013; Ruscheweyh et al., 2011). For example, cardiovascular training for 6 months suggests improvement specifically in the memory scores of the elderly (Ruscheweyh et al., 2011). Several findings show that better scoring in cognitive tasks is related to changes in VO2max (Voelcker-Rehage & Niemann, 2013). This leads us to consider increased oxygen uptake and consequently better oxygen supply in the brain regions involved in executive control as the mechanism responsible for improvement in cognitive task performance. This may be a plausible mechanism in studies of the elderly. However, it is likely that this mechanism is not responsible for the difference we detected between inactive and active young men.

First of all, the present brain function measure does not assess task-relevant conscious cognitive processing but brain’s automatic response to added complexity in the sensory environment. There is very little previous data for us to compare with. In the present data, inactive and active men differed from each other not only in their MET profiles but in cardiovascular functions and body composition (Table 1). They were similar in age, weight and even in BMI but different in fat% and VO2max. In our young men higher VO2max was found in the active group who besides may present with smaller sMMR. It should also be remembered that the present twins were initially very carefully selected, twins reporting heavy use of alcohol or any medication for chronic diseases were excluded before the present study, for more details of the selection see Rottensteiner et al. (2015). Their preceptive somatosensory brain processing was in general well corresponding to previous studies of sMMR (Strömmer et al., 2014; Akatsuka, Noguchi, Harada, Sadato, & Kakigi, 2008) but the intrapair comparison of nine discordant pairs showed different amplitudes of their automatic response to sensory violation, the inactive ones showing a significantly larger response.

In our previous study, utilizing similar location difference paradigm, general population sample of young healthy participants produced corresponding sMMR wave forms (Strömmer et al., 2014). Our previous study also showed that small variations in stimulus intensity do not affect sMMR latencies and amplitudes. The stimulus intensity criteria was “twice sensory threshold” in the previous study as well as in the present one (intensities in the present study were mean 0.44 mAMP, range 0.32–0.58, small variations were mainly related to skin conductance). Thus intensity difference does not explain our result, neither does the difference in VO2max as it would point to opposite direction. If worse oxygen supply to the brain of the inactive ones would be the explanation it should yield reduced sMMR amplitudes in them. More likely is that larger automatic somatosensory activation reflects enhanced brain response to sensory distraction coming from fingers of one hand. sMMR is considered to reflect a process that is specific to sensory discrimination in the somatosensory modality (Spackman et al., 2007) and we can speculate that persons who are physically active are exposed to more and diverse sensory stimulation over time and may deal with it more efficiently.

Our pairwise analysis of the sub-group of discordant twin pairs resulted in significant differences even though our group was very small. The purpose of searching for twins, who have same genetic make-up, are healthy, and long-term discordant for physical activity, is to reduce the inevitable contribution of genetic selection explaining the factors in the benefits obtainable from physical activity, and to control for multiple other non-genetic potential confounding factors. In addition, we were careful to exclude persons with chronic diseases or medications in order to be able to connect any potential difference between groups solely with physical activity. Remarkably, sMMR difference in discordant monozygotic twins was present in pairwise analysis which controlled for the variance due to sequence level genetic differences and it demonstrated the exercise effect sensitively. Of course the small size of our material clearly limits the possibilities to exploit our finding and the present study should be considered preliminary. The area of significant differences covers SI–SII region supporting the idea that somatosensory mismatch is generated mainly in the SII and supramarginal gyrus, both of which are somatosensory associative regions. This same source location was reported by Akatsuka et al. (2007) for a sMMR component of 150–250 ms in their magnetoencephalographic study also fitting well to the presently analyzed time window (Akatsuka et al., 2007). SII is known to be heavily involved in sensory discrimination and integration of sensory inputs (Noback, Strominger, Demarest, & Ruggiero, 2007) and thus it is plausible that it is involved also in the detection of somatosensory deviance. In auditory sensory modality, persistent automatic orienting to deviant stimuli is described as distractibility and seen in enlarged cortical potentials e.g., in distractible children (Russele, Kowalczyk, Johannes, Wieringa, & Munte, 2002; Kilpeläinen et al., 1999). The larger sMMR in inactive healthy individuals may imply that their sensory processing is more easily detecting sensory change, i.e., they are distracted.

In conclusion, utilizing unattended sMMR recording on the scalp, we suggest that long-term physically active young men may be more efficient in gating precognitive sensory information ascending from the body. In the present preliminary study, the smaller mismatch response in the secondary somatosensory area of the stimulated hand implies that the physically active young men may be less vulnerable to distractions received via somatosensory system from their surroundings.

Disclosures

The authors report no conflict of interest.

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