UC Irvine
ICTS Publications

Title
The BDNF val^{66} met polymorphism is not related to motor function or short-term cortical plasticity in elderly subjects

Permalink
https://escholarship.org/uc/item/81j639hm

Journal
Brain research, 1495

ISSN
1872-6240

Authors
McHughen, Stephanie A.
Cramer, Steven C.

Publication Date
2012-12-13

Peer reviewed

eScholarship.org Powered by the California Digital Library
University of California

NIH Public Access
Author Manuscript
Brain Res. Author manuscript; available in PMC 2014 February 07.

Published in final edited form as:
Brain Res. 2013 February 7; 1495: 1–10. doi:10.1016/j.brainres.2012.12.004.

The BDNF val^{66} met polymorphism is not related to motor function or short-term cortical plasticity in elderly subjects

Stephanie A. McHughen[1] and **Steven C. Cramer**[1,2]

[1]Departments of Anatomy and Neurobiology, University of California, Irvine; Irvine, CA, USA

[2]Department of Neurology, University of California, Irvine; Irvine, CA, USA

Abstract

The brain derived neurotrophic factor (BDNF) val^{66} met polymorphism affects function of the motor system in young subjects, but little is known about motor system effects in the elderly. The current study assessed motor system physiology and behavior, plus a measure of short-term motor cortex plasticity using transcranial magnetic stimulation, in 38 elderly subjects, then examined whether findings varied in relation to BDNF genotype. Baseline data were also collected from 14 young subjects. At baseline, elderly subjects had poorer motor performances, larger motor cortex maps, and smaller motor evoked potentials compared to young subjects. Degree of age-related differences in neurophysiology correlated inversely with motor performance, for example, larger map area correlated with weaker pinch grip force ($r = -0.42$, $P=0.01$). In elderly subjects, baseline behavior and neurophysiology did not differ in relation to BDNF genotype. In addition, although map area increased significantly ($P=0.03$) across 30 minutes of exercise, this change did not vary according to BDNF genotype. Aging is associated with changes in neurophysiology that might represent a compensatory response. The data do not support an association between BDNF genotype and behavior, neurophysiology, or short-term cortical plasticity in the motor system of healthy elderly subjects.

Keywords

Plasticity; Neurophysiology; Genetics; Aging; Motor System

1. Introduction

Aging is accompanied by a decline in many aspects of motor performance, and these changes can be associated with significant loss of function and with secondary effects such as falls. The basis for these changes includes peripheral nervous system events such as reduced conduction velocity and loss of muscle fibers, as well as central nervous system events such as decreases in brain volume and synapse number (Adams, 1987; Adams and Victor, 1985; Doherty et al., 1993; Drachman, 1997; Mahncke et al., 2006). A number of neurophysiological changes have been described in association with normal aging, including decreased motor evoked potential (MEP) amplitude, decreased intracortical inhibition,

© 2012 Elsevier B.V. All rights reserved.

PLEASE DIRECT CORRESPONDENCE TO Steven C. Cramer, MD, University of California, Irvine Medical Center, 101 The City Drive South, Building 53 Room 203, Orange, CA 92868-4280, PHONE: (714) 456-6876, FAX: (714) 456-8805, scramer@uci.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

$watermark-text
$watermark-text
$watermark-text

$watermark-text

$watermark-text

$watermark-text

increased variability, and a decrease in traininginduced brain plasticity (Eisen et al., 1996; Fathi et al.; Oliviero et al., 2006; Peinemann et al., 2001; Pitcher et al., 2003; Rogasch et al., 2009; Sawaki et al., 2003).

The current study is focused on understanding how a genetic influence on brain plasticity, the val^{66} met polymorphism in the gene for the growth factor brain-derived neurotrophic factor (BDNF), impacts function and plasticity in the motor system of healthy elderly subjects. BDNF is the most abundant neurotrophin in the brain. This neurotrophin influences a wide range of brain events related to plasticity and repair in both health and disease (Cotman and Berchtold, 2002), including processes specifically linked to short-term cortical plasticity such as neuronal recruitment (Monfils et al., 2005) and long-term potentiation (Patterson et al., 1996). A single nucleotide polymorphism in the human BDNF gene at codon 66 (val^{66} met) is present in one or both alleles in approximately 30% of people in the United States (Shimizu et al., 2004). The BDNF val^{66} met polymorphism has been previously shown to be associated with alterations in brain structure and function (Egan et al., 2003; Hariri et al., 2003; Pezawas et al., 2004). Studies in young healthy subjects have found that presence of the polymorphism is associated with reduced short-term, experience-dependent cortical plasticity (Cheeran et al., 2008; Kleim et al., 2006; McHughen et al., 2010; McHughen et al., 2011), as well as greater error on learning a driving-based cognitive motor task (McHughen et al., 2010). The effect of this polymorphism has been measured in elderly subjects, particularly in reference to cognitive function, with mixed ‘results. For example, the val^{66} met polymorphism has been associated with favorable (Harris et al., 2006), deleterious (Miyajima et al., 2008), or no cognitive effects (Benjamin et al., 2010) in the elderly. However, effects of this polymorphism have not been examined in the motor system of elderly subjects, at baseline or in relation to cortical plasticity. This question is potentially of high importance given the role that BDNF plays in healthy aging (Nemoto et al., 2006; Silhol et al., 2005; Webster et al., 2006) as well as in the expression of outcome from neurological conditions common in the elderly such as stroke (Chen et al., 2005; Zhang and Pardridge, 2006; Zhao et al., 2001).

The main hypothesis examined in the current study was that presence of the BDNF val^{66} met polymorphism in healthy elderly subjects is associated with reduced short-term cortical plasticity, as has been demonstrated in healthy young subjects (Cheeran et al., 2008; Kleim et al., 2006; McHughen et al., 2010; McHughen et al., 2011). This question was examined measuring the change in area of the motor cortex representational map of the right first dorsal interosseus (FDI) muscle across a 30-minute period of exercise, a model that has been found sensitive to polymorphism effects in young subjects (Kleim et al., 2006; McHughen et al., 2011). Secondary aims include examining the association that BDNF genotype has with motor behavior and neurophysiology at baseline in healthy elderly subjects. The study also affords an opportunity to further characterize aging effects on neurophysiology, independent of BDNF genotype, including effects on motor cortex representational maps, which have not been specifically examined in relation to aging.

2. Results

2.1 Subjects

A total of 52 subjects participated in this study. There were 38 enrollees in the elderly group, which was composed of 25 Val/Val and 13 Val/Met subjects, and 14 enrollees in the young group, which contained 7 Val/Val and 7 Val/Met subjects, with the BDNF gene being in Hardy-Weinberg equilibrium. All were right-handed. Elderly and young subjects did not differ in handedness or gender, though a minor difference was present in ethnicity (Table 1).

$watermark-text
$watermark-text
$watermark-text

2.2 Effect of Age

2.2.1 Age Effects on Behavioral Data—When compared to the young subjects, elderly subjects showed significantly poorer performance on all five baseline behavioral measures, each of which survived correction for multiple comparisons: slower tapping speed, longer time to complete nine-hole pegboard, weaker pinch grip force, slower reaction times, and greater error over the 15 trials on the driving game (Figure 1A and Table 1).

2.2.2 Age Effects on Neurophysiology at Baseline—An age-related difference was found at baseline for the primary TMS endpoint, map area, with elderly subjects showing a significantly larger map area compared to young subjects (P=0.03, Wilcoxon Rank Sums test, see Figure 1B and Table 2). Of the four secondary TMS measures, elderly subjects showed smaller MEP amplitude at 110% LMT (P=0.039, Wilcoxon Rank Sums test), which does not survive correction for multiple comparisons. The coefficient of variation was consistently larger in the elderly subjects, as compared to young subjects, for map area and for each of the secondary TMS measures. LMT, which reflects cortical excitability, did not differ in relation to age.

