Journal of the International Neuropsychological Society (2015), **21**, 831–840.

doi:10.1017/S1355617715001095

Influence of Physical Activity on Human Sensory Long-Term Potentiation

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(RECEIVED March 15, 2015; FINAL REVISION October 7, 2015; ACCEPTED October 13, 2015)

Abstract

A growing body of literature has explored the influence of physical activity on brain structure and function. While the mechanisms of this relationship remain largely speculative, recent research suggests that one of the effects of physical exercise is an increase in synaptic long-term potentiation (LTP). This has not yet been explored directly in humans due to the difficulty of measuring LTP non-invasively. However, we have previously established that LTP-*like* changes in visual-evoked potentials (VEPs) can be measured in humans. Here, we investigated whether physical fitness status affects the degree of visual sensory LTP. Using a self-report measure of physical activity, participants were split into two groups: a high-activity group, and a low-activity group. LTP was measured and compared between the two groups using the previously established electroencephalography-LTP paradigm, which assesses the degree to which the N1b component of the VEP elicited by a sine grating is potentiated (enhanced) following a rapid "tetanic" presentation of that grating. Both groups demonstrated increased negativity in the amplitude of the N1b component of the VEP immediately after presentation of the visual "tetanus," indicating potentiation. However, after a 30-min rest period, the N1b for the high-activity group remained potentiated while the N1b for the low-activity group returned to baseline. This study presents the first evidence for the impact of self-reported levels of physical activity on LTP in humans, and sheds light on potential neurological mechanisms underlying the relationship between physical fitness and cognition. (*JINS*, 2015, *21*, 831–840)

Keywords: Brain Derived Neurotrophic Factor (BDNF), Synaptic plasticity, Physical activity, Visual evoked potential, EEG, ERP

INTRODUCTION

Influence of Physical Fitness on Human Sensory Long-Term Potentiation

Whether searching popular media or scientific research, the relationship between exercise and cognition is not hard to come by. At the behavioral level, the impact of exercise on cognition has been assessed across a range of cognitive tasks and using a variety of measures for physical fitness, and physical activity (Ferris, Williams, & Shen, 2007; Hoffman et al., 2008; Lautenschlager et al., 2008; van Uffelen, Chinapaw, van Mechelen, & Hopman-Rock, 2008; Williamson et al., 2009; Winter et al., 2007). Despite huge variations in the methodology and results of individual studies, the over-arching conclusion from such research has been relatively consistent: increased physical activity is associated with increases in performance on tasks of executive function, processing speed, or memory (Angevaren, Aufdemkampe, Verhaar, Aleman, & Vanhees, 2008; Chang, Labban, Gapin, & Etnier, 2012; Smith et al., 2010). Be that as it may, there remains much to be elucidated regarding the mechanisms through which physical activity influences cognition, for which a greater understanding of the neurological underpinnings is required.

To address this issue, a growing body of neuroimaging research has begun to assess the changes in neuronal structure and function associated with exercise. MRI studies have demonstrated an increase in cortical grey and white matter volume in response to exercise programs (Chaddock et al., 2010; Erickson et al., 2009, 2011). Additionally, Colcombe et al. (2004) have indicated that high cardiovascular fitness (measured both cross-sectionally and after a 12-month

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aerobic exercise program) is associated with an increase in BOLD activation within the frontal and parietal lobes, as well as a decreased activation in the anterior cingulate cortex during a modified version of the Erickson Flanker Paradigm. Using a similar paradigm, Liu-Ambrose, Nagamatsu, Voss, Khan, and Handy (2012) also identified functional changes in the frontal and temporal lobes in elderly participants following 12-months of resistance-training. Electrophysiological (EEG) studies indicate that regular, intensive physical activity is associated with an increase in baseline theta, alpha, and beta activation (Lardon & Polich, 1996), as well as an increased amplitude of the P300 component of the visually evoked potential (VEP; Polich & Lardon, 1997). Increased physical activity is also associated with a decreased latency of this same VEP across a range of tasks (Dustman et al., 1990; Hillman, Belopolsky, Snook, Kramer, & McAuley, 2004; Hillman, Kramer, Belopolsky, & Smith, 2006). Together, the above body of research indicates that physical activity influences not only the structure, but also the function of the human brain across age groups.

