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Interindividual variability in response to continuous theta-burst stimulation (cTBS) in healthy adults

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Abstract

Objective—We used complete-linkage cluster analysis to identify healthy subpopulations with distinct responses to continuous theta-burst stimulation (cTBS).

Methods—21 healthy adults (age±*SD*, 36.9±15.2 years) underwent cTBS of left motor cortex. Natural log-transformed motor evoked potentials (LnMEPs) at 5–50 minutes post-cTBS (T5–T50) were calculated.

Results—Two clusters were found; Group 1 (n=12) that showed significant MEP facilitation at T15, T20, and T50 (*p*'s<.006), and Group 2 (n=9) that showed significant suppression at T5–T15 (*p*'s<.022). LnMEPs at T10 and T40 were best predictors of, and together accounted for 80% of, cluster assignment.

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Conflict of Interest Statement

A.P.-L. serves on the scientific advisory boards for Magstim, Nexstim, Neuronix, Starlab Neuroscience, Neuroelectrics, Axilum Robotics, Constant Therapy, and Neosync; and is listed as inventor on several issued and pending patents on real-time integration of transcranial magnetic stimulation (TMS) with electroencephalography (EEG) and magnetic resonance imaging. A.R. is a founder and advisor for Neuromotion, serves on the medical advisory board for NeuroRex, and is listed as inventor on a patent related to integration of TMS and EEG. The remaining authors declare no competing interests.

In an exploratory analysis, we examined the roles of brain-derived neurotrophic factor (*BDNF*) and apolipoprotein E (*APOE*) polymorphisms in the cTBS response. Val66Met participants showed greater facilitation at T10 than Val66Val participants (p=.025). *BDNF* and cTBS intensity predicted 59% of interindividual variability in LnMEP at T10. *APOE* did not significantly affect LnMEPs at any time point (p's>.32).

Conclusions—Data-driven cluster analysis can identify healthy subpopulations with distinct cTBS responses. T10 and T40 LnMEPs were best predictors of cluster assignment. T10 LnMEP was influenced by *BDNF* polymorphism and cTBS intensity.

Significance—Healthy adults can be sorted into subpopulations with distinct cTBS responses that are influenced by genetics.

Keywords

transcranial magnetic stimulation; continuous theta-burst stimulation; plasticity; interindividual variability; cluster analysis; *BDNF*

1. Introduction

Transcranial magnetic stimulation (TMS) is a form of noninvasive brain stimulation through electromagnetic induction. TMS was originally developed as a neurophysiological tool to investigate the integrity of corticospinal pathways in humans (Barker et al., 1985). When applied within the recommended guidelines (Rossi et al., 2009; Rossini et al., 2015), TMS provides a safe means to trigger or modulate neural activity. A single TMS pulse applied to the primary motor cortex (M1) can generate a compound muscle action potential in a target muscle, referred to as the motor evoked potential (MEP). Various TMS protocols have been designed to study neural processes, including plasticity, in the motor and non-motor systems by applying single, paired, or repetitive TMS pulses at specific intensities and frequencies to one or more cortical areas.

Theta burst stimulation (TBS) is a form of repetitive TMS developed more than ten years ago (Huang et al., 2005). TBS was originally conceived based on the 4–7 Hz burst discharge (the theta range in electroencephalography) recorded from the hippocampus of rats during exploratory behavior (Diamond et al., 1988) and used to study synaptic plasticity in animal brain slices (Larson and Lynch, 1986, 1989; Capocchi et al., 1992). TBS consists of 50Hz bursts of three TMS pulses repeated every 200ms (at 5 Hz), for a total of 600 pulses, in one of two protocols: (1) a 2-sec on, 8-sec off intermittent TBS (iTBS) pattern for 190 sec, which in most individuals increases MEP amplitude by approximately 35% for up to 60 min, or (2) a continuous TBS (cTBS) pattern for 40 sec, which can reduce MEP amplitude by approximately 25% for up to 50 min (Wischnewski and Schutter, 2015). Suppression of MEPs by cTBS and their enhancement by iTBS are considered indices of long-term depression- (LTD-) and long-term potentiation- (LTP-) like mechanisms, respectively (Huang et al., 2005; Huerta and Volpe, 2009). Once MEP amplitudes have been altered by cTBS, the time it takes for MEP amplitudes to return to their baseline levels is considered a neurophysiologic index of the mechanisms of cortical plasticity (Oberman et al., 2010; Pascual-Leone et al., 2011; Wischnewski and Schutter, 2015; Suppa et al., 2016).