2.3 Effect of Genotype in Elderly Subjects

2.3.1 Genotype Effects on Behavioral Measures in Elderly Subjects—Among the 38 elderly subjects, bivariate analysis found no significant association of genotype with demographics, mental status, depression score, or with any of the five behavioral measures ($P > 0.05$, see Table 3).

2.3.2 Genotype Effects on Neurophysiology at Baseline in Elderly Subjects— Genotype was also not related to baseline neurophysiological measures in the 38 elderly subjects. Bivariate analysis found no significant effect of genotype on map area or on any of the four secondary TMS measures ($P > 0.05$, see Table 3). Genotype was also not related to LMT.

2.3.3 Genotype Effects on Cortical Plasticity in Elderly Subjects—Due to technical difficulties, post-exercise maps could not be obtained in six elderly subjects (five Val/Val and one Val/Met), leaving 32 elderly subjects for cortical plasticity analyses. Across all of these 32 elderly subjects, map area increased significantly over the 30 minutes of right FDI exercise (map area increased by 1.9 ± 1.2 cm^2, mean ± SEM, P=0.03 by Wilcoxon Signed Rank test), though none of the secondary TMS measures changed significantly over the 30 minutes of exercise. However, BDNF genotype was not related to this change in map area over time, nor to change in any of the secondary TMS measures over time ($P > 0.4$, Table 3).

2.4 Behavioral Correlates of Neurophysiology at Baseline in Elderly Subjects

Among the 38 elderly subjects, map area at baseline correlated significantly with two of the five baseline behavioral measures. Larger map area correlated with a reduction in the maximum rate of finger tapping (rho = −0.37, $P < 0.03$, Spearman Rank Order Correlation) and with a reduction in pinch grip force (rho = −0.42, P=0.01, Spearman Rank Order Correlation, see Figure 2), with the latter surviving correction for multiple comparisons.

2.5 Relative Contributions of Age and Genotype

In order to examine the relative influence of age and BDNF genotype across all 52 subjects, these two variables served as independent measures in multivariate models that used a baseline measure of either behavior or neurophysiology as the *dependent measure*. When predicting *baseline TMS map area*, age remained significant (for age, beta=0.10, SE=0.04, P

< 0.025; for overall model, F (2,49)=4.3, $P < 0.02$) but BDNF genotype did not. This was also true for one of the secondary TMS measures, *MEP at 110%,* (beta=−0.02, SE=0.01, $P < 0.04$; for overall model, F (2,49)=2.4, $P < 0.11$) and for three of the five behavioral measures: *tapping speed* (beta=−0.15, SE=0.05, $P < 0.003$; for overall model, F (2,49)=6.1, $P < 0.005$), *nine-hold pegboard* (beta=0.11, SE=0.02, $P < 0.0001$; for overall model, F (2,49)=18.9, $P < 0.0001$), and *pinch grip force* (beta=−0.11, SE=0.03, $P = 0.0003$; for overall model, F (2,49)=8.5, $P = 0.007$). In a single instance (*reaction time*), both age (beta=0.0015, SE=0.0002, $P < 0.0001$) and BDNF genotype (beta=0.014, SE=0.006, $P = 0.025$) survived as significant predictor variables (for overall model, F (2,49)=21.1, $P < 0.0001$). Thus, in all but one case, age was a significant predictor of behavior or neurophysiology when BDNF genotype was not.

3. Discussion

The current study examined motor physiology and behavior in elderly subjects, and also evaluated an established (Kleim et al., 2006; McHughen et al., 2011) probe of experiencedependent, short-term cortical plasticity. The primary aim was to address the hypothesis that the BDNF val[66] met polymorphism, associated with reduced short-term cortical plasticity in the motor system of young subjects (Cheeran et al., 2008; Kleim et al., 2006; McHughen et al., 2010; McHughen et al., 2011), has the same relationship in elderly subjects. The current results do not support this hypothesis, as in elderly subjects, as BDNF genotype was not associated with differences in baseline behavior, baseline neurophysiology, or short-term cortical plasticity. Indeed, when age and BDNF genotype were evaluated side by side, age was consistently a significant correlate of behavior and neurophysiology while BDNF genotype was not. The current study also documented that increased age is associated with enlarged motor cortex representational maps at baseline, a finding that might reflect a compensatory strategy to maintain behavioral status.

BDNF genotype did not have a significant association with a neurophysiological measure of short-term experience-dependent cortical plasticity in healthy elderly subjects. Map area increased significantly across the 30 minutes of exercise in the elderly group, but this change did not vary according to BDNF genotype. This result is in contrast to prior studies that did identify such an association of the BDNF val[66] met polymorphism with altered short-term cortical plasticity in young subjects (Cheeran et al., 2008; Kleim et al., 2006; McHughen et al., 2010; McHughen et al., 2011). The extent to which the current findings generalize across other shortterm motor cortex plasticity paradigms remains to be determined, including paradigms that emphasize more skilled movements, less induction of fatigue, or paradigms that rely on electromagnetic cortical perturbations. The robustness of the current paradigm used to induce short-term experience-dependent motor cortex plasticity has been demonstrated in several prior studies, three of which used the same 30 minutes of exercise as in the current study (Kleim et al., 2006; McHughen et al., 2010; McHughen et al., 2011) and two of which (Kleim et al., 2006; McHughen et al., 2011) also used the same primary measure of cortical plasticity, i.e., change in map area. Findings in elderly subjects at baseline were concordant, with no significant association between BDNF genotype and measures of behavior or neurophysiology. This too contrasts with a prior study in young subjects, which found that young subjects with the BDNF val[66] met polymorphism made significantly greater error over the 15 trials on the driving game as compared to young subjects lacking the polymorphism (McHughen et al., 2010).

Prior studies examining motor cortex plasticity in relation to BDNF genotype have reached divergent conclusions, possible because of differences in study power or in the method used to induced plasticity. The BDNF val[66] met polymorphism has been associated with significant differences in motor cortex plasticity, generally assessed in the short-term (i.e.,

$watermark-text $watermark-text $watermark-text

over a time period measured in minutes), using TMS (Antal et al., 2010; Cheeran et al., 2008; Kleim et al., 2006; McHughen et al., 2011) and fMRI (McHughen et al., 2010) metrics to assess plasticity. Two studies have not found such as association: Nakamura et al found no difference in effects of quadri-pluse stimulation between 7 subjects with, and 5 subjects without, the BDNF polymorphism (Nakamura et al., 2011); and Li Voti et al found no difference in effects of three different experimental settings between 7 subjects with, and 14 subjects without, this polymorphism (Li Voti et al., 2011). Whether these two studies would have found polymorphism-related differences with a larger sample size is unclear. It is also unclear the extent to which differences in study findings are related to use of different techniques to induce plasticity, as not all plasticity-inducing techniques might be expected to have the same relationship with BDNF genotype. This point was well summarized by Antal et al (Antal et al., 2010), who noted "BDNF polymorphism has a definite impact on plasticity in humans, which might differ according to the mechanism of plasticity induction." It is unclear whether differences in motor cortex reported in relation to BDNF genotype reflect alterations in synaptic connections, neuronal excitability, brain anatomy, or other factors, a perspective that could also be useful to interpret divergent findings across multiple studies. In light of these points, future studies might use a wider range of techniques to examine whether BDNF genotype is associated with differences in motor cortex plasticity in elderly subjects.

Results of the multivariate analyses were consistent, again suggesting little effect of BDNF genotype on baseline behavioral and neurophysiological measures in healthy elderly subjects. That age was associated with differences in the current behavioral and neurophysiological measures of the motor system is not unexpected and likely related to the myriad effects that aging has on the peripheral and central nervous systems (Adams, 1987; Adams and Victor, 1985; Doherty et al., 1993; Drachman, 1997; Mahncke et al., 2006). That BDNF genotype was not associated with differences at baseline or across 30 minutes of exercise might in part be related to the fact that BDNF expression and signaling decrease with normal aging (Erickson et al., 2010; Silhol et al., 2005; Tapia-Arancibia et al., 2008). The current findings in the motor system are consistent with prior studies in the hippocampus, where function has been found to vary according to BDNF genotype in young (Egan et al., 2003; Hariri et al., 2003; Pezawas et al., 2004), but not in elderly (Benjamin et al., 2010), human subjects.