At the cellular level, alterations in synaptic plasticity are understood to facilitate the gross brain changes suggested by the above studies. Specifically, increases in physical activity have been associated with increased neurogenesis in the rodent and human dentate gyrus (Pereira et al., 2007; Van Praag, Shubert, Zhao, & Gage, 2005). Additionally, the process of long-term potentiation (LTP) has been of increasing interest across the field of physical activity and cognition. LTP refers to an activity-dependent increase in synaptic efficacy following sustained stimulation between neurons (Cooke & Bliss, 2006; Teyler, 2000). Typically, assessments of LTP have involved *in vitro* or *in vivo* application of high frequency electrical stimulation to the rodent hippocampus, which induces an enhancement of the post-synaptic response from the affected synapses (Bliss & Lømo, 1973; Figurov, Pozzo-Miller, Olafsson, Wang, & Lu, 1996; Harris, Ganong, & Cotman, 1984; Teyler & DiScenna, 1987). Conversely, low frequency stimulation leads to an opposing decrease in synaptic efficacy, a process referred to as long-term depression (LTD; Bliss & Cooke, 2011; Heynen, Bear, & Abraham, 1995; Mulkey & Malenka, 1992; Xu, Anwyl, & Rowan, 1997). The above research has also established the presence of Hebbian characteristics in LTP and LTD, such as input specificity, associativity, longevity, saturation, and *N*-methyl-D-aspartate receptor (NMDAR) dependence (Clapp, Eckert, Teyler, & Abraham, 2006; Cooke & Bliss, 2006). In humans, LTP and LTD have only been demonstrated *in vitro* due to the invasive nature of stimulating hippocampal neurons (Beck, Goussakov, Lie, Helmstaedter, & Elger, 2000; Chen et al., 1996). Based on such findings, LTP and LTD represent the primary candidates for modelling the neural basis of learning and memory formation in the mammalian brain (Cooke & Bliss, 2006; Teyler & DiScenna, 1987), and are thus of interest in understanding the impact of physical fitness on cognition.

Rodent studies have demonstrated the relationship between increased physical activity (both forced and voluntary) and an increase in memory performance (O'Callaghan, Ohle, & Kelly, 2007; van Praag, Christie, Sejnowski, & Gage, 1999) as well as Hebbian LTP (Farmer et al., 2004; O'Callaghan, et al., 2007; van Praag et al., 1999, 2005). However, due to the invasive nature of the above procedures, to date few *in vivo* human studies have been conducted, limiting our understanding of the relationship between physical activity and LTP in the human brain. However, after Heynen and Bear (2001) demonstrated in rodents that visually induced alterations in neural activation could be observed following rapid stimulation, Teyler et al. (2005) presented one of the first non-invasive measures of synaptic plasticity in the human visual cortex. Using electroencephalography scalp recordings, Teyler et al. (2005) measured VEPs during the presentation of a checkerboard stimulus flashed to the right or left visual hemifield at a low temporal frequency (1 Hz). After being presented with a high-frequency (9 Hz) "tetanic" presentation of the checkerboard stimulus, the amplitude of occipital lobe VEPs increased in both hemispheres. Closer examination revealed that this increase in amplitude was specific to the N1b component of the VEP; a bilateral, negative event-related potential (ERP) component occurring approximately 170 to 190 milliseconds following stimulus onset. The selective increase in the amplitude of the N1b following tetanization suggests an LTP-*like* alteration of the VEP. This has been replicated in several subsequent human and rodent studies, which have also demonstrated the presence of the Hebbian characteristics of LTP identified in early rodent studies, such as input-specificity (McNair et al., 2006; Ross et al., 2008), locality in the cortex (Clapp, Zaehle, et al., 2005), longevity, NMDAR dependence (Clapp et al., 2006), and a dependence on neurotrophin expression (Lamb et al., 2014; Thompson et al., 2011). Additionally, an equivalent paradigm has demonstrated similar LTP-*like* alterations in the N1 of auditory evoked potentials (AEPs) following tetanization of auditory tone pips (Clapp, Kirk, Hamm, Shepherd, & Teyler, 2005; Zaehle, Clapp, Hamm, Meyer, & Kirk, 2007) and a recent rodent study has also demonstrated similar long-lasting, NMDAR dependent potentiation following somatosensory stimulation (Han, Huang, Sun, Duan, & Yu, 2015). Therefore, while there has been some inconsistency in inducing changes in sensory evoked potentials *via* sensory tetanization (e.g., Eckert, Guevermont, Williams, & Abraham, 2013), the aforementioned body of human and rodent research does support the potential for inducing LTP-*like* alterations using non-invasive sensory stimulation (Clapp, Hamm, Kirk, & Teyler, 2012; Kirk et al., 2010). As such, this non-invasive potentiation of sensory ERPs presents an exciting method for investigating the link between exercise and LTP in humans.

