
Long-Term Physical Activity may Modify Brain Structure and Function: Studies in Young Healthy Twins

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Abstract

Background: Physical activity (PA) is agreed to be beneficial to many bodily functions. However, effects of PA in the brain are still inadequately known. We aimed to uncover possible brain modulation linked with PA. Here we combine four of our studies with monozygotic (MZ) twins, who were within-pair discordant in PA for a minimum of one year.

Methods: We performed brain imaging, brain electrophysiology, cardiovascular and body composition assessments and collected questionnaire-based data. The present synopsis elucidates the differences associated with differing PA history in conditions without genetic variability. We present new structural and electrophysiological results. Participants, healthy, male 45 MZ twins, mean age 34.5(1.5) y, differed in aerobic capacity and fat% ($p<0.001$).

Results: More active co-twins showed larger gray matter (GM) volumes in striatal, prefrontal and hippocampal regions and smaller GM volume in anterior cingulate area than less active co-twins. Functionally, visual and somatosensory automatic change detection processes differed between more and less active co-twins.

Conclusions: In MZ twins, who differed in their PA history, differences were observed in identifiable anatomic brain locations involved with motor control and memory functions, as well as in electrophysiological measures detecting brain's automatic processes. Better aerobic capacity may modify brain morphology and sensory function.

Abbreviations:

CSF Cerebrospinal Fluid

GM Gray Matter

LTMET Leisure Time Metabolic Equivalent of Task

MRI Magnetic Resonance Imaging

MZ Monozygotic

PA Physical activity

T Tesla

VBM Voxel-based Morphometry

WM White Matter

Introduction

The human brain undergoes many plastic changes during an individual's lifetime and both the structural and functional plastic changes are known to be modulated by experience [1-3]. It has been shown with animals [4,5] and also with humans that physical activity (PA) promotes morphological brain differences [6,7]. Several studies show evidence that more PA is associated with better cognition, however it is noteworthy that most of those studies examine effects of PA in older adults or even persons already diagnosed with mild cognitive impairment or dementia and hence insufficient data is currently available regarding young healthy adults [8-11]. Interestingly, in adolescents and young adults, a cross-lagged analysis of longitudinal data indicates that better school achievement promotes more PA, but not the reverse [12].

The age category of the participants is an important variable when studying relationships between physical fitness, physical activity and cognition because ageing and diseases lead to various limitations. These limitations include decreased ability to exercise, which may have been overlooked, and still played a significant role, in previous studies. In order to avoid complications caused by ageing and the large individual variability caused by unrelated participants, we selected a cohort of young twin males as participants to see whether dissimilarities in the amount of habitual physical activity are associated with structural and/or functional brain plasticity. In our cohort there is no contribution from genetic factors; monozygotic (MZ) twins have same genetic make-up and thus any possible difference between them in our measures is presumably associated with PA and other possible factors that correlate with PA independent from genes. Furthermore, our selected young males (mean age 34 (1.5) y) were in an age when chronic diseases associated with physical inactivity are uncommon, and besides, only males were selected in order to avoid

possible hormonal effects due to menstruation and child-bearing of women in this age. Thorough medical examination was also performed for each participant to ensure that no signs or symptoms of any illnesses were present.

Structural plasticity in the brain was assessed with the whole brain magnetic resonance imaging (MRI) and sensitive neurophysiological assessments of automatic, involuntary somatosensory and visual cortical functions were performed to detect possible functional brain plasticity unrelated to conscious cognitive tasks. Our aim was to explore any associations of these structural and functional electrophysiological measures with PA. We carefully confirmed that our participants differed in physical activity history, physical fitness and body composition. The present synopsis links our four separate studies and new additional analysis in young male twins [13-16] and discusses the implications of our findings. We observed new gray matter (GM) volume difference in whole brain comparison of structural MR images in larger group of young male twins than what we had previously. On the whole, we hypothesized that differences in brain structure and/or automatic neurophysiological function may exist between those who habitually exercise more and those who exercise less, when the influence of genetic factors is eliminated.