One potential confounder when interpreting the cortical plasticity findings is that elderly subjects had a significantly enlarged cortical map at baseline (Figure 1B, Table 2). Larger maps at baseline might introduce a ceiling effect, impeding the ability to fully detect an increase in map area across the 30 minutes of exercise. Against this point is the fact that prior studies using alternative TMS-based models of short-term plasticity have also documented an age-related decrease in short-term plasticity following simple motor training (Fathi et al.; Rogasch et al., 2009; Sawaki et al., 2003), and that animal studies have described age-related decreases in the neurobiological underpinnings of cortical plasticity (Gooney et al., 2004; Pang and Lu, 2004; Rex et al., 2005). The convergence of findings suggests that among healthy elderly subjects, BDNF genotype does not have a significant association with motor behavior or neurophysiology and also does not have the same association with altered short-term motor system plasticity that have been described in healthy young subjects.

The current study found that elderly subjects had a significantly larger motor cortex representational map area. This has not been previously reported with TMS motor mapping methods and is concordant with prior fMRI studies of age effects, which found that during hand movement, increased age is associated with increased activation within primary and secondary motor and sensory areas (Naccarato et al., 2006; Ward and Frackowiak, 2003).

$watermark-text $watermark-text $watermark-text

$watermark-text

$watermark-text

$watermark-text

The validity of this finding is supported by the concordance that several other baseline neurophysiological findings in the current investigation (Table 2) have with prior reports: increased age is associated with a smaller MEP amplitude at baseline (Eisen et al., 1996; Hortobagyi et al., 2006; Oliviero et al., 2006; Pitcher et al., 2003), here at 110% LMT stimulation level; higher variability in neurophysiological measures (Pitcher et al., 2003), here indicated by the age-related increase in coefficient of variation of all TMS measures; and that increased age is not associated with a difference in cortical excitability (Fathi et al.; Pitcher et al., 2003; Rogasch et al., 2009; Sawaki et al., 2003; Talelli et al., 2008), here defined on the basis of LMT. Several interpretations can be advanced regarding the meaning of this age-related increase in motor map area. Larger map area might primarily reflect an age-related abnormality of motor cortex function, akin to the enlargement of motor map area described in conditions such as dystonia (Byrnes et al., 1998; Tamburin et al., 2002). Alternatively, the age-related map enlargement might in part be artifactual, reflecting altered conduction of the TMS magnetic pulse through the enlarged CSF and extra-axial spaces associated with aging. A third and favored possibility is that larger maps with aging are a secondary reaction, reflecting increased effort or compensation. This interpretation is supported by the correlation observed between larger map area and slower tapping rate plus weaker pinch grip force (Figure 2). Further support for this interpretation comes from the finding of a similar increase in TMS motor map area in studies of fatigue (Svensson et al., 2003; Taylor and Gandevia, 2001) and in the context of complex task demands (Roosink and Zijdewind, 2010; Svensson et al., 2003). The current age-related difference in map area was not associated with a difference in LMT (Table 2), suggesting that these results reflect an age-related difference in cortical organization rather than simply a difference in cortical excitability. Increased map area in the elderly might therefore reflect dedication of a larger amount of cortical resource for generating movement as a reaction to an age-related decline in motor behavior.

There are several limitations to the current study. Subjects with two copies of the val^{66} met polymorphism were not examined, due to their low frequency in the US population (<5%) (Shimizu et al., 2004), and so a gene-dose relationship could not be explored. Although sample sizes smaller than those used here have provided sufficient power to detect differences in brain function related to BDNF genotype (Kleim et al., 2006; McHughen et al., 2010; McHughen et al., 2011), these prior studies focused on young subjects, and the increased variability in TMS measures found in the current elderly population might have reduced study power to detect a genotype effect if one is indeed present. Serial TMS measurements were not acquired in the cohort of young subjects, although data from our prior studies (Kleim et al., 2006; McHughen et al., 2010; McHughen et al., 2011) were useful for comparisons with elderly subjects. A measure of the motor unit in the peripheral nervous system might have clarified the extent to which the current MEP measurements were strictly attributable to CNS changes. Finally, the current study did not evaluate whether BDNF genotype is associated with differences in cortical plasticity outside of motor cortex, as was suggested by a prior fMRI study (McHughen et al., 2010). Motor cortex plasticity was the focus of the current, and many prior, studies because of its central importance in many geriatric and neurological settings, and because motor cortex lends itself to assessment of plasticity, e.g., because it is highly accessible to non-invasive TMS methods. Future studies might examine whether BDNF genotype is related to plasticity in other regions of neocortex in elderly subjects.

The current study found that the val^{66} met polymorphism in the BDNF gene did not impact short-term cortical plasticity in elderly subjects, in contrast to prior studies of young subjects (Cheeran et al., 2008; Kleim et al., 2006; McHughen et al., 2010; McHughen et al., 2011). BDNF genotype effects are of interest in part because of the role this growth factor plays in a number of conditions that commonly affect elderly subjects, for example, a spontaneous

increase in brain BDNF levels after stroke is thought to contribute to spontaneous behavioral recovery (Ploughman et al., 2009). The current results in healthy subjects might not directly extend to elderly subjects with such conditions, however, as brain BDNF levels are increased in conditions such as stroke, seizure, and traumatic brain injury (Kokaia et al., 1998; Lindvall et al., 1994), and so effects of the BDNF polymorphism in elderly subjects with such diagnoses might vary from the current results in healthy subjects. The current study also described neurophysiological changes in association with healthy aging, such as enlarged motor cortex representational map area, and suggests that these changes might represent a compensatory response to maintain function.

4. Experimental Procedures

4.1 Protocol Overview

Healthy elderly subjects made two separate visits as part of study participation. At the first visit, subjects completed a series of motor behavioral assessments, and blood was collected for genotyping. At the second visit, neurophysiology and cortical plasticity were assessed as described previously (Kleim et al., 2007; Kleim et al., 2006): first, a baseline transcranial magnetic stimulation (TMS) study was performed, measuring the motor cortex representational map and neurophysiological parameters for the right FDI muscle. Next, subjects completed 30 minutes of right index finger exercises that targeted the FDI muscle, after which TMS data were reacquired to provide a measure of short-term cortical plasticity. Baseline behavior and TMS measures were also acquired in a cohort of young healthy subjects.

4.2 Subjects

Entry criteria included right handedness (Oldfield, 1971), no neurological or psychiatric diagnoses, and no contraindication to TMS (Kleim et al., 2007). Subjects provided written, informed consent using procedures approved by the Institutional Review Board. A 10 cc venous blood sample was obtained for genotyping. Subjects with 0 or 1 copy of the val^{66} met BDNF polymorphism were invited to return for full study participation. This yielded 38 elderly and 14 young subjects, none of whom were enrolled in our prior studies of BDNF genotype (Kleim et al., 2006; McHughen et al., 2010; McHughen et al., 2011).