Application of cTBS to M1 and other brain areas has been used to measure abnormalities in cortical plasticity and to assess therapeutic responses to interventions aimed at restoring normal cortical plasticity in several neurological and psychiatric disorders, including Alzheimer's disease (Freitas et al., 2011a), autism spectrum disorders and fragile X syndrome (Oberman et al., 2010, 2012, 2014, 2016), dementia (Cantone et al., 2014), epilepsy (Carrette et al., 2016), essential tremor (Chuang et al., 2014), hemispatial neglect (Cazzoli et al., 2012; Koch et al., 2012), major depression (Li et al., 2014), multiple sclerosis (Mori et al., 2013), obsessive-compulsive disorders (Wu et al., 2010; Suppa et al., 2014), Parkinson's disease (Koch et al., 2009), schizophrenia (Poulet et al., 2009; Eberle et al., 2010; McClintock et al., 2011), stroke (Ackerley et al., 2010; Hsu et al., 2012; Di Lazzaro et al., 2013, 2016), tinnitus (Forogh et al., 2014), and Tourette syndrome (Suppa et al., 2014).

Despite the numerous TBS studies conducted among clinical populations, there is large interindividual variability in TBS response among healthy individuals that remains largely unexplained (Hamada et al., 2013; Hinder et al., 2014; López-Alonso et al., 2014). Given such high interindividual variability, it has been estimated that in order to reliably detect a 20% difference in M1 TBS response between two groups, each group may need to have at least 30 participants (Suppa et al., 2016), which is a larger sample size than used in most previous TBS studies (Wischnewski and Schutter, 2015). The large interindividual variability in TBS response among healthy individuals and, consequently, the relatively large sample sizes required to detect a meaningful difference, can limit the utility of TBS in the assessment of mechanisms of plasticity in healthy individuals and patients with neuropsychiatric disorders.

Several factors have been suggested as potential contributors to the interindividual variability in response to TBS, including the activated intracortical networks (Hamada et al., 2013), functional connectivity in the motor system (Nettekoven et al., 2014, 2015), state-dependent factors (Suppa et al., 2016), and single-nucleotide polymorphisms (SNPs) that can influence neuroplasticity.

Brain-derived neurotrophic factor (*BDNF*) is the most abundantly available protein of the neurotrophine family (Allen and Dawbarn, 2006) and critically involved in *N*-methyl-*D*-aspartate (NMDA)-type glutamate receptor-dependent LTP (Figurov et al., 1996) and LTD (Woo et al., 2005). A frequent *BDNF* polymorphism (Val66Met) influences the intracellular trafficking and packaging of the precursor peptide (pro-*BDNF*), which is associated with LTD, and the regulated secretion of the mature (m)*BDNF*, involved in LTP (Egan et al., 2003; Bramham and Messaoudi, 2005). Several studies have shown effects of *BDNF* polymorphism on neuroplasticity in humans, including reduced hippocampal plasticity and activity-dependent secretion of *BDNF* (Egan et al., 2003), reduced training-dependent facilitation of MEPs (Kleim et al., 2006; Lee et al., 2013), reduced cTBS-induced suppression (Cheeran et al., 2008) and iTBS-induced facilitation of MEPs (Cheeran et al., 2008; Antal et al., 2010; Lee et al., 2013; Di Lazzaro et al., 2015), reduced plasticity induced by paired associative stimulation (Cirillo et al., 2012), and reduced rTMS-induced motor recovery after stroke (Chang et al., 2014).

Apolipoprotein E (*APOE*) codes for a protein component of triglyceride-rich lipoproteins and is an important factor in cholesterol metabolism (Mahley, 1988). *APOE* has three major alleles (ε2, ε3, and ε4), and the presence of its ε4 allele is a major risk factor for Alzheimer's disease (AD; Poirier et al., 1993; Saunders et al., 1993). Functional consequences of the presence of *APOE* ε4 in the central nervous system include poor clinical outcome after acute head trauma and stroke (Mahley and Rall Jr, 2000), reduced neuronal and hippocampal plasticity (White et al., 2001; Nichol et al., 2009), greater impairment in episodic memory among AD patients (Wolk et al., 2010), and differential patterns of rTMS-induced activation (Peña-Gomez et al., 2012).