Using a similar human LTP paradigm to that first presented by Teyler et al. (2005), the aim of the current study was to pilot an assessment of the impact of physical activity on sensory LTP. ERP data were collected and compared between two groups of participants differing in self-reported level of physical activity: a high-activity group, and a low-activity group. It was hypothesized that highly active participants would show greater potentiation of tetanized

stimuli than less active participants, as evidenced by greater increases in the amplitude of the N1b both immediately following tetanization, as well as after a 30-min break.

METHOD

Participants

Twenty-one participants were recruited through advertisement at the University of Auckland, New Zealand. Due to the use of EEG and rapid visual stimulation in the current study, only participants who reported that they did not suffer from any neurological conditions, epilepsy, or migraine were included. All participants had normal or corrected to normal vision and provided informed written consent. BMI and demographic details were collected and are presented in Table 1. All were normally distributed ($D = p \geq .05$). All experimental procedures were approved by the University of Auckland Human Subject Ethics Committee (ref 2011-063).

International Physical Activities Questionnaire

The International Physical Activities Questionnaire (IPAQ)-Long Form was used as a measure of self-reported physical activity. Since its development in 1998, the IPAQ has been used extensively across the globe as a self-report measure of physical activity (Craig et al., 2003). While there has been some inconsistency (e.g., Maddison et al., 2007), the IPAQ has demonstrated both reliability and validity when compared with accelerometers (Boon, Hamlin, Steel, & Ross, 2008; Craig et al., 2003) and measures of maximal oxygen volume consumption (Fogelholm et al., 2006). It was, therefore, deemed an appropriate tool for self-report physical activity in this current study.

As has been done in previous studies (Fogelholm et al., 2006), the IPAQ was used to separate participants into two groups based on self-reported levels of daily activity; a "high" activity (11 participants) group and a "low" activity (10 participants) group. Activity levels were calculated in accordance with the IPAQ guidelines for analysis (International Physical Activity Questionnaire, 2005). Briefly, overall physical activity was calculated as MET-min/week. METs (metabolic equivalent of task) are multiples of resting metabolic rates dependent on type of activity and are used to estimate energy requirements for varying tasks (Hagstromer, Oja, & Sjostrom, 2006). As the IPAQ specifically asks about activity within the past 7 days, participants were also asked whether the past 7 days were an accurate reflection of exercise over the preceding 2 months, to which all participants agreed.

Apparatus

EEG recordings were carried out in an electrically shielded room and measured from a 128-channel Ag/AgCl electrode net (Electrical Geodesics Inc., Eugene, OR) at a continuous 250 Hz sampling rate (0.1–100 Hz analogue bandpass filter). All electrode impedances were below 50 kΩ, which is considered an acceptable level for this system (Ferree, Luu, Russell, & Tucker, 2001). A common vertex reference (Cz) was used to acquire EEG, which was later referenced to the average off-line.

Stimuli

The visual stimuli were circular horizontally and vertically oriented sine gratings with a one cycle per degree (cpd) spatial frequency. The gratings were presented at full contrast in the center of the screen against a grey background subtending a diameter of 8° of visual angle (size: 9.6 × 9.6 cm, 272 × 272 pixels; Figure 1A). Stimuli were presented on a SVGA computer monitor (1024 × 768 pixel resolution; 60 Hz refresh rate) at a distance of 57 cm. Presentation was controlled using E-Prime v1.1 (Psychology Software Tools).

Procedure

LTP was assessed *via* our previously established paradigm using visual-evoked potential EEG scalp-recording (McNair et al., 2006; Ross et al., 2008; Teyler et al., 2005; Thompson et al., 2011). As demonstrated in Figure 1B, the procedure consisted of two pre-tetanus blocks, a photic tetanus, two early post-tetanus blocks, a 30-min rest period, and two late post-tetanus blocks. The pre-tetanus, early post-tetanus, and late post-tetanus blocks each consisted of 120 presentations of each of the horizontal and vertical sine gratings, at a temporal frequency of 0.67–1 Hz (stimulus presentation ~33 ms, jittered ISI of 1000–1500 ms). The photic tetanus consisted of a rapid (8.6 Hz) presentation of 1000 horizontal or vertical

Table 1. participant demographics

Group	Low fitness			High fitness		
N	10			11		
N females	7			5		
N left handed	3			0		
	M	*SD*	Range	*M*	*SD*	Range
age (years)	23.9	2.92	19–28	26.2	4.29	21–37
BMI (kg/m^2)	22.53	3.72	16.65–27.78	23.78	3.24	18.23–29.97
IPAQ score	1187.85	827.72		6694.77	827.70	