4.3 Genotyping

BDNF genotype was determined from blood samples as described previously (Kleim et al., 2006; McHughen et al., 2010; McHughen et al., 2011). In sum, genomic DNA was extracted from leukocytes by standard DNA extraction procedure. Polymerase chain reaction amplifications of the 274-bp fragment were set up with the following forward and reverse primers (5’-aaagaagcaaacatccgaggacaag-3’, 5’-attcctccagcagaaagagaagagg- 3’). Reactions were performed in a 50 μl volume containing 50 ng of total genomic DNA as template, 0.2 mM each deoxynucleotide triphosphate, 0.5 um each of the forward and reverse primers, and 1.5 U of Taq polymerase (Roche) in its 1X supplied buffer from the manufacturer. PCR conditions were 30 cycles of 95°C for 30 s, 55°C for 30 s, and 72°C for 1 min, followed by cooling to 4°C. The initial denaturation was at 95°C for 5 min, and the final elongation was at 72°C for 5 min. PCR products were tested by gel electrophoresis on a 1% agarose gel stained with ethidium bromide.

Genotype screening was performed with denaturing high-performance liquid chromatography analysis on Transgenomic WAVE system (Transgenomic, Omaha, NE). PCR products were first denatured at 95°C for 10 min and then slowly cooled to 65°C at a rate of 1°C/min. Following this 5 min incubation at 65°C, PCR products were cooled to 4°C at a rate of 1°C every 5 s to form heteroduplexes. Temperature for successful detection of

$watermark-text $watermark-text $watermark-text

$watermark-text $watermark-text $watermark-text

heteroduplexes was calculated using the Wavemaker software package (Transgenomic) and was also experimentally determined at 60.8°C. First, we detected all heterozygous variants carriers of the polymorphism after heteroduplex formation. In order to detect homozygous carriers, PCR products were mixed with control DNA that lacked the polymorphism to form heteroduplexes and run another time through the Wave system.

Heterozygous and homozygous carriers of the polymorphism were controlled by sequencing. PCR products were purified by ExoSAP-IT® (Amersham) and directly sequenced using the PRISM™ Ready Reaction Sequencing Kit (PE Applied Biosystems) on an automatic sequencer (ABI 3130), PE Applied Biosystems). Sequence data were analyzed using Sequencher software (version 4.0.5, Genecode Corp).

4.4 Behavioral Assessments

Subjects completed a medical history questionnaire and a handedness inventory (Oldfield, 1971). Elderly subjects also completed a Mini-Mental Status Exam and the 15-item Geriatric Depression Scale (GDS), followed by five behavioral assessments: maximum rate of index finger tapping, nine-hold pegboard performance, maximum pinch grip strength, reaction time, and a driving test of cognitive/motor learning.

Three of the behavioral assessments represent fine motor tasks. Each was examined in the right (dominant) upper extremity. The first measured the maximum rate of index finger tapping, using a mechanical counter attached to a wooden board. Subjects placed the right hand firmly on the board with index finger flat on the tapping key, and with the thumb and fingers flat on the board, and were asked to tap as rapidly as possible for ten seconds, followed by a 15 second rest. After every third trial, subjects rested for two minutes. Trials were administered until five consecutive trials produced scores whose values were within five of each other, up to a maximum of ten total trials. The mean of these five trials was recorded. The second fine motor task assessed dexterity via time to complete the nine-hole pegboard. The pegboard was positioned horizontally, two peg-lengths from the edge of the table, with the center of the round container at the subject's midline and with the holes projecting laterally away from the tested hand. Subjects placed pegs into the pegboard, in any order, until all the holes were filled, and then removed the pegs, in any order, individually. Two trials were performed, separated by a one-minute rest period, with the time to complete placement/removal noted. The mean time was recorded. The third fine motor task measured maximum force of lateral pinch grip strength, using a standard pinch gauge. Subjects sat with shoulders adducted and neutrally rotated, elbow flexed at 45 degrees, forearm in neutral position, and wrist between 0 and 30 degrees dorsiflexion and between 0 and 15 degrees ulnar deviation. Subjects held a Jamar pinch dynamometer between thumb and forefinger, with thumb placed on top, and were told to squeeze down with the pad of the thumb as hard as possible. Maximum force exerted over each of three successive trials, separated with one-minute breaks, was recorded and averaged.

For reaction time testing, subjects were seated comfortably in front of a computer screen, with left arm relaxed at the side and right index finger positioned on top of a keyboard spacebar. An in-house program displayed an 'X' in the center of the screen. Subjects were instructed to press the spacebar as soon as the 'X' turned into a blue circle. Subjects completed 5 practice trials to ensure they understood the task. The test then consisted of two sets of 20 trials each, separated by a 1-minute break. The 20 trials were randomly generated to have various delays between "X" and blue circle that ranged from 500ms-3500ms. The mean reaction time across all 40 trials was noted.

The fifth behavioral assessment was a driving-based motor learning task, results of which were previously found to vary according to genotype in young subjects (McHughen et al.,

$watermark-text $watermark-text $watermark-text

2009). Current methods were identical to the prior study and in sum had subjects seated in front of a computer screen with a steering wheel (Logitech MOMO) attached to the desk. Subjects were told to use the steering wheel to keep the vehicle centered a black line down the center of the track, with a computer recording deviation from the black line as extent of error. The vehicle was programmed such that subjects had to begin turning the steering wheel *before* the track changed in order to minimize tracking errors. At the completion of each circuit, subjects were given a 10-second rest before the next circuit began. Subjects completed this circuit 15 times, each taking approximately 60 seconds.

4.5 Neurophysiology

The TMS protocol employed herein is the same as that used by our lab in prior studies (Kleim et al., 2006; McHughen et al., 2011), and follows our standard TMS protocol for serial measurements within subject (Kleim et al., 2007), summarized below.

4.5.1 Setup—Subjects were seated upright in a stereotaxic apparatus with their eyes open and right arm resting on a foam cushion. Surface electromyography was recorded from the right FDI using cup electrodes in a belly-tendon montage (gain=10,000x, bandpass filters 30–1,000 Hz) with ground electrodes over wrist and biceps. The TMS rig consisted of a Magstim 200^2 magnetic stimulator and 70-mm figure-of-eight stimulation coil (Magstim; Whitland, UK).

The protocol is designed to maximize the consistency of TMS coil placement, and the maintenance of a precise distance between stimulation sties (Kleim et al., 2007). A gender-specific T1-weighted high resolution volumetric anatomical MRI scan from a single healthy control subject was registered to each TMS subject. This was done by importing the MRI scan into Brainsight stereotactic software (Rogue Research; Montreal, QC), displaying it with a clear view of the cortical surface, then magnifying it to match the skull size of the TMS subject. TMS target markers were placed 1 cm apart within a 10×10 grid that was superimposed upon the MRI scan, in a manner that followed the contour of the brain and that included premotor and peri-Rolandic areas, then a static image of these grid markers atop the brain was produced. This static image was used to guide brain stimulation during TMS. This approach does not provide insight into the anatomical location of motor maps for the TMS subject, but it does provide a grid that improves the precision and consistency of brain stimulation.

4.5.2 Baseline TMS—The site of lowest motor threshold (SOLMT), defined as the site which required the least amount of intensity to produce a motor evoked potential (MEP) in at least six of 10 pulses (Rossini et al., 1994), was determined to the nearest 1% of stimulator output. The threshold used to define an MEP in the current study was 100 μV, as suggested by Rossini et al (Rossini et al., 1994). Once the lowest motor threshold (LMT) and its respective SOLMT were determined, the SOLMT was probed by delivering ten pulses at each of three stimulus intensity levels (110%, 130%, and 150% LMT) in a pseudorandomized order. Following this, stimulation was applied systematically at 110% LMT in 1-cm increments across the cortical surface in a spiral pattern surrounding the SOLMT. Positive sites, defined as sites which, when stimulated at 110% LMT, produced an MEP 100 μV in at least six of ten pulses, were noted. Sites which did not produce 100μV in at least six of 10 pulses were deemed negative sites, and the mapping procedure was repeated until all the positive sites were surrounded by negative sites, thus generating a motor map of cortical responses for FDI (Rossini et al., 1994). For elderly subjects, this was then followed by the below exercise paradigm and post-exercise TMS.