To investigate the contributors to interindividual variability in TBS response without unfeasibly large sample sizes, one option may be to use statistical approaches such as cluster analyses (Kaufman and Rousseeuw, 2009; Rencher and Christensen, 2012). Due to their data-driven nature, cluster analyses can identify subpopulations of individuals with distinct patterns of response to TBS in a manner that is minimally biased by *a priori* hypotheses. The resulting subpopulations can then be compared against each other in terms of potentially important predictors. Identifying subpopulations that are more similar in their TBS response can increase the power of TBS studies that investigate differences between healthy individuals and clinical populations. In the present study, we examined the utility of cluster analysis, in the form of complete-linkage cluster analysis, for identification of subpopulations of healthy individuals with distinct patterns of response to cTBS.

As an exploratory analysis, we also assessed the effects of *BDNF* and *APOE* polymorphisms on interindividual variability in cTBS-induced plasticity. We did not set out to determine which genetic variants (from among numerous plausible genes) are associated with a particular trait, disease, or outcome measure. Rather, we aimed to test the specific hypothesis that these two well-characterized genetic polymorphisms described in signalling pathways that mediated cortical plasticity (Kleim et al., 2006; Cheeran et al., 2008; Antal et al., 2010; Li Voti et al., 2011; Cirillo et al., 2012; Peña-Gomez et al., 2012; Witte et al., 2012; Lee et al., 2013; Chang et al., 2014; Di Lazzaro et al., 2015) also contributed to the interindividual variability in response to cTBS. Since certain clinical populations, including individuals with Alzheimer's disease, autism spectrum disorders, schizophrenia, and type-2 diabetes show TBS-induced hyper- or hypoplasticity (Freitas et al., 2011a; McClintock et al., 2011; Oberman et al., 2012; Fried et al., 2017), examining the effects of these polymorphisms on cTBS-induced plasticity would allow for comparing them between healthy individuals and clinical populations in the future.

2. Methods

2.1. Participants

21 healthy adults participated in the study that was conducted in accordance with the Declaration of Helsinki and was approved by the local Institutional Review Board. All participants provided written informed consent prior to enrollment and received monetary compensation upon completion. None of the participants had a history of medical disease or contraindication to TMS, and all of them had normal physical and neurological examinations.

Participants were predominantly male (19 out of 21) because they had been recruited as neurotypical controls in a larger ongoing study that involved individuals with ASD who were predominantly male. To maintain comparability in gender ratio between the two groups, it was necessary to have predominantly male participants in the neurotypical group as well.

2.2. Neuropsychological testing

Mini-Mental State Examination (MMSE) (Folstein et al., 1975; Crum et al., 1993) and the Abbreviated Battery of Stanford-Binet IV intelligence scale, consisting of Verbal Knowledge and Nonverbal Fluid Reasoning subscores (Thorndike et al., 1986) were conducted.

2.3. Genetic analyses

Saliva samples from 18 out of the 21 participants were used to assess brain-derived neurotrophic factor (*BDNF*) Val66Met polymorphism and the presence of apolipoprotein-E (*APOE*) ε4 allele. Two participants did not consent to providing DNA samples and one sample was deemed unusable.

Aliquot (700μL) extraction of genomic DNA was performed on saliva samples collected using the Oragene Discover OGR-250 Kit (DNA Genotek Inc., Ottawa, ON, Canada). DNA was extracted from samples using standard methodology and the prepIT•L2P reagent (DNA Genotek Inc., 2015). The following quality control metrics were performed on each sample: PicoGreen fluorometry for double stranded DNA quantification, Nanodrop spectrophotometry as an estimate of sample purity using A260/A280 ratios and agarose gel electrophoresis for visualization of DNA integrity. The rs6265 SNP of the *BDNF* gene, the rs429358 and the rs7412 SNPs of the *APOE* gene were analyzed using a TaqMan single tube genotyping assay, which uses polymerase chain reaction (PCR) amplification and a pair of fluorescent dye detectors that target the SNP. One fluorescent dye is attached to the detector that is a perfect match to the first allele and a different fluorescent dye is attached to the detector that is a perfect match to the second allele. During PCR, the polymerase releases the fluorescent probe into solution where it is detected using endpoint analysis in an Applied Biosystems, Inc. (Foster City, CA, USA) 7900HT Real-Time instrument. Primers and probes were also obtained through Applied Biosystems.