Methods

Subjects

Participants were a segment of FITFATTWIN study, and all the participants for the FITFATTWIN study (MZ male twins, 202 pairs) were initially identified from the FinnTwin16 Cohort, which is a population based, longitudinal study of Finnish twins born between 10/1974 and 12/1979 [17] with five waves of questionnaires conducted between age of 16 y to their mid-thirties. Selection of the twin pairs to the present studies was performed on the basis of the data on the wave 5 web-based questionnaire and a structured telephone

interview. Further details of the selection process are in Rottensteiner et al. (2015) [15]. The participants discussed in the present paper included 46 male individuals from 23 MZ twin pairs. The whole brain MR images reported here include data from 22 pairs because one twin pair was represented by only one member, as MRI of the other member was unfortunately corrupted by artefact. All the 23 pairs were MZ confirmed by genetic testing. A unique feature of our participants was that co-twins differed in their leisure-time and commuting PA for a minimum duration of one year preceding the study. Among the MZ 23 pairs, 10 were pairs who were within pair discordant for leisure-time physical activity even longer and with larger discrepancy, at least for the past 3 years based on further personal interview [18] and medical examination at the laboratory (Fig. 1). All participants took part in comprehensive two-day FITFATTWIN clinical experiments. All experimental procedures involving human participants 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 ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments. All participants volunteered to the studies and gave a written informed consent prior to their participation.

PA estimation, fitness and body composition

Physical activity levels and twin pairwise discordance were based on structured retrospective PA interview covering leisure-time PA, including commuting activity, at one-year intervals over the past three years. PA volume for leisure-time was quantified as a leisure-time MET index. Leisure-time PA was calculated as frequency (per month) x duration (min) x intensity (MET) and commuting PA as frequency as five times per week x duration (min) x intensity of 4 METs, and total PA was expressed as the sum-score of MET hours/day (MET index). The mean leisure-time MET index covering previous one year's leisure-time

PA, including commuting activity, was calculated (LTMET 1 y) and used for dividing twins within each pair to more or less active co-twin. Furthermore, the previous three years, 3-yr-LTMET index, (as MET hours/day) was also calculated. The difference in leisure-time PA between more active and less active individual of each twin pair was a minimum of ≥1 METh/day. The most common types of leisure-time PA among participants were jogging and walking. Weight, height, waist circumference, body mass index, maximal oxygen uptake (VO_{2max}) and the whole body composition (DXA Prodigy; GE Lunar Corp., Madison, Wisconsin) were recorded, more methodological details of these measures in [15].

Accurate assessment of leisure-time physical activity (LTPA), including commuting physical activity, was accomplished with two interviews. One interview was used to estimate past 3-year LTMET index. First, physical activity levels were determined over the preceding 6 years, one year at a time. Then, MET index (MET^xh/d) was calculated for past 3 years based on monthly frequency, minute duration and MET intensity of reported physical activities. Commuting physical activity was calculated by multiplying standard 4 MET intensity with daily commuting duration and weekly frequency (five times/week). Second interview was used to determine past 12-month physical activity level. Interview was based on Kuopio Ischemic Heart Disease Risk Factor Study Questionnaire with added activities. Participants were asked how many times and for how long they participated in 20 different types of physical activities each month. Participants were also asked to classify the intensity of physical activity based on 4-level scale. Similarly, to the past 3-year LTMET index, 12-month LTMET index was calculated as MET hours/day. Physical activity was assessed also with Baecke questionnaire which consists of 16 questions covering work, sport and leisure time related physical activity as in Rottensteiner et al. (2015).

MRI recording and preprocessing

Brain MR images (MRI) were acquired using a 1.5 T whole body magnetic resonance scanner (Siemens Symphony, Siemens Medical Systems, Erlangen, Germany) on the same day as other data was gathered. The 3D T1-weighted MPRAGE images of the whole brain were collected with the following parameters: TR = 2180 ms, TE = 3.45 ms, TI = 1100 ms, flip angle = 15˚, slice thickness = 1.0 mm, in-plane resolution 1.0 mm × 1.0 mm, and matrix size = 256 × 256. Voxel-based morphometric (VBM) analyses were performed with VBM8 toolbox (http://dbm.neuro.uni-jena.de/vbm/) for SPM8 (Wellcome Trust Center for Neuroimaging, UCL, UK) running under Matlab R2010a (Mathworks Inc., Natick, MA, USA). First, MR images were segmented into gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF). Images were then normalized to the Montreal Neurological Institute (MNI) brain template using a high-dimensional DARTEL algorithm. Nonlinearly modulated GM images were created to preserve relative differences in regional GM volume. GM volumes were spatially smoothed with 12 mm full width at half maximum Gaussian kernel. Previously GM, WM and CSF volumes were compared in only nine twin pairs between co-twins and reported in our previous paper [13], where we utilized Region-Of-Interest analysis after finding the anatomical regions in brain electrical source analysis of somatosensory processing. In the present paper, we report new full voxel-wise analysis of the whole brain in GM using VBM within-pair comparison between more active and less active co-twins of 22 MZ pairs.