$watermark-text $watermark-text $watermark-text

4.5.3 Exercise Paradigm—The right FDI exercise paradigm employed herein is precisely that used in our prior studies (Kleim et al., 2006; McHughen et al., 2010; McHughen et al., 2011). Immediately following baseline TMS measures, elderly subjects completed 30 minutes of exercise targeting the right FDI, consisting of rapid movements and forceful movements. An experimenter was present to ensure proper exercise performance.

4.5.4 Post-Exercise TMS—In elderly subjects, immediately following the FDI training, TMS was again used to deliver 10 pulses at each of the three levels of stimulation, and the mapping procedure was also repeated.

4.6 Data Analysis

TMS and driving data were analyzed blinded to genotype data. For the driving game, mean tracking error, defined as the mean of the absolute value between the black line and the actual steered path, was calculated across all 15 trials, expressed as root mean squared (RMS). For TMS data, the MEP peak-to-peak amplitude was measured offline using Scope software (ADI; Colorado Springs, CO). MEP amplitude was averaged over the ten stimulations acquired at each site, for each of the three stimulation intensities. Map area was defined as described elsewhere (Kleim et al., 2007; Kleim et al., 2006). The primary TMS endpoint was map area given its established value as a robust measure of short-term cortical plasticity (Pascual-Leone et al., 1995) and its demonstrated utility for detecting differences in cortical plasticity according to BDNF genotype in young subjects (Kleim et al., 2006; McHughen et al., 2011). Secondary TMS endpoints included recruitment curve slope, calculated at baseline data for each subject using the approach of Swayne et al (Swayne et al., 2008), and MEP at the three stimulus intensity levels. Cortical plasticity was defined as the change in each TMS measure across the 30 minutes of exercise.

Statistical testing used JMP 5 (SAS, Cary, NC) and in all cases was two-tailed. The normality of distribution of data was tested using the Shapiro-Wilk W test. For differences according to age group or according to genotype group, behavioral assessments were normally distributed and were analyzed using parametric methods (t-test for continuous data, Chi Square test for categorical data), while neurophysiology data generally were not normally distributed and could not be transformed, and were analyzed using non-parametric statistical methods (differences according to age group or according to genotype were analyzed using Wilcoxon Rank Sums test for continuous data and using Chi Square test for categorical data; correlations with continuous variables were analyzed using Spearman Rank Order Correlation). Genotype effects on cortical plasticity were assessed using serial TMS studies and so were analyzed using paired testing (Wilcoxon Signed Rank test). The relative influence of age vs. BDNF genotype was examined by using these two measures as independent variables in multivariate models that used baseline neurophysiological or behavioral measures as the dependent variable.

Power estimates indicated that a sample size of 13 subjects in each of the two elderly groups was needed to have 80% power at alpha = 0.05 in order to detect a genotype-based difference in map area change of 5.8 cm^2, which is the value observed previously in young subjects undergoing the same procedures (Kleim et al., 2006), with the added assumption that variance in elderly subjects is 40% higher (Pitcher et al., 2003) than with young subjects; additional subjects were subsequently recruited.

$watermark-text
$watermark-text
$watermark-text

Acknowledgments

We thank Kristin Pearson-Fuhrhop for her assistance with data collection. This study was supported by funds provided by the National Center of Research Resources, 5M011 RR-00827-29, US Public Health Service, P50 AG16573, and by R01 NS058755.

References

Adams I. Comparison of synaptic changes in the precentral and postcentral cerebral cortex of aging humans: a quantitative ultrastructural study. Neurobiol Aging. 1987; 8:203–212. [PubMed: 3600951]

Adams, R.; Victor, M. Principles of Neurology. Vol. Vol. New York: McGraw-Hill; 1985.

Antal A, Chaieb L, Moliadze V, Monte-Silva K, Poreisz C, Thirugnanasambandam N, Nitsche MA, Shoukier M, Ludwig H, Paulus W. Brain-derived neurotrophic factor (BDNF) gene polymorphisms shape cortical plasticity in humans. Brain Stimul. 2010; 3:230–237. [PubMed: 20965453]

Benjamin S, McQuoid DR, Potter GG, Payne ME, MacFall JR, Steffens DC, Taylor WD. The brain-derived neurotrophic factor Val66Met polymorphism, hippocampal volume, and cognitive function in geriatric depression. Am J Geriatr Psychiatry. 2010; 18:323–331. [PubMed: 20220593]

Byrnes ML, Thickbroom GW, Wilson SA, Sacco P, Shipman JM, Stell R, Mastaglia FL. The corticomotor representation of upper limb muscles in writer's cramp and changes following botulinum toxin injection. Brain. 1998; 121(Pt 5):977–988. [PubMed: 9619198]

Cheeran B, Talelli P, Mori F, Koch G, Suppa A, Edwards M, Houlden H, Bhatia K, Greenwood R, Rothwell JC. A common polymorphism in the brain-derived neurotrophic factor gene (BDNF) modulates human cortical plasticity and the response to rTMS. J Physiol. 2008; 586:5717–5725. [PubMed: 18845611]

Chen J, Zhang C, Jiang H, Li Y, Zhang L, Robin A, Katakowski M, Lu M, Chopp M. Atorvastatin induction of VEGF and BDNF promotes brain plasticity after stroke in mice. J Cereb Blood Flow Metab. 2005; 25:281–290. [PubMed: 15678129]

Cotman CW, Berchtold NC. Exercise: a behavioral intervention to enhance brain health and plasticity. Trends Neurosci. 2002; 25:295–301. [PubMed: 12086747]

Doherty TJ, Vandervoort AA, Brown WF. Effects of ageing on the motor unit: a brief review. Can J Appl Physiol. 1993; 18:331–358. [PubMed: 8275048]

Drachman D. Aging and the brain: a new frontier. Ann Neurol. 1997; 42:819–828. [PubMed: 9403473]

Egan MF, Kojima M, Callicott JH, Goldberg TE, Kolachana BS, Bertolino A, Zaitsev E, Gold B, Goldman D, Dean M, Lu B, Weinberger DR. The BDNF val66met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function. Cell. 2003; 112:257–269. [PubMed: 12553913]

Eisen A, Entezari-Taher M, Stewart H. Cortical projections to spinal motoneurons: changes with aging and amyotrophic lateral sclerosis. Neurology. 1996; 46:1396–1404. [PubMed: 8628489]

Erickson KI, Prakash RS, Voss MW, Chaddock L, Heo S, McLaren M, Pence BD, Martin SA, Vieira VJ, Woods JA, McAuley E, Kramer AF. Brain-derived neurotrophic factor is associated with age-related decline in hippocampal volume. J Neurosci. 2010; 30:5368–5375. [PubMed: 20392958]

Fathi D, Ueki Y, Mima T, Koganemaru S, Nagamine T, Tawfik A, Fukuyama H. Effects of aging on the human motor cortical plasticity studied by paired associative stimulation. Clin Neurophysiol. 121:90–93. [PubMed: 19910248]

Gooney M, Messaoudi E, Maher FO, Bramham CR, Lynch MA. BDNF-induced LTP in dentate gyrus is impaired with age: analysis of changes in cell signaling events. Neurobiol Aging. 2004; 25:1323–1331. [PubMed: 15465630]

Hariri AR, Goldberg TE, Mattay VS, Kolachana BS, Callicott JH, Egan MF, Weinberger DR. Brain-derived neurotrophic factor val66met polymorphism affects human memory-related hippocampal activity and predicts memory performance. J Neurosci. 2003; 23:6690–6694. [PubMed: 12890761]

Harris SE, Fox H, Wright AF, Hayward C, Starr JM, Whalley LJ, Deary IJ. The brain-derived neurotrophic factor Val66Met polymorphism is associated with age-related change in reasoning skills. Mol Psychiatry. 2006; 11:505–513. [PubMed: 16446742]

$watermark-text
$watermark-text
$watermark-text

Hortobagyi T, del Olmo MF, Rothwell JC. Age reduces cortical reciprocal inhibition in humans. Exp Brain Res. 2006; 171:322–329. [PubMed: 16307241]

Kleim J, Kleim E, Cramer S. Systematic assessment of training-induced changes in corticospinal output to hand using frameless stereotaxic transcranial magnetic stimulation. Nature Protocols. 2007; 2:1675–1684.