Exact tests for deviations of *BDNF* and *APOE* SNPs from Hardy-Weinberg equilibrium (HWE) proportions (Guo and Thompson, 1992; Wigginton et al., 2005) were conducted in Python for Population Genomics (PyPop) software version 0.7.0 (Lancaster et al., 2003, 2007), implementing a Markov chain Monte-Carlo (MCMC) with 2000 dememorization steps, 1000 chain samples, and a chain sample size of 1000 (for a total of 1,000,000 steps).

The Ewens–Watterson homozygosity tests of neutrality (Ewens, 1972; Watterson, 1978) were conducted in PyPop using the Slatkin's implementation (Slatkin, 1994). Fisher's exact tests were used to compare the minor allele frequencies of rs6265 (*BDNF*), rs429358 (*APOE*), and rs7412 (*APOE*) SNPs against the corresponding frequencies in the admixed American (AMR) population in the 1000 Genomes Project (1KGP) (Auton et al., 2015), i.e., 0.1527, 0.1037, and 0.0476, respectively.

2.4. Transcranial magnetic stimulation

Participants were seated in a comfortable chair with the right arm and hand in a pronated position on a pillow. They were instructed to keep their right hand as still and relaxed as possible throughout the experiment.

All study parameters followed the current guidelines for the safe application of TMS recommended by the International Federation of Clinical Neurophysiology (Rossi et al., 2009; Rossini et al., 2015). Single TMS pulses and cTBS were applied to the left primary motor cortex as biphasic pulses with the current flowing in the brain with antero-posterior and then postero-anterior (AP-PA) direction by a MagPro X100 stimulator (with the current direction set to 'Normal') and a MC-B70 Butterfly Coil (outer diameter: 97mm; MagPro, MagVenture A/S, Farum, Denmark). Note that this direction is opposite to most commercial rTMS stimulators. The coil was held tangentially to the participant's head surface, with the handle pointing occipitally and positioned at 45° relative to the mid-sagittal axis of the participant's head. With this orientation, the induced electric current flows perpendicular to the central sulcus and results in achieving the lowest motor threshold. The optimal spot for the maximal responses of the right first dorsal interosseous muscle (FDI) was localized. A Polaris infrared-optical tracking system (Northern Digital Inc., Waterloo, ON, Canada) and a Brainsight TMS neuronavigation system (Rogue Research Inc., Montreal, QC, Canada) with a brain MRI template was used to ensure consistent targeting throughout the experiment.

To collect electromyogram (EMG) signal, two surface electrodes were placed on the belly and on the tendon of the right FDI and connected to a PowerLab 4/25T data acquisition device (ADInstruments, Colorado Springs, CO, USA). The TMS system delivered triggered pulses that synchronized the TMS and EMG systems. EMG data were digitized at 1 kHz for 500 ms following each stimulus trigger and 100 ms pre-trigger, amplified with a range of ± 10 mV (band-pass filter 0.3–1000 Hz). Peak-to-peak MEP amplitude of the non-rectified signal was calculated on individual waveforms using LabChart 8 software (ADInstruments, Colorado Springs, CO, USA). Live EMG was monitored in order to maintain hand relaxation throughout the experiment. The participants were also monitored for drowsiness and asked to keep their eyes open throughout the experiment.

Resting motor threshold (RMT) and active motor threshold (AMT) were measured individually and used to set the intensity of subsequent stimulation. RMT was defined as the lowest intensity of stimulation that elicited motor evoked potentials (MEPs) ≥ 50 μV in at least five of ten pulses in the relaxed right FDI, and AMT was defined as the lowest intensity that elicited MEPs ≥ 200 μV in at least five of ten pulses with the FDI slightly contracted.