Table 1. Characteristics of the 44 twin males (mean ± SD), who participated in brain MR imaging, divided according to their within-pair physical activity to more active and less active individuals[1]. Their mean age was 34.5 (1.5) y.

	More active	Less active	p-value*
Height, cm	178 (7.7)	178 (7.2)	0.663
Weight, kg	75.0 (9.2)	78.4 (10.7)	0.054
Waist, cm	84 (6)	88 (9)	**0.016**
BMI	23.5 (1.9)	24.7 (3.4)	0.053
Fat% (DXA)	19.7 (5.9)	22.9 (7.7)	**0.001**
VO_{2max}[¢]	44.0 (7.9)	39.8 (9.3)	**0.001**
LTMET (1 y)	5.4 (5.6)	3.1 (3.2)	**0.013**
GM (ml)	663 (37)	658 (35)	0.200
WM (ml)	683 (57)	674 (56)	0.209
TIV (ml)	1569 (100)	1555 (97)	0.125

[1] More active n=22, less active n=22.
*Paired samples t-test.
BMI= body mass index
[¢] VO_{2max}= maximal oxygen uptake (n=19 in both groups)
LTMET (1y)=leisure and commuting activity MET for minimum of one year
GM=gray matter
WM=white matter
TIV=total intracranial volume

Electrophysiological recordings

Somatosensory (sMMR) [13] and visual mismatch responses (vMMR) [14] were registered with continuous electroencephalography, EEG, with Cz reference, using 128-channel sensor net, (Electrical Geodesics, Inc., Portland, Oregon) and analyzed with average reference. Data collection was sampled at 1000 Hz using 0.1 Hz - 400 Hz filter settings. Event-related potential (ERP) data was further filtered offline and segmented for analysis. Epochs containing artefacts were rejected, such as eye-blinks and facial movements, and

noise-free epochs were baseline corrected and averaged to form deviant wave form and standard wave form for each individual for somatosensory and visual mismatch wave forms. Mismatch response is generated by a cortical automatic change-detection process of the incoming sensory stimuli and it can be elicited by any detectable change when the ongoing sensory input differs from the preceding standard stimuli [19, 20]. In our experimental design, no voluntary attention was directed either to visual or somatosensory stimuli, and furthermore no voluntary response of any kind was requested. The mismatch was detected as the difference between standard and deviant stimuli. The mismatch responses of each modality were compared between more active and less active co-twins.

sMMR was elicited by location deviance detection. Somatosensory stimuli were delivered through metal ring electrodes to the left index and little fingers (Digitimer Ltd., model DS7A, Welvyn Garden City, UK). Stimulus intensity was set twice the individual sensory threshold and of 1000 delivered stimuli 10 % were deviants, delivered in a random order, more details in [13,16]. To obtain vMMR, participants were instructed to fix their gaze at the cross in the center of the screen placed at the distance of 1.2 m in front of them at their eye level where also the visual stimuli were presented. Participants were asked not to pay attention to the visual stimuli but to attend to the audio play recording played for them during the experiment. Visual stimuli consisted of black bars in a light grey background and the changing bar orientation elicited the mismatch. The standard stimuli bars were tilted 18º to the right and the deviant stimuli 18º to the left [21]. Total of 1000 stimuli were delivered, of which 10 % were deviant stimuli, and interstimulus interval was 1100 ms, more details in [14].

sMMR and vMMR were analyzed with custom routines written in Matlab (Mathworks Inc., Natick, MA, USA) and sMMR also with Brain Electrical Source Analysis (BESA, Besa GmbH, Gräfelfing, Germany). Grand averages for more active and less active twins were formed for both deviant and standard conditions. Topographic voltage and current

source density (CSD) maps were plotted from deviant and standard grand average wave forms. Whole-head spatio-temporal multiple dipole source models were developed for sMMR with BESA and vMMR integrals were analyzed in selected occipital and frontal electrode locations in Matlab. For the VBM SPM analysis paired t-test was used to compare whole brain MRI of more active co-twin to the less active co-twin. For other statistical tests SPSS Statistics 20-24 and Stata 12 were used testing normality with Shapiro-Wilk test and for paired samples t-tests to compare more active co-twin to less active co-twin in each study. Significance was set at $p<0.05$.