Kleim JA, Chan S, Pringle E, Schallert K, Procaccio V, Jimenez R, Cramer SC. BDNF val66met polymorphism is associated with modified experience-dependent plasticity in human motor cortex. Nat Neurosci. 2006; 9:735–737. [PubMed: 16680163]

Kokaia Z, Andsberg G, Yan Q, Lindvall O. Rapid alterations of BDNF protein levels in the rat brain after focal ischemia: evidence for increased synthesis and anterograde axonal transport. Exp Neurol. 1998; 154:289–301. [PubMed: 9878168]

Li Voti P, Conte A, Suppa A, Iezzi E, Bologna M, Aniello MS, Defazio G, Rothwell JC, Berardelli A. Correlation between cortical plasticity, motor learning and BDNF genotype in healthy subjects. Experimental brain research. 2011

Lindvall O, Kokaia Z, Bengzon J, Elmer E, Kokaia M. Neurotrophins and brain insults. Trends Neurosci. 1994; 17:490–496. [PubMed: 7531892]

Mahncke HW, Bronstone A, Merzenich MM. Brain plasticity and functional losses in the aged: scientific bases for a novel intervention. Prog Brain Res. 2006; 157:81–109. [PubMed: 17046669]

McHughen SA, Rodriguez PF, Kleim JA, Kleim ED, Crespo LM, Procaccio V, Cramer SC. BDNF val66met polymorphism influences motor system function in the human brain. Cereb Cortex. 2010; 20:1254–1262. [PubMed: 19745020]

McHughen SA, Pearson-Fuhrhop K, Ngo VK, Cramer SC. Intense training overcomes effects of the val66met BDNF polymorphism on short-term plasticity. Experimental brain research. 2011; 213:415–422.

Miyajima F, Ollier W, Mayes A, Jackson A, Thacker N, Rabbitt P, Pendleton N, Horan M, Payton A. Brain-derived neurotrophic factor polymorphism Val66Met influences cognitive abilities in the elderly. Genes Brain Behav. 2008; 7:411–417. [PubMed: 17973920]

Monfils MH, Plautz EJ, Kleim JA. In search of the motor engram: motor map plasticity as a mechanism for encoding motor experience. Neuroscientist. 2005; 11:471–483. [PubMed: 16151047]

Naccarato M, Calautti C, Jones PS, Day DJ, Carpenter TA, Baron JC. Does healthy aging affect the hemispheric activation balance during paced index-to-thumb opposition task? An fMRI study. Neuroimage. 2006; 32:1250–1256. [PubMed: 16806984]

Nakamura K, Enomoto H, Hanajima R, Hamada M, Shimizu E, Kawamura Y, Sasaki T, Matsuzawa D, Sutoh C, Shirota Y, Terao Y, Ugawa Y. Quadri-pulse stimulation (QPS) induced LTP/LTD was not affected by Val66Met polymorphism in the brain-derived neurotrophic factor (BDNF) gene. Neurosci Lett. 2011; 487:264–267. [PubMed: 20970479]

Nemoto K, Ohnishi T, Mori T, Moriguchi Y, Hashimoto R, Asada T, Kunugi H. The Val66Met polymorphism of the brain-derived neurotrophic factor gene affects age-related brain morphology. Neurosci Lett. 2006; 397:25–29. [PubMed: 16388901]

Oldfield R. The assessment and analysis of handedness: The Edinburgh Inventory. Neuropsychologia. 1971; 9:97–113. [PubMed: 5146491]

Oliviero A, Profice P, Tonali PA, Pilato F, Saturno E, Dileone M, Ranieri F, Di Lazzaro V. Effects of aging on motor cortex excitability. Neurosci Res. 2006; 55:74–77. [PubMed: 16584795]

Pang PT, Lu B. Regulation of late-phase LTP and long-term memory in normal and aging hippocampus: role of secreted proteins tPA and BDNF. Ageing Res Rev. 2004; 3:407–430. [PubMed: 15541709]

Pascual-Leone A, Nguyet D, Cohen L, Brasil-Neto J, Cammarota A, Hallett M. Modulation of muscle responses evoked by transcranial magnetic stimulation during the acquisition of new fine motor skills. J Neurophysiol. 1995; 74:1037–1045. [PubMed: 7500130]

Patterson SL, Abel T, Deuel TA, Martin KC, Rose JC, Kandel ER. Recombinant BDNF rescues deficits in basal synaptic transmission and hippocampal LTP in BDNF knockout mice. Neuron. 1996; 16:1137–1145. [PubMed: 8663990]

Peinemann A, Lehner C, Conrad B, Siebner H. Age-related decrease in paired-pulse intracortical inhibition in the human primary motor cortex. Neurosci Lett. 2001; 313:33–36. [PubMed: 11684333]

Pezawas L, Verchinski BA, Mattay VS, Callicott JH, Kolachana BS, Straub RE, Egan MF, Meyer-Lindenberg A, Weinberger DR. The brain-derived neurotrophic factor val66met polymorphism and variation in human cortical morphology. J Neurosci. 2004; 24:10099–10102. [PubMed: 15537879]

Pitcher JB, Ogston KM, Miles TS. Age and sex differences in human motor cortex input-output characteristics. J Physiol. 2003; 546:605–613. [PubMed: 12527746]

Ploughman M, Windle V, MacLellan CL, White N, Dore JJ, Corbett D. Brain-derived neurotrophic factor contributes to recovery of skilled reaching after focal ischemia in rats. Stroke. 2009; 40:1490–1495. [PubMed: 19164786]

Rex CS, Kramar EA, Colgin LL, Lin B, Gall CM, Lynch G. Long-term potentiation is impaired in middle-aged rats: regional specificity and reversal by adenosine receptor antagonists. J Neurosci. 2005; 25:5956–5966. [PubMed: 15976084]

Rogasch NC, Dartnall TJ, Cirillo J, Nordstrom MA, Semmler JG. Corticomotor plasticity and learning of a ballistic thumb training task are diminished in older adults. J Appl Physiol. 2009; 107:1874–1883. [PubMed: 19833810]

Roosink M, Zijdewind I. Corticospinal excitability during observation and imagery of simple and complex hand tasks: Implications for motor rehabilitation. Behav Brain Res. 2010

Rossini PM, Barker AT, Berardelli A, Caramia MD, Caruso G, Cracco RQ, Dimitrijevic MR, Hallett M, Katayama Y, Lucking CH, et al. Non-invasive electrical and magnetic stimulation of the brain, spinal cord and roots: basic principles and procedures for routine clinical application. Report of an IFCN committee. Electroencephalogr Clin Neurophysiol. 1994; 91:79–92. [PubMed: 7519144]

Sawaki L, Yaseen Z, Kopylev L, Cohen LG. Age-dependent changes in the ability to encode a novel elementary motor memory. Ann Neurol. 2003; 53:521–524. [PubMed: 12666120]

Shimizu E, Hashimoto K, Iyo M. Ethnic difference of the BDNF 196G/A (val66met) polymorphism frequencies: the possibility to explain ethnic mental traits. Am J Med Genet B Neuropsychiatr Genet. 2004; 126:122–123. [PubMed: 15048661]

Silhol M, Bonnichon V, Rage F, Tapia-Arancibia L. Age-related changes in brain-derived neurotrophic factor and tyrosine kinase receptor isoforms in the hippocampus and hypothalamus in male rats. Neuroscience. 2005; 132:613–624. [PubMed: 15837123]