Single TMS pulses were applied at 120% of individual RMT and were separated by a random 4–6 s interval. The cTBS protocol consisted of bursts of three pulses of 50Hz stimulation at 80% of individual AMT, repeated at 200ms inter-burst intervals for 40 seconds (for a total of 600 pulses). This protocol has been shown to inhibit cortico-motor reactivity for up to 50 minutes in healthy individuals (Huang et al., 2005; Oberman et al., 2010, 2012, 2016; Wischnewski and Schutter, 2015). Prior to cTBS, participants received three blocks of 30 single TMS pulses. There was a 5–min interval between the onsets of successive blocks. The peak-to-peak amplitude of each MEP was measured and averaged for

each participant as a measure of baseline cortico-motor reactivity. To control the effects of voluntary hand movements on cTBS aftereffects (Iezzi et al., 2008), there was a 5-min break between the AMT measurement and the onset of cTBS, during which participants were instructed to maintain hand relaxation.

Following cTBS, cortico-motor reactivity was reassessed in blocks of 30 single TMS pulses at 5, 10, 15, 20, 30, 40, and 50 minutes (*T5*, *T10*, etc.). The timing of each block was centered on the time point of interest. For each block, individual MEPs > 2.5 SD from the mean were excluded.

2.5 Statistical analyses

Stata software version 13.1 (StataCorp, College Station, TX, USA) was used for statistical analyses. TMS data included two motor thresholds (RMT and AMT), assessed in terms of the percent of maximum stimulator output, one measure of baseline cortico-motor reactivity (average baseline MEP amplitude), and seven post-cTBS time-points (T5–T50), with the average amplitude of MEPs at each time-point normalized by forming a ratio of MEP amplitudes after TBS relative to the average baseline MEP amplitude for each participant. The Shapiro–Wilk test found significant deviations from normal distribution; thus, natural log-transformed data were used for statistical analyses. Log-transformed, baseline-corrected MEP amplitudes at each of the seven post-cTBS time points (*LnMEP)* were averaged over all participants. Additional analyses were conducted on LnMEP values at T5 and T10 as they commonly exhibit the maximal effect of cTBS (Wischnewski and Schutter, 2015). Additional analyses were also conducted on LnMEP values at T40 and T50 considering the results of some of the analyses. All comparisons of proportions were conducted with Fisher's exact test. All analyses were two-tailed, and the α level was set to 0.05.

To identify potential subpopulations of healthy adults with distinct patterns of response to cTBS, cluster analyses were performed on the MEP data. In hierarchical agglomerative clustering methods, observations are clustered into larger and larger groups by progressively lowering the threshold for determining whether two or more observations are similar enough to belong to the same group. As more and more observations are grouped together, the dissimilarity among members of each cluster is increased (Rencher and Christensen, 2012).

The clustering algorithm results in a *dendrogram* (or cluster tree) that illustrates which observations are clustered at different levels of dissimilarity (Figure 1). Each observation belongs to its own cluster at the bottom of the hierarchy. Moving up in the dendrogram, observations are linked via horizontal lines to form progressively larger clusters until they are all grouped together at the top of the cluster tree. The length of the vertical lines extending from the observations, as well as the range of the dissimilarity axis, indicate the dissimilarity between the groups (StataCorp, 2013).

Complete-linkage clustering method, previously used in an rTMS study (Gangitano et al., 2002), calculates the (dis)similarity between every pair of clusters at each step, as measured by the Euclidean distance between the farthest pair of observations in each pair of clusters, and joins the two clusters with the smallest distance from each other (Kaufman and Rousseeuw, 2009; Rencher and Christensen, 2012).

To avoid bias in selecting the time points for the cluster analysis, all time points from T5 through T50 were included in the analysis. A recent meta-analysis found that cTBS aftereffects on average last approximately 50 min among healthy individuals (Wischnewski and Schutter, 2015). LnMEPs at each of the seven post-cTBS time points were averaged separately for each of the two clusters, were compared against zero using one-sample *t* tests, and were compared against each other using two-sample *t*-tests. False discovery rate (FDR) was used to adjust *p* values for multiple testing (Simes, 1986; Benjamini and Hochberg, 1995; Benjamini and Yekutieli, 2001).