Results

Structural and functional differences in the brains were observed among the 23 healthy MZ male twin pairs divided according to their long-term PA amount. Participant pairs were divided into more active and less active individuals within each pair according to interviews and questionnaires of PA. It is noteworthy that nine pairs, all of whom had MRIs registered, were more than 3 years within-pair discordant in PA. All 22 pairs with MRI data, who were minimum one year or longer PA discordant, differed in body composition and fitness level (see Table 1), i.e. significant difference in the total body fat% registered with DXA and waist circumference and also in VO_{2max} were seen. Total body weight and BMI showed a tendency towards intra-pair difference within 22 pairs, albeit non-significantly. The mean activity level, as indicated by at least one year leisure time and commuting MET values, was almost twice in the more active co-twins than that of the less active co-twins. The majority of the more active twins reported aerobic activities, such as jogging, as their main type of exercise. The majority of the inactive co-twins reported that work and/or family commitments were the primary reasons for their physical inactivity.

Total brain WM, GM and total intracranial (TIV) volumes, as estimated from non-normalized images, were not significantly different between more or less active co-twins (see Table 1). This similarity was already seen in 9 pairs and presently shown in 22 twin pairs. Here we demonstrate with the population of 22 MZ pairs a regional differentiation in GM volumes, based on whole brain VBM, between more or less active co-twins, where more active co-twins seem to encompass higher GM volume in the left hippocampus than less active co-twins (Fig. 2). The hippocampal cluster, which indeed is significant ($p<0.001$) only when uncorrected (note the small number of subjects), extends to 214 voxels (peak T score = 4.1009) with the peak at 28.5, -27, -19.5 coordinates. Furthermore, the MNI coordinates place the peak of this cluster unequivocally in left hippocampus.

The brain's automatic change detection mechanisms, as observed in our previous neurophysiological analysis, were also sensitive to long-term exercise status. In the visual modality, the peak latency of vMMR, identified in an ERP waveform component peaking between 200-250 ms in all 32 participants from 16 twin pairs, was significantly shorter in the more active co-twins compared to less active co-twins. This was observed in the occipital cortex, where large part of the primary and secondary visual processing of these stimuli in this time-frame takes place [14]. Contrary to the visual mismatch stimuli processing, in somatosensory modality sMMR occurred in 32 participants with smaller amplitude in the more active co-twins compared to the less active co-twins. This was observed in postcentral gyrus and superior temporal gyrus, where primary and secondary somatosensory processing takes place [13,16,22]. In the present paper, topographic mapping of the current distribution over the whole head elucidates the differences observed in somatosensory deviance processing between more and less active co-twins. Figure 2 shows current source density (CSD) maps of sMMR, which demonstrate the field patterns indicative of source locations better than more

traditional voltage maps. The CSD maps of the sMMR component at 184 ms after the deviant stimulus demonstrate the presence of stronger source in the right hemisphere postcentral gyrus and superior temporal gyrus in less active co-twins compared to more active co-twins (Fig. 3). Our morphological and functional brain findings in young adult MZ twin pairs discordant for PA history are summarized in Table 2.

Table 2. Summary of the structural and functional brain differences associated with amount of physical activity in healthy twin males in our series of MZ twin studies.

	More active co-twin compared to less active	Difference direction in more active co-twin	Reference
Morphological GM (voxels)			
- anterior cingulate	536	↓	Hautasaari et al. 2017
- putamen	395	↑	Rottensteiner et al. 2015
- prefrontal cortex	99	↑	Rottensteiner et al. 2015
- hippocampus	214	↑	Tarkka et al. (this ms)
Functional (ERP)			
- vMMR latency (ms)	up to 16 % faster	↓	Pesonen et al. 2017
- sMMR (μVs)	up to 30% lower amplitude	↓	Tarkka et al. 2016
- sMMR (nAm)	lower dipole strength	↓	Hautasaari et al.2017

Discussion

PA and exercise at large drive adept control of muscle activation and are known to benefit particularly cardiometabolic factors [23, 24]. PA is also known to boost angiogenesis [25] and hence it is plausible that it drives also neuronal plasticity in the brain. Long-term increased use of a limb has been long known to lead to an expansion in the cortical representation of that limb leading to enduring neuronal plasticity [26]. MR images of our present data on PA discordant MZ twin pairs suggest morphological unilateral hippocampal

GM plasticity, which may be associated with larger amount of habitual exercise, and consequently better fitness level, in more active co-twins when compared to their less active co-twins. This finding is in general in concordance with reports based on larger MRI materials [7,10,27,28], though our data is unique in a sense that there is no genetic variation within pairs and furthermore, our subjects are much younger than in most other studies relating GM volumes and fitness level.