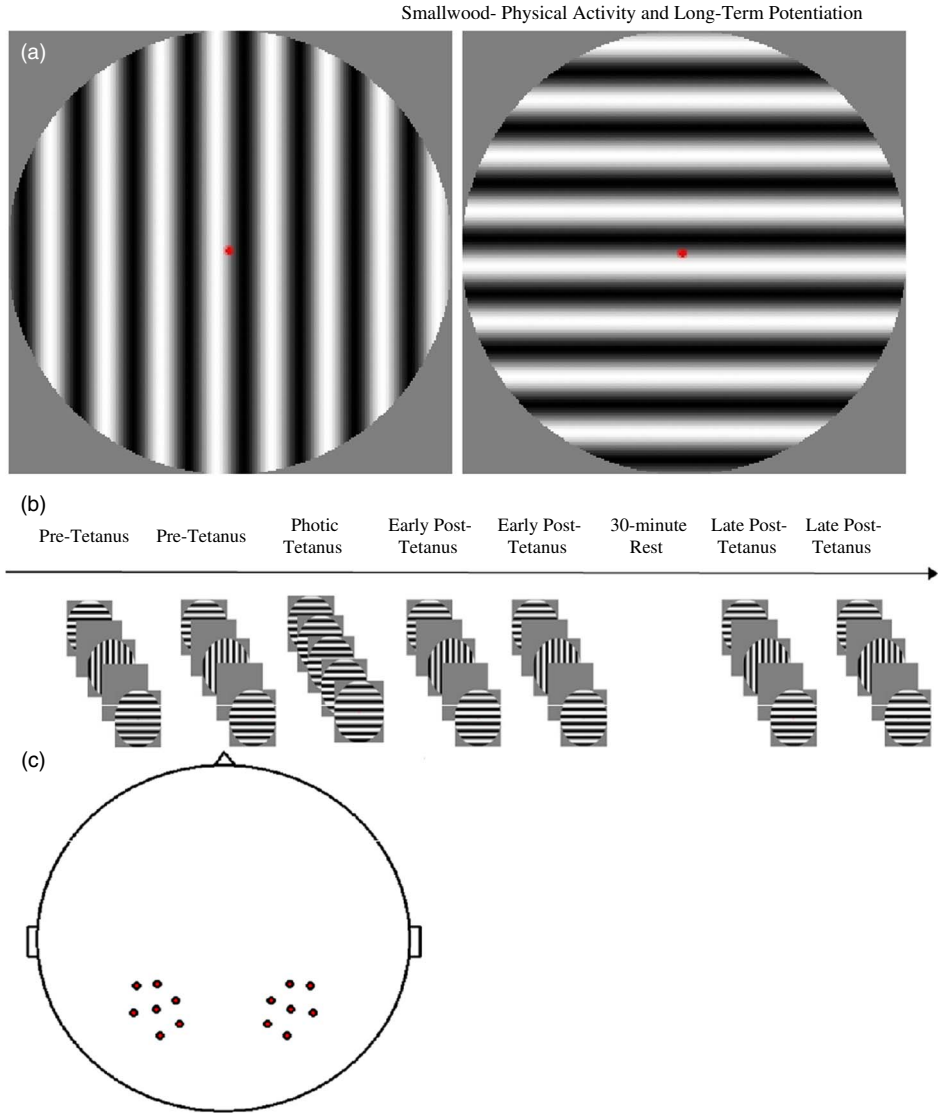

Fig. 1. (a) The visual stimuli were 9.6 × 9.6 cm circular horizontal and vertical sine gratings (actual size) with a spatial frequency of one cycle per degree and 100 percent contrast presented against a grey background. (b) A schematic representation of the experimental procedure. Participants were presented with two pre-tetanus (baseline) blocks, a photic tetanus block, two early post-tetanus blocks, a 30-min rest period and lastly, two late post-tetanus blocks. The pre-tetanus blocks, early post-tetanus blocks, and late post-tetanus blocks each consisted of 120 presentations of horizontal and vertical circular sine gratings at a frequency of 0.67–1 Hz. The photic tetanus involved 1000 presentation of a single orientation at a frequency of 8.6 Hz. (c) Approximate location of left and right hemisphere electrodes (centered on approximately P7 and P8 under the 10–20 system) used to measure amplitude of N1b component.

sine gratings (counterbalanced between participants; jittered ISI of 67–100 ms). This frequency has been shown to induce the alpha rhythm but not be beyond flicker fusion rate. Following the photic tetanus, participants were asked to close their eyes for 2 min to allow retinal after-images to dissipate. During the 30-min rest period, participants were instructed to sit quietly with their eyes closed.