To determine the time point(s) at which the LnMEPs had the most discriminatory power, i.e., would best predict the participants' assignment to one of the clusters, we conducted multiple logistic regression analyses of clusters with LnMEP at each of the seven time points as a predictor and then calculated the pseudo-R^2 for each model (McFadden, 1973).

To reduce the probability of failure in identifying important confounding variables (Bendel and Afifi, 1977; Mickey and Greenland, 1989), selecting covariates for potential inclusion in the linear and logistic regression models was based on a *p*-value cutoff of 0.25 for univariate regression (Bursac et al., 2008). Neurophysiologically important measures including RMT, AMT, and baseline MEP amplitude were always considered for potential inclusion in the model as covariates. RMT and AMT were highly correlated (R_{21} = 0.67, $p < .001$) and were never included in the same model to avoid multicollinearity. Given the sample size, up to three predictors were considered for simultaneous inclusion in any regression model.

3. Results

Demographics, single-nucleotide polymorphisms, and neuropsychological measures for individual participants are presented in Table 1. Descriptive statistics for those measures and baseline neurophysiological measures are presented in Table 2.

3.1. Genetic analyses

Among 18 participants with available *BDNF* and *APOE* results, the frequencies of *BDNF* Val/Val and Val/Met genotypes were 0.67 and 0.33, respectively, while the frequencies of *APOE* ε3/ε4, ε3/ε3, and ε2/ε3 genotypes were 0.44, 0.39, and 0.17, respectively.

None of the three SNPs (rs6265, rs429358 and rs7412) significantly deviated from HWE proportions (all *p*'s > .52) or from neutrality (all *p*'s > .31). Similarly, Fisher's exact tests did not find a significant difference between the ratio of major: minor alleles of any of the SNPs in our participants and the expected ratio of those alleles based on the AMR population in the 1KGP (all *p*'s > .33).

3.2. cTBS-induced plasticity results

Grand-average cTBS-induced plasticity results are shown in Figure 2. The overall results did not show a statistically significant change in cortico-motor reactivity at any of the seven time points following cTBS (all *p*'s > .18). There was no significant association between any of the demographic, neuropsychological or baseline neurophysiological measures listed in Table 2 and LnMEP at T5 or T10 (all *p*'s > .10).

Multiple regression analyses of LnMEP at T5 or T10 with AMT and baseline MEP amplitude as predictors did not result in a significant model (both p's > .09).

3.3. Cluster analyses of cTBS-induced plasticity results

Complete-linkage cluster analysis of LnMEP values at T5 through T50 indicated the presence of two subgroups consisting of 12 and 9 individuals in Groups 1 and 2, respectively, with distinct patterns of response to cTBS (Figures 1 and 2). Comparisons of demographics, neuropsychological and baseline neurophysiological measures between the two groups are presented in Table 2.

Group 1, by itself, showed significant facilitation of cortico-motor reactivity at T15 [$t(11) = 3.48$, $p = .005$], T20 [$t(11) = 3.98$, $p = .002$], T50 [$t(11) = 3.65$, $p = .004$], and nonsignificant changes at other time points (all p's > .07). In contrast, Group 2 showed significant suppression of cortico-motor reactivity at T5 [$t(8) = 3.73$, $p = .006$], T10 [$t(8) = 4.36$, $p = .002$], T15 [$t(8) = 2.87$, $p = .021$], and nonsignificant changes at other time points (all p's > .08).

The difference between LnMEPs in Groups 1 and 2 was statistically significant at T5 [$t(19) = 3.43$, $p = .003$], T10 [$t(19) = 4.11$, $p < .001$], T15 [$t(19) = 4.29$, $p < .001$], T20 [$t(19) = 3.57$, $p = .002$], T30 [$t(19) = 2.11$, $p = .048$], T40 [$t(19) = 4.29$, $p < .001$], and T50 [$t(19) = 3.56$, $p = .002$].

Pooling the 21 p values in these three analyses (comparing Group 1's LnMEPs against zero, Group 2's LnMEPs against zero, and Groups 1 and 2's LnMEPs against each other), all significant p values survived FDR adjustment for multiple testing (all adjusted p's < .034), except the p value for comparing the LnMEPs at T30 between the two groups (adjusted $p = .072$).