Previously we showed with nine MZ pairs who were minimum of three years PA discordant, that active co-twins had larger striatal and prefrontal cortex GM volumes than their inactive co-twins based on voxel-based morphometry [15] and additionally we showed that anterior cingulate GM volume was larger in inactive co-twins compared to their active counterparts [13].

Regarding the present data, it is important to remember that the age group in our studies presents typically very stable total cortical GM and WM volumes, and these volumes are remarkably similar in co-twins of MZ twin pair. This was also true in the present data of 22 pairs when looking at the total GM, WM and intracranial volume data (Table 1), hence our findings provide a suggestion for structural effects of long-term PA on the healthy young adult human brain. The possibly larger left hippocampal GM volume in more active co-twins compared to their less active brothers is to our knowledge first observation of hippocampal modulation in young twins. Possible larger GM volume in hippocampus in more active co-twins may indicate the ability of this structure to modulate its function, conceivably by enhancing local dendritic complexity with the hypothetical contribution of improved microvasculature. We hypothesize that neuroplasticity is the mechanism behind the increased hippocampal GM volume. For some time important association has been recognized between hippocampus activation and several cognitive processes, i.e., memory formation and memory encoding with especially spatial memories and more recently also the

temporal contexts of memory are linked with hippocampal activation [29]. Overall, it may be that the capacity of the brain to coordinate motor activities and the necessary associative and cognitive functions is enhanced in relation to vigorous PA history. But it is still possible that slight acquired differences from various exposures and experiences between the co-twins in childhood or adolescence, unrelated to PA, generate the observed structural and functional differences, which in turn may drive differences in PA. Though we here control for genetic effects, the causal nature and direction of causality requires yet further elucidation.

Plasticity of GM volume is usually thought to associate with cellular and synaptic plasticity that underlies volumetric change. An important factor, which is often overlooked in studies of neural plasticity, is the role of cerebral vasculature, especially microvasculature, in driving neurogenesis. Diminished blood flow in cerebral capillaries may be a risk factor in small vessel disease and provide a substantial source of neurodegeneration. Ostergaard et al. (2016) [30] elegantly suggest that capillary dysfunction is part of the cause both in cerebrovascular stroke and cognitive decline, even though there are considerable differences in etiologies of these syndromes and in their clinical presentations. Aging impairs cerebrovascular plasticity and may induce cerebral hypoperfusion, which accelerates age-related cognitive dysfunction and neurodegenerative diseases associated with impaired neuronal plasticity. Evidence from recent years demonstrates that high level of physical activity is an effective non-pharmacological approach to improve brain function and general brain health [31].

Animal studies have indicated that exercise increases angiogenesis in the hippocampus and that angiogenesis is coupled with hippocampal neurogenesis [32]. In an original work on mice and humans, Pereira et al. 2007 showed the connection of increased blood volume with neurogenesis, thus in human blood volume increase may be a correlate of enhanced hippocampal function. Brain regions showing increased GM volumes associated

with larger amount of PA are also those which are most vulnerable to ageing and show early structural markers of cognitive decline [3]. If PA and exercise do more than preserve function in vulnerable brain regions in the elderly is yet to be elucidated; but it may be that PA is effective as a neuroprotective formula.

In humans, studies using structural and functional brain imaging, and electrophysiology of brain activity, suggest that physical exercise induces both transient and permanent changes at structural and functional characteristics in the aging brain. Using voxel-based morphometry, or detailed image segmentation of high-resolution brain scans, Colcombe et al. (2003) reported that a higher cardiorespiratory fitness level was associated with reduced loss of gray and white matter in the frontal, prefrontal, and temporal regions in older adults [33]. Furthermore, Erickson et al. (2011) later performed a region-of-interest analysis on MR images in over 100 non-demented older adults and found that greater fitness levels were associated with larger left and right hippocampi [7, 27]. Current reports indicate that the beneficial changes in the brain associated with PA cluster in the frontal cortex and hippocampus in adults and older persons [6,7,27]. We are aware that the number of our subjects is small and their range of PA discordancy varies and these factors limit the generalization of our results. However, as genetic determinants of PA are multifactorial and their markers largely unknown, then discordant twin study design provides an available path to address the role of genetic factors in exercise research. Our studies extend the findings on GM plasticity to young twin males and, in an exploratory stage of research, emphasize the role of PA in triggering plasticity in conditions where genetic factors have a minimal role. We can place the structural and functional modulations we detected in brain locations involved with motor control and memory functions.