Analysis

EEG data for each participant were segmented into 600 ms time epochs (100 ms before and 500 ms after stimulus onset), bandpass filtered offline [0.10–30 Hz, bi-directional three-pole Butterworth filter (Alarcon, Guy, & Binnie, 2000)], and epochs were averaged by condition according to orientation (horizontal or vertical), and block (pre-tetanus, early post-tetanus, late post-tetanus). Epochs were baselined to the 100 ms pre-stimulus period. Epochs with eye blinks or artifacts were rejected (range: 0–10% of epochs per participant, no significant differences between groups). The amplitude of the N1b component of the pre-tetanus, early post-tetanus and late post-tetanus VEPs were averaged for clusters of electrodes positioned over the left and right visual cortex (Figure 1C). In accordance with previously validated measures (McNair et al., 2006), the amplitude of the N1b component was defined as the mean amplitude of the section of the evoked potential

extending from the peak of the N1 component to halfway between the N1 and P2 components. For each participant individually, the N1b was identified (latencies were between 100 ms and 200 ms for all participants) and the magnitude of LTP was calculated by subtracting pre-tetanus N1b amplitude from early and late post-tetanus amplitudes. There were no significant differences between pre- and post-tetanus amplitudes for the non-tetanized gratings ($p \geq .05$) and, therefore, these were excluded from further analyses.

Changes in amplitude as a function of level of activity were analyzed using a 2×2 Split-Plot analysis of variance (ANOVA) with Activity Level (low or high) as the between-subjects variable and Time (early or late post tetanus) as the within-subjects variable (alpha level $p \leq .05$). All statistical analyses were performed using the statistical analysis software package SPSS 20.0. A Greenhouse-Geisser correction was used to control for violations of sphericity where required.

RESULTS

There were no significant differences in BMI between the two groups, $t(19) = -0.83$, $p = .417$. Conversely, as expected, the IPAQ scores for the Low Activity group were significantly lower than the High Activity group, $t(11.54) = -5.65$, $p < .01$. Figure 2 presents the difference in N1b amplitude between pre-tetanus and the early and late post-tetanus blocks for the two groups separately. The two-way split-plot ANOVA revealed a significant main effect for Time, indicating that LTP amplitude was greater for the early post-tetanus block ($M = -0.70\,\mu V$; $SE = .17\,\mu V$) than the late post-tetanus block ($M = -.39\,\mu V$; $SE = 0.15\,\mu V$), $F(1,19) = 7.02$, $p = .016$, $\eta_p^2 = .270$. Importantly, the interaction between Activity Level and Time was significant, $F(1,19) = 10.705$, $p = .004$, $\eta_p^2 = .360$. For the early post-tetanus block, there was no significant difference in N1b amplitude between the High Activity ($M = -0.77\,\mu V$; $SE = 0.24\,\mu V$) and the Low Activity group ($M = -0.64\,\mu V$; $SE = 0.25\,\mu V$; $p > .05$). However, while the N1b remained potentiated (negative compared to pre-tetanus baseline) in the late post-tetanus block for the High Activity group ($M = -0.84$; $SE = 0.21$), it returned to baseline for the Low Activity group ($M = 0.07$; $SE = 0.22$; $p = .008$), leading to significant group differences in the late post-tetanus block. The main effect for Activity Level was non-significant, $F(1,19) = 2.96$, $p = .102$, $\eta_p^2 = .134$. These trends are illustrated for one subject in each group in Figure 3.

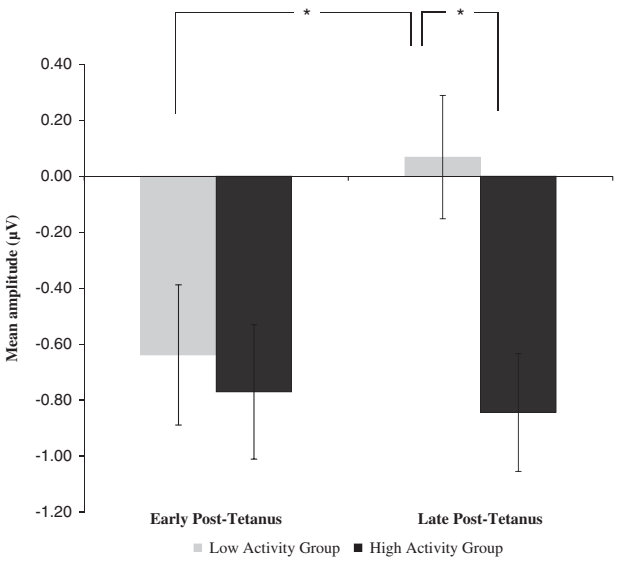

Fig. 2. Bar graph showing the mean amplitude of N1b for early and late LTP post-tetanus for the high and low activity groups (error bars depicting standard error). There was a significant difference between early and late LTP for the low activity group. There was a significant difference between the low and high activity groups for late post-tetanus LTP. * indicates a statistically significant effect ($p \leq .05$).