Svensson P, Romaniello A, Arendt-Nielsen L, Sessle B. Plasticity in corticomotor control of the human tongue musculature induced by tongue-task training. Exp Brain Res. 2003; 152:42–51. [PubMed: 12830348]

Swayne OB, Rothwell JC, Ward NS, Greenwood RJ. Stages of motor output reorganization after hemispheric stroke suggested by longitudinal studies of cortical physiology. Cereb Cortex. 2008; 18:1909–1922. [PubMed: 18234688]

Talelli P, Ewas A, Waddingham W, Rothwell JC, Ward NS. Neural correlates of age-related changes in cortical neurophysiology. Neuroimage. 2008; 40:1772–1781. [PubMed: 18329904]

Tamburin S, Manganotti P, Marzi CA, Fiaschi A, Zanette G. Abnormal somatotopic arrangement of sensorimotor interactions in dystonic patients. Brain. 2002; 125:2719–2730. [PubMed: 12429599]

Tapia-Arancibia L, Aliaga E, Silhol M, Arancibia S. New insights into brain BDNF function in normal aging and Alzheimer disease. Brain Res Rev. 2008; 59:201–220. [PubMed: 18708092]

Taylor JL, Gandevia SC. Transcranial magnetic stimulation and human muscle fatigue. Muscle Nerve. 2001; 24:18–29. [PubMed: 11150962]

Ward N, Frackowiak R. Age-related changes in the neural correlates of motor performance. Brain. 2003; 126:873–888. [PubMed: 12615645]

Webster MJ, Herman MM, Kleinman JE, Shannon Weickert C. BDNF and trkB mRNA expression in the hippocampus and temporal cortex during the human lifespan. Gene Expr Patterns. 2006; 6:941–951. [PubMed: 16713371]

Zhang Y, Pardridge WM. Blood-brain barrier targeting of BDNF improves motor function in rats with middle cerebral artery occlusion. Brain Res. 2006; 1111:227–229. [PubMed: 16884698]

$watermark-text $watermark-text $watermark-text

Zhao L, Risedal A, Wojcik A, Hejzlar J, Johansson B, Kokaia Z. Enriched environment influences brain-derived neurotrophic factor levels in rat forebrain after focal stroke. Neurosci Lett. 2001; 305:169–172. [PubMed: 11403932]

$watermark-text
$watermark-text
$watermark-text

Elderly subjects had larger motor cortex maps and smaller motor evoked potentials.

Age-related changes in neurophysiology correlated inversely with motor behavior.

Cortical plasticity did not differ in relation to BDNF genotype in elderly subjects.

$watermark-text

$watermark-text

$watermark-text

$watermark-text
$watermark-text
$watermark-text

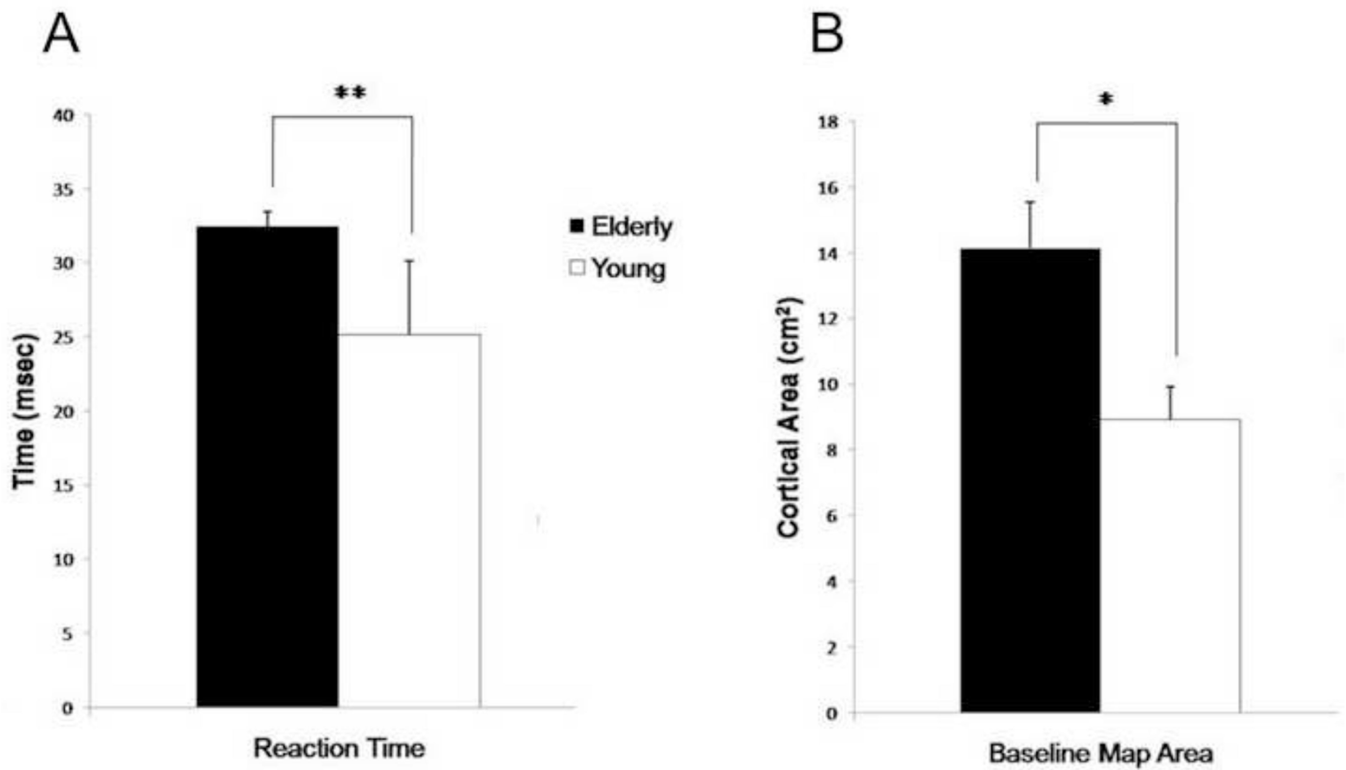

Figure 1.
Baseline differences between elderly and young subjects in neurophysiological and behavioral measures. Elderly subjects show significantly (A) slower reaction time and (B) larger baseline map area as compared to young subjects. Values are mean ± SEM. *P 0.03. **P 0.0001.