Multiple logistic regression analyses of Group found significant models with LnMEP at T5 (pseudo-$R^2 = 0.35$, $p = .002$), T10 (pseudo-$R^2 = 0.49$, $p < .001$), T15 (pseudo-$R^2 = 0.45$, $p < .001$), T20 (pseudo-$R^2 = 0.35$, $p = .002$), T30 (pseudo-$R^2 = 0.16$, $p = .03$), T40 (pseudo-$R^2 = 0.53$, $p < .001$), or T50 (pseudo-$R^2 = 0.40$, $p < .001$) as predictor. The two models with LnMEP at either T10 or T40 resulted in the largest pseudo-R^2 values.

A multiple logistic regression analysis of Group with both the LnMEP at T10 and the LnMEP at T40 as predictors found a significant model (pseudo-$R^2 = 0.80$, $p < .001$) but nonsignificant effects for both predictors (both p's > 0.11). Adding either *BDNF* status, RMT, AMT, or baseline MEP amplitude as a predictor to the logistic regression analysis of Group with LnMEP at either T10 or T40 as the predictor did not find a significant effect of any of those additional predictors (all p's > 0.13). None of the other predictors listed in Table 2 contributed significantly to any of the linear or logistic regression models.

3.4. Exploratory analysis of the effect of BDNF polymorphism on cTBS-induced plasticity

Among 18 participants, the LnMEP at T10 was significantly more positive in *BDNF* Val66Met (Met+) participants (mean ± *SD*, 0.27 ± 0.42) than in *BDNF* Val66Val (Met−) participants (−0.29 ± 0.27), $t(16) = 3.42$, $p = .004$ (FDR-adjusted $p = .025$). LnMEPs at

other time points were not significantly different between *BDNF* Met+ and Met− participants (all p's > .07). cTBS results in *BDNF* Met+ and Met− participants are illustrated in Figure 3.

Multiple regression analysis of LnMEP at T10 with *BDNF* status (0 for Met−,1 for Met+) and AMT as predictors resulted in a significant model (adjusted $R^2 = 0.59$, $p < .001$) and significant effects for both *BDNF* status ($\hat{B} = 0.73$, $t = 5.02$, $p < .001$) and AMT ($\hat{B} = -0.04$, $t = 3.00$, $p = .009$).

Among variables listed in Table 2, *BDNF* status was found to have significant associations with Race (lower Met+ frequency in Whites), Verbal IQ subscore (lower in Met+ participants) and RMT (higher in Met+ participants), all p's < .05. None of these variables, however, were found to have a significant effect on LnMEPs at any time point (all p's > .20). Moreover, when added (one at a time) to the multiple regression analysis of LnMEP at T10, Race, Verbal IQ, and RMT were nonsignificant predictors (all p's > .14), while *BDNF* status (all p's < .003) and AMT (all p's < .019) remained significant predictors in all models.

3.5. Effect of APOE polymorphisms on cTBS-induced plasticity

Among 18 participants, the LnMEP at T20 was significantly more positive in *APOE* ε4+ (ε3/ε4) participants (mean ± *SD*, 0.20 ± 0.17) than in *APOE* ε4− (ε2/ε3 or ε3/ε3) participants (−0.14 ± 0.40), $t(16) = 2.17$, $p = .046$, but the p-value did not survive adjustment for multiple comparisons (FDR-adjusted $p = .32$). cTBS results in *APOE* ε4+ and *APOE* ε4− participants are illustrated in Figure 4.

Multiple regression analysis of LnMEP at T20 with *BDNF* and *APOE* statuses as predictors found a nonsignificant effect of *APOE* status ($p = .056$) and a nonsignificant effect of *BDNF* status ($p = .42$). Adding *APOE* status as a predictor to the regression analyses of LnMEP at T10, T40, or T50 with *BDNF* status as the other predictor found a significant effect of *BDNF* status at T10 ($p = .005$), but no other significant effect of either *BDNF* or *APOE* status (all p's > .21).

4. Discussion

Interindividual variability in TBS response can limit the utility of TBS aftereffects as indices of neuroplasticity. The present work examined the interindividual variability in response to cTBS among healthy individuals applying a data-driven statistical approach, i.e., cluster analysis, to identify subgroups of healthy individuals with distinct patterns of response to cTBS applied to M1. A further, exploratory objective was to assess the effect of *BDNF* and *APOE* polymorphisms on cTBS-induced plasticity.