DISCUSSION

The aim of the current study was to use an established non-invasive measure of LTP to pilot an assessment of the impact of physical activity on neuroplasticity. Using the IPAQ, participants were divided into two groups (highly active and less active) and ERPs were recorded during the presentation of "tetanized" and "non-tetanized" sine gratings. Both groups demonstrated a significant "early" LTP effect. That is, the tetanus resulted in an increase in the amplitude of the N1b component of the VEPs immediately following tetanization. Importantly, however, there was a significant difference in "late" LTP (measured 30 min after induction) between the High Activity group and the Low Activity group. The High Activity group demonstrated significantly greater potentiation of the N1b in the late post-tetanus block than the Low Activity group. This study, therefore, presents the first *in vivo* evidence to suggest that chronic levels of physical activity can influence the maintenance of LTP-*like* changes in the human visual cortex, and thus illuminates potential neurological mechanisms underlying the relationship between exercise and cognition.

The overall increase in amplitude of the N1b following tetanization for both groups supports previous research indicating that an LTP-*like* response can be invoked through non-invasive visual stimulation (Clapp, Zaehle, et al., 2005; Clapp, Kirk, et al., 2005; McNair et al., 2006; Ross et al., 2008; Zaehle et al., 2007). Previous assessments of LTP in rodents have largely taken place within the hippocampus, a structure undoubtedly involved in memory (e.g., Bliss & Lømo, 1973; Figurov et al., 1996; Harris et al., 1984). Conversely, the current study focused on the sensory cortex which allowed the implementation of a non-invasive design. There is ample evidence indicating that neuroplasticity in the visual cortex represents the same underlying processes as hippocampal LTP (for review, Cooke & Bear, 2014). Additionally, both rodent and human studies using versions of the current paradigm have demonstrated Hebbian characteristics

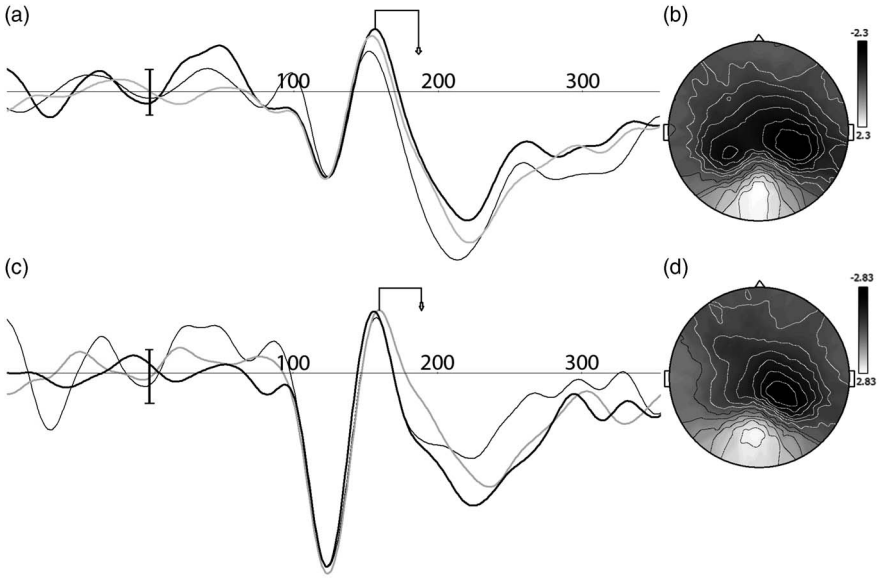

Fig. 3. Exemplars from single subjects showing the trends described in Figure 2. Negative plotted up. (a, c) ERPs from pre-tetanus (thin black line), early (thick gray line), and late (thick black line) post-tetanus for the high and low activity groups, respectively. (b, d) topographic maps at the mid N1b of the pre-tetanus potential for the high and low activity groups, respectively. Time on x-axis in ms. Scale bar at 0 ms ±1 μV.

in these LTP-*like* changes such as specificity (McNair et al., 2006; Ross et al., 2008) longevity (Clapp et al., 2006), and NMDA dependence (Clapp et al., 2006). However, it must be acknowledged that future studies are required to elucidate the generalizability of these LTP-*like* changes to the rest of the cortex. As such, while potentiation of VEPs may not directly represent declarative memory formation, this does represent activity-dependent neuroplasticity in the human cortex, and thus has implications in our understanding of the neural basis of cognition and memory. Importantly, this provides direction for potential intervention studies in the future.