$watermark-text
$watermark-text
$watermark-text

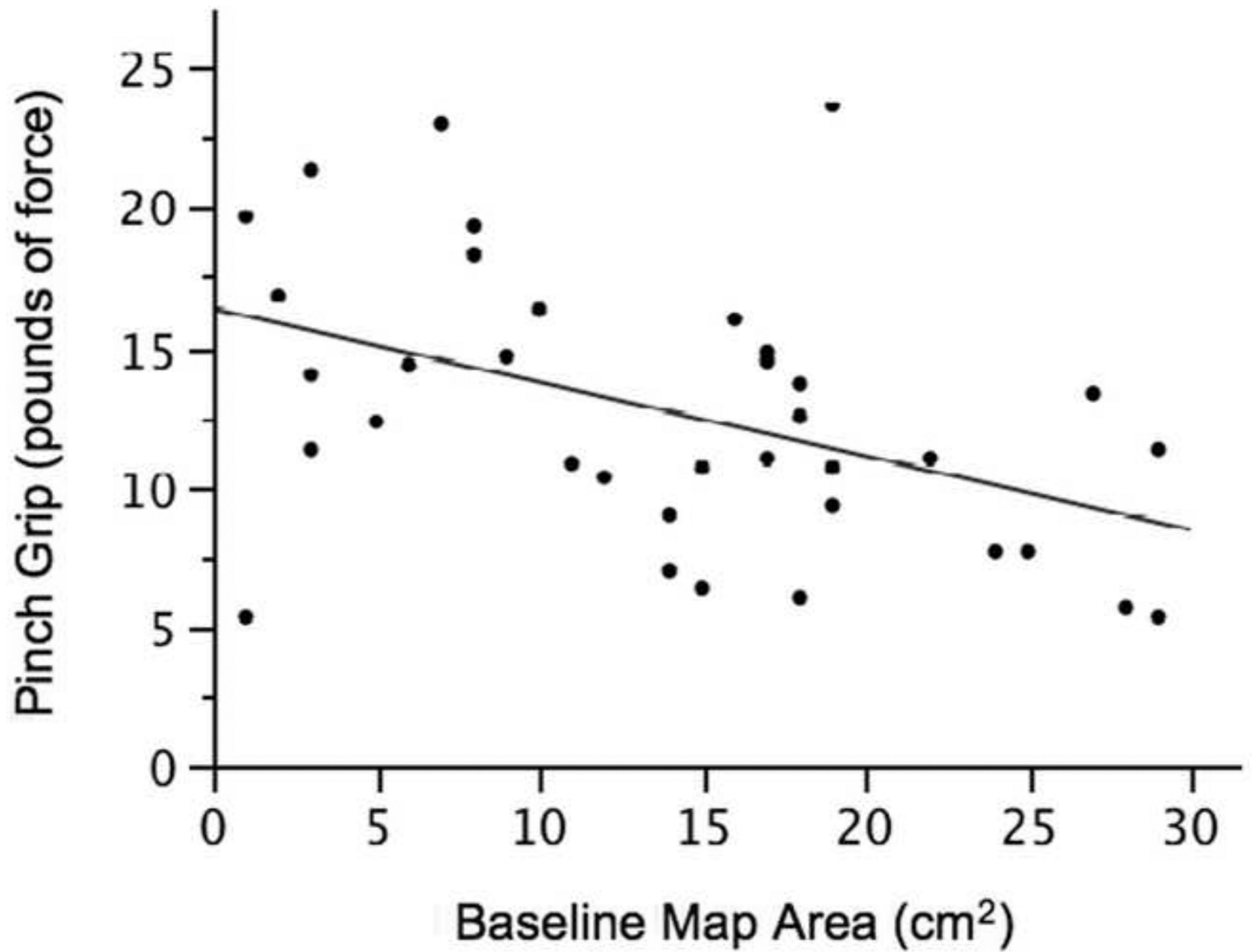

Figure 2.

Bivariate analysis of pinch grip force as a function of baseline cortical map area for the right FDI muscle among elderly subjects. Larger map area correlated significantly with weaker pinch grip (rho = −0.42, P=0.01).

$watermark-text
$watermark-text
$watermark-text

Table 1

Subject Demographics and Baseline Behavior

	Elderly	Young	t (DF) / X^2	p
n	38	14		
Age (years)	73.2 ± 1.8	24.3 ± 1.1	−16.4 (50)	<0.0001
Gender (M/F)	14/24	7/7	0.73	0.39
Ethnicity			8.2	0.04
Asian	2	4		
Caucasian	34	8		
Hispanic	2	2		
Handedness	1.92 ± 0.03	1.96 ± 0.05	0.72 (50)	0.47
Pegboard (seconds)	21.9 ± 0.5	17.3 ± 0.9	−4.3 (50)	<0.0001
Finger tapping rate (Hz)	37.0 ± 1.3	46.1 ± 2.2	3.7 (50)	0.0006
Force of pinch grip (pounds)	12.5 ± 0.8	18.4 ± 1.1	3.9 (50)	0.0003
Speed of reaction time (milliseconds)	324 ± 7	252 ± 12	−5.4 (50)	<0.0001
Error across 15 driving laps	0.31 ± 0.03	0.10 ± 0.01	−3.9 (50)	<0.0005

Values are mean ± SEM. In column 4, for continuous variables, "t" provides the value for the t ratio and "DF" provides degrees of freedom; for categorical variables, X^2 provides the value for Chi Squared. Pegboard scores are time to complete the 9-hole pegboard test, in seconds. Handedness scores indicate subjects were strongly right-handed, as −2=Left-handed and +2=Right-Handed. Two scales that were tested only in elderly subjects were the Geriatric Depression Scale (0.9 ± 0.2) and the Mini-Mental Status Exam (29.1 ± 0.2). M = male, F = female, Hz = Hertz.

$watermark-text

$watermark-text

$watermark-text

Table 2

Effect of Age on Neurophysiology Measures at Baseline

	Elderly	Young	X^2	p
n	38	14		
LMT (% device output)	45 ± 1.4	45 ± 2.3	0.07	0.79
Map Area (cm^2)	14.14 ± 1.23	8.93 ± 1.97	4.59	0.03
MEP at 110% (mV)	2.59 ± 0.29	3.78 ± 0.47	4.26	0.039
MEP at 130% (mV)	6.32 ± 0.42	7.04 ± 0.69	0.49	0.48
MEP at 150% (mV)	7.78 ± 0.35	8.53 ± 0.57	1.31	0.25
Recruitment curve slope	0.13 ± 0.007	0.14 ± 0.008	0.09	0.76

Values are mean ± SEM. Column 4 presents the X^2 approximation used to calculate the p value in the Wilcoxon Rank Sums test.

$watermark-text
$watermark-text
$watermark-text

Table 3

Association of BDNF Genotype with Behavior, Neurophysiology, and Cortical Plasticity in Elderly Subjects

	Polymorphism absent	Polymorphism present	t (DF) / X^2	p
n	25	13		
Age (years)	75.0 ± 1.8	70 ± 3.8	1.5 (36)	0.15
Baseline measures				
Geriatric Depression Scale	0.8 ± 0.3	1.0 ± 0.3	−0.32 (36)	0.75
Mini-Mental Status Exam	29 ± 0.2	29 ± 0.3	0.30 (36)	0.76
Pegboard (seconds)	21.7 ± 0.8	22.1 ± 1.0	−0.27 (36)	0.79
Maximum finger tapping rate (Hz)	36.1 ± 1.5	38.8 ± 2.1	−1.1 (36)	0.29
Pinch grip force (pounds)	11.9 ± 1.0	13.5 ± 1.3	−0.91 (36)	0.37
Speed of reaction time (milliseconds)	318 ± 10	336 ± 11	−1.2 (36)	0.25
Error across 15 driving laps	0.32 ± 0.05	0.31 ± 0.06	0.002	0.97
LMT (% output)	44 ± 1.6	46 ± 2.8	−0.77 (36)	0.79
Map area (cm^2)	15.6 ± 1.6	115. ± 2.5	1.5 (36)	0.14
MEP at 110% (mV)	2.6 ± 0.35	2.6 ± 0.49	0.11 (36)	0.91
MEP at 130% (mV)	6.4 ± 0.53	6.2 ± 0.85	0.14 (36)	0.75
MEP at 150% (mV)	8.2 ± 0.44	7.0 ± 0.67	1.5 (36)	0.13
Recruitment curve slope	0.14 ± 0.008	0.12 ± 0.01	1.2 (36)	0.24
Change with 30 minutes of exercise				
Change in map area (cm^2)	1.7 ± 1.6	2.3 ± 2.0	0.2	0.70
Change in MEP at 110% (mV)	−0.12 ± 0.47	0.42 ± 0.75	0.2	0.67
Change in MEP at 130% (mV)	0.20 ± 0.78	−0.15 ± 0.59	0.5	0.46
Change in MEP at 150% (mV)	0.61 ± 0.42	0.27 ± 0.36	0.2	0.62

Values are mean ± SEM. In column 4, for behavioral variables and age, “t” provides the value for the t ratio and “DF” provides degrees of freedom; for neurophysiological variables, X^2 provides the X^2 approximation used in the Wilcoxon Rank Sums test. Change in TMS measures refers to measurements before vs. after 30-minutes of exercise targeting the right FDI muscle; for these measures, n=32 (20 without and 12 with the polymorphism). Hz = Hertz, mV = millivolts.