ACKNOWLEDGEMENTS

The authors wish to thank the participants of the study and the personnel at the Faculty of Sport and Health Sciences and Department of Psychology, University of Jyväskylä, for their help during data collection. This work was supported by the Ministry of Education and Culture, Helsinki, Finland, Meta-Predict (within the European Union Seventh Framework Program, Health-F2-2012-277936), and Juho Vainio Foundation, Helsinki, Finland. The FinnTwin16 cohort study data collection has been supported by National Institute of Alcohol Abuse and Alcoholism (grants AA-12502, AA-00145, and AA-09203 to R J Rose) and the Academy of Finland. The funding agencies had no role in the interpretation of the data or writing this report.

DISCLOSURES

The authors report no conflict of interest.

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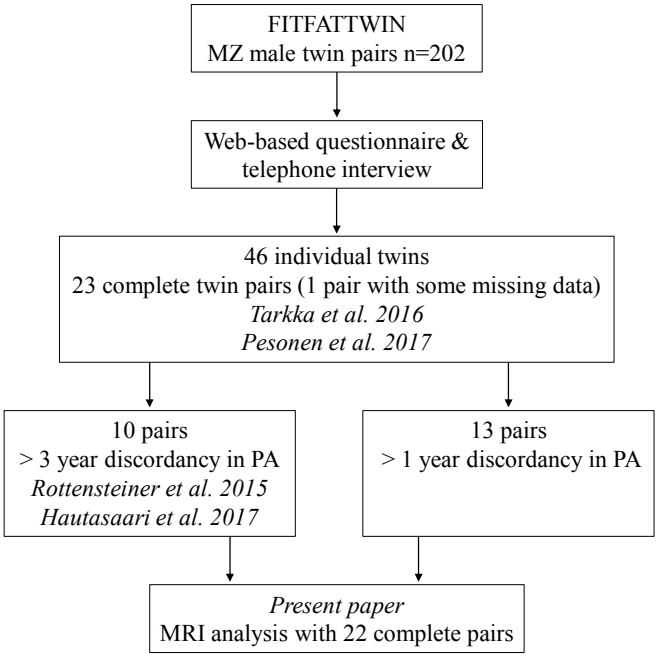
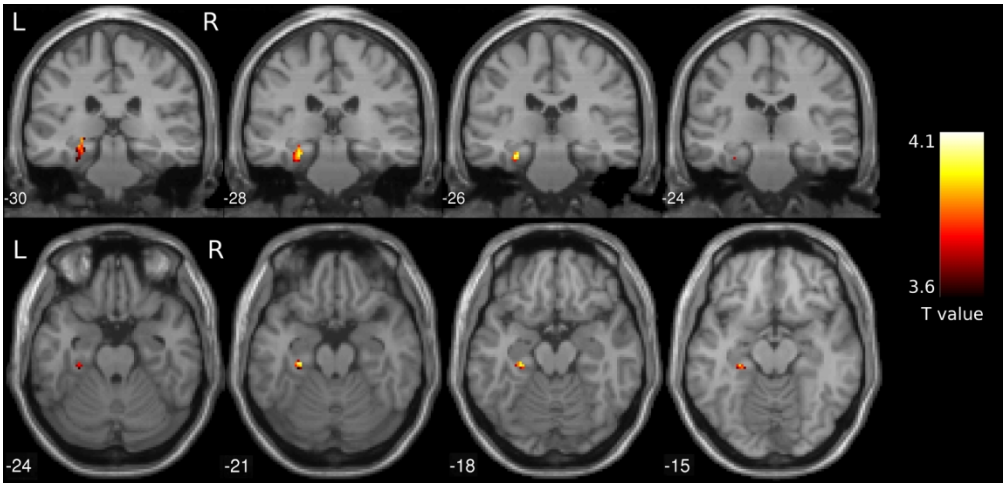
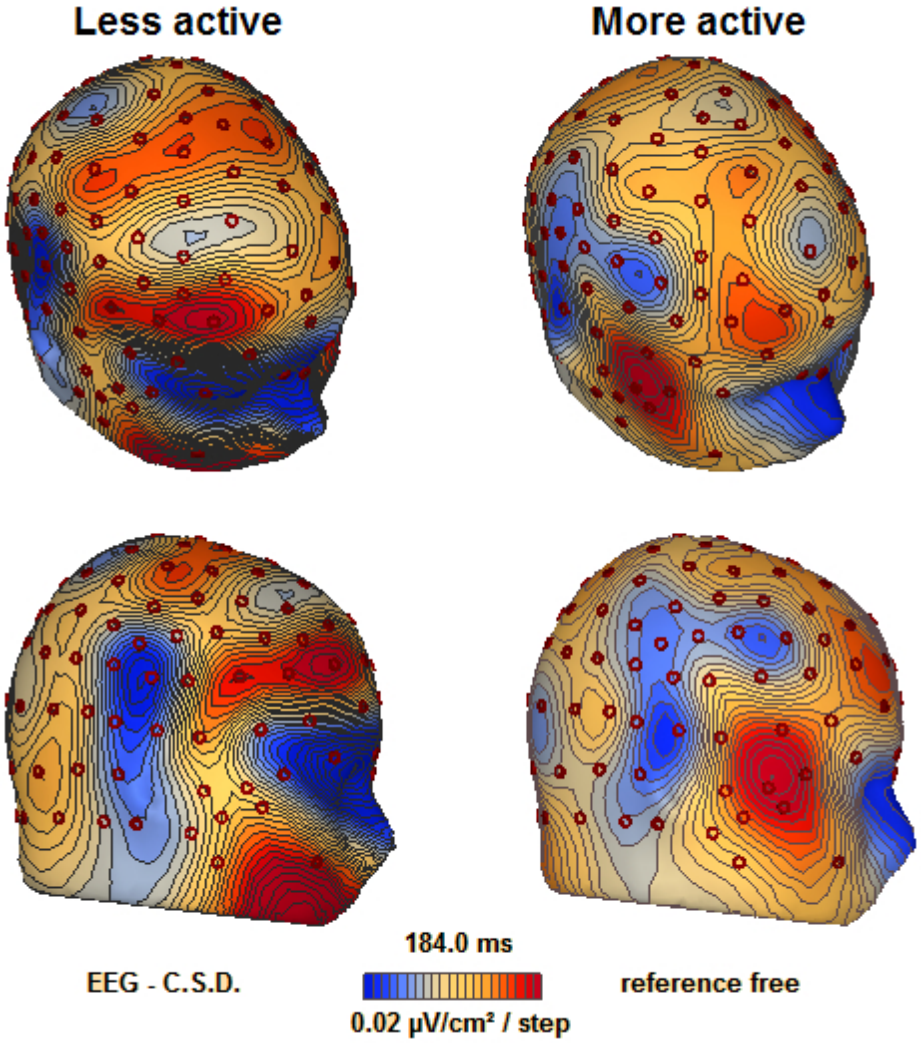

FITFATTWIN
MZ male twin pairs n=202
Web-based questionnaire &
telephone interview
46 individual twins
23 complete twin pairs (1 pair with some missing data)
Tarkka et al. 2016
Pesonen et al. 2017
10 pairs
> 3 year discordancy in PA
Rottensteiner et al. 2015
Hautasaari et al. 2017
13 pairs
> 1 year discordancy in PA
Present paper
MRI analysis with 22 complete pairs



Coronal (top row) and axial (bottom row) MR image slices illustrating increased GM volume in yellow and red colours in the left hippocampus in more active co-twins versus less active co-twins. The area is comprised of 214 voxels ($p<0.001$, uncorrected, T score = 4.1009) with the peak activity occurring at -28.5, -27, -19.5, i.e., in the left hippocampus.



Current source density (C.S.D.) topographic maps of somatosensory mismatch response (sMMR) at 184 ms (in the peak of the mismatch response). Maps are from deviant waveform grand averages of 9 twin pairs who were discordant in PA for 3 years, less active co-twins (left panel) and more active co-twins (right panel) are illustrated in the same scale in two views (upper row viewed from top of the head and lower row from the right). Small circles illustrate the 128 EEG sensor locations. Note, the weaker activation in the more active co-twins in the sensorimotor area.