This study, therefore, presents an insight into the potential neuronal mechanisms behind the large body of human and rodent research indicating that physical activity increases cognitive performance (e.g., Colcombe et al., 2004; Ferris et al., 2007; Lautenschlager et al., 2008; Winter et al., 2007). As expected, the highly active group demonstrated a greater increase in the amplitude of the N1b following tetanization than the less active group; thus indicating greater LTP-*like* changes in the VEP. As LTP is believed to underlie memory formation and maintenance (Cooke & Bliss, 2006; Teyler & DiScenna, 1987), this result suggests that greater levels of physical activity increase neural plasticity, which may in turn increase an individual's capacity for learning and memory. However, an unexpected finding in the current study was that this group difference was only significant for the late post-tetanus block, 30 min after tetanization. This suggests that while there is no influence of chronic physical activity on the induction of experience-dependent plasticity, higher levels of physical activity may be beneficial for the maintenance of these changes. While it is unclear why differences in activity level specifically targeted late LTP, several potential hypotheses can be proposed. Largely, these hypotheses are centered on the potential mediating effect of brain derived neurotrophic factor (BDNF) in exercise-induced cognitive improvements and LTP.

BDNF is one of four neurotrophins found in the mammalian central nervous system that are responsible for the regulation of neuronal growth, maintenance, and survival, as well as sustaining the malleable state required for learning and memory (Reichardt, 2006; Tyler, Alonso, Bramham, & Pozzo-Miller, 2002). Importantly, the activity-dependent nature of BDNF renders it a primary candidate for modulating the induction and maintenance of LTP (Bekinschtein et al., 2008; Poo, 2001; Tyler et al., 2002), and it is believed to be involved in the regulation of pre-synaptic neurotransmitter release, as well as post-synaptic protein synthesis and transcription (Bekinshtein, Cammarota, & Medina, 2014; Christie et al., 2008). Rodent models have illustrated a positive relationship between physical fitness and expression of hippocampal BDNF (Cotman & Berchtold, 2002; Garza, Ha, Garcia, Chen, & Russo-Neustadt, 2004; Gómez-Pinilla, Ying, Roy, Molteni, & Edgerton, 2002; Marais, Stein, & Daniels, 2009; Neeper, Gómez-Pinilla, Choi, & Cotman, 1996). A limited number of human studies have also exemplified the link between both chronic and acute increases in physical activity and increased BDNF expression (Erickson et al., 2011; Ferris et al., 2007; Zoladz et al., 2008), as well as an increase in visually evoked LTP in individuals expressing greater levels of BDNF (based on the *BDNF* Val66Met polymorphism; Thompson et al., 2011, 2015; Lamb et al., 2014).

One possible mechanism by which BDNF may be pivotal in the current results is that activity-induced increases in BDNF expression may specifically impact LTP maintenance (synthesis and transcription), while LTP induction remains

unaffected. This would only be apparent in the late post-tetanus block of the current study where LTP maintenance is required. However, as previous human research has indicated a general increase in BDNF expression with increased exercise, it is unclear why this would be the case (Ferris et al., 2007; Zoladz et al., 2008). As an alternative hypothesis, *in vitro* human studies have indicated that low frequency stimulation (1 Hz) induces LTD (Beck et al., 2000; Chen et al., 1996) and, as proposed by Teyler et al. (2005) and Ross et al. (2008), it is possible that the baseline stimulation used in the current paradigm (0.67–1 Hz) induces LTD, thus actively depotentiating (reducing) the previously enhanced N1b. Importantly, Ikegaya, Ishizaka, and Matsuki (2002) demonstrated a significant reduction in the LTD induced by low frequency stimulation in hippocampal slices bathed in BDNF. This indicates that increased BDNF buffers against active depotentiation, and an increased expression of BDNF in highly active individuals may facilitate this protective effect. It must be noted that the current pilot study cannot delineate between the above proposals. However, it lays the foundations for future studies incorporating neurotrophin expression and gene interactions such as the *BDNF* Val66Met polymorphism into our understanding of the cellular and molecular mediators of exercise-induced LTP.

It is important to note that, while the N1b in the late post-tetanus block for the low activity group appears to return to an amplitude almost identical to that recorded pre-tetanus, this does not indicate that low fitness is associated with a complete inability to maintain LTP. As suggested above, individuals from the low activity group may be more susceptible to active depotentiation induced by low frequency stimulation. Additionally, Farmer et al. (2004) indicated that increased fitness level lowers the threshold for the induction of long-lasting LTP. Therefore, highly active participants may be more susceptible to LTP following a 8.6 Hz tetanus than less active participants. As such, the current results are not inconsistent with previous rodent studies demonstrating an enhancement of LTP magnitude with increased physical fitness (O'Callaghan et al., 2007; van Pragg et al., 1999) as these results indicate an enhancement in the maintenance of experience-dependent plasticity for highly active individuals. It is anticipated that future research will further illuminate the mechanisms underlying these differences.

The current pilot study presents the first evidence for fitness related differences in the maintenance of LTP-*like* changes in the human visual cortex. However, certain caveats must be highlighted when interpreting the current results. First, it is important to acknowledge that the measure of physical activity used in the current study was a self-report measure and not a direct physiological measure of physical fitness. While the IPAQ has shown test–retest reliability and validity as a measure for activity status (Brown, Trost, Bauman, Mummery, & Owen, 2004; Craig et al., 2003), the gold standard for physical fitness is the maximal volume of oxygen consumption (VO2 max) (Garber et al., 2011). Nevertheless, in a comparison of the validity of the IPAQ and VO2 max by ergometer, Fogelholm et al. (2006) demonstrated that responses categorized as "high" and "low" physical fitness based on the IPAQ correlated with higher and lower cardiorespiratory fitness (with the exception of a small proportion of young men who over-reported physical activity). Furthermore, the IPAQ has been successfully used to distinguish between physically active and sedentary individuals to measure cognition as a function of fitness level (Kamijo, O'leary, Pontifex, Themanson, & Hillman, 2010). It would be interesting to explore additional measures of fitness in future research to further elucidate the relationship between fitness and LTP.

Second, previous research has indicated that different types of exercise can have substantially different effects on cognition and neuroplasticity. For example, in a series of experiments, Erickson and colleagues demonstrated a positive relationship between an aerobic exercise program and gray and white matter volume (Colcombe et al., 2006; Erickson et al., 2009, 2010, 2011), while Liu-Ambrose et al. (2010) identified a decrease in whole brain volume following a 12-month resistance training intervention. Colcombe and Kramer (2003) suggested aerobic exercise combined with resistance training may provide the greatest benefit for cognitive function. However, the current study did not differentiate between different types of activity.

Finally, it is important to note the lack of significant difference in BMI between the two participant groups. While several previous studies have demonstrated a relationship between BMI and physical fitness (Frändin & Grimby, 1994; Leyk et al., 2006), this has not been consistent across all studies (Mak et al., 2010). Additionally, there are several lifestyle (Tavani, Negri, & La Vecchia, 1994), genetic (Speliotes et al., 2010), and demographic (Leyk et al., 2006; Tavani et al., 1994) factors that can influence BMI beyond physical activity that would be difficult to exclude as confounds if group differences in BMI were to emerge. As highlighted by Leyk et al. (2006), while fitness and BMI may correlate, the concepts of being "overweight" and being "physically unfit" are not synonymous (as is true for being "underweight" and being "physically fit"); therefore, one should not be used as a marker or criteria for the other. Be that as it may, future research may wish to investigate the influence of BMI on LTP, as well as their potential interaction.

The non-invasive paradigm created by Teyler et al. (2005) has been used to demonstrate that LTP impairments are associated with a range of neuropsychological disorders such as depression (Holderbach, Clark, Moreau, Bischofberger, & Normann, 2007; Normann et al., 2007), bipolar-II disorder (Elvsåshagen et al., 2012), and schizophrenia (Mears & Spencer, 2012). As suggested by Kirk et al. (2010), numerous neurocognitive disorders may manifest synaptic deficiencies in varying affected cortical areas, and Krystal et al. (2009) advocate for increased research focusing on psychiatric treatments that could manipulate neuroplasticity in conjunction with behavioral interventions. The results of the current study indicate a potential candidate for the neural basis for exercise-induced cognitive enhancements, and as such, it is worth considering exercise as a non-pharmaceutical option to alterations in neural plasticity.

ACKNOWLEDGEMENTS

This work was supported by a NZ Royal Society Marsden Grant (I.J.K., grant number 06-UoA-077). There are no conflicts of interest to report.

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