4.1. Overall cTBS-induced plasticity results

The grand-average cTBS aftereffects showed no significant MEP modulation at any time point in the first 50 minutes. The interindividual variability in cTBS response was indicated by the large variability in MEP modulation around zero at T10, which typically shows the maximal effect of cTBS. While these results are inconsistent with the average cTBS response among healthy individuals reported in recent reviews (Wischnewski and Schutter,

2015; Suppa et al., 2016), they are consistent with the large interindividual variability in cTBS responses reported previously (Hamada et al., 2013).

Three possible factors could be suggested to account for the finding that the grand-average cTBS results were not consistent with the results of recent systematic reviews of cTBS studies (Wischnewski and Schutter, 2015; Suppa et al., 2016). First, the less-common AP-PA current direction induced in the brain (by using the 'Normal' current-direction setting on the MagPro X100 stimulator and the MC-B70 Butterfly Coil) may have influenced the cTBS results compared to those obtained with other rTMS stimulators. Second, individual participants in some of the previous cTBS studies that had not shown the expected suppression of MEPs during the first few post-cTBS time points may have been excluded as "non-responders", even though some of them might have shown significant facilitation of MEPs at certain time points (similar to many of the participants in Group 1). Third, there might have been some publication bias in reporting the effects of cTBS; i.e., studies that did not find the conventional suppressive effects of cTBS in their grand-average MEP results might have been less likely to be published.

4.2. Cluster analysis of cTBS-induced plasticity results

To examine the interindividual variability in the overall response to cTBS, we conducted a complete-linkage cluster analysis (Kaufman and Rousseeuw, 2009; Rencher and Christensen, 2012) on LnMEPs at all T5–T50 data points and found two subgroups with distinct patterns of cTBS response. The LnMEPs in the two subgroups were significantly different from each other at all time points except at T30. Group 1 showed significant facilitation of MEPs at T15, T20, and T50 (i.e., no clear return to baseline), whereas Group 2 showed significant suppression of MEPs at T5, T10, and T15. LnMEPs at T10 and at T40 had the most discriminatory power between inhibitory and facilitatory responses to cTBS. When considered together, LnMEPs at T10 and T40 predicted 80% of interindividual variability in cluster assignment.

The proportion of participants with facilitatory response to cTBS (~ 57%) was comparable with the results reported by Hamada and colleagues who found approximately 58% of their participants showed facilitatory responses to cTBS (Hamada et al., 2013). This pattern of results indicates: (1) the large interindividual variability in cTBS response among healthy individuals, and (2) the utility of cluster analysis for identification of subpopulations with distinct patterns of cTBS response in a data-driven and minimally biased manner.

Approximately 43% of participants (Group 2) showed suppression of cTBS aftereffects that, on average, returned to baseline by T20. This duration of cTBS aftereffects was shorter than expected considering the results of a recent meta-analysis of cTBS aftereffects in healthy individuals (Wischnewski and Schutter, 2015). The reduced duration of the TBS aftereffects might be due to unmeasured characteristic(s) of our participants or to the relatively small number of participants.

12 participants in Group 1 showed facilitatory cTBS aftereffects that did not return to baseline by T50. This long-lasting facilitation following cTBS could have stemmed from a combination of *BDNF* polymorphism and cumulative facilitatory effects of single TMS

pulses: (1) if a majority of participants in Group 1 were *BDNF* Met+, they would likely not show the conventional suppressive effects of cTBS due to impaired GABAergic synaptic transmission (Abidin et al., 2008) presumed to be involved in cTBS aftereffects (Stagg et al., 2009; Trippe et al., 2009); (2) receiving blocks of single TMS pulses, even with a jittered 4–5s inter-pulse interval, has been shown to have cumulative, within- and between-block facilitatory effects on corticospinal excitability (Pellicciari et al., 2016).

Applying numerous single TMS pulses may gradually skew the overall MEP amplitudes towards facilitation (Pellicciari et al., 2016) and perhaps even more so among *BDNF* Met+ individuals following cTBS (present results). This concern, however, needs to be balanced against the findings that at least 20 pulses are required to obtain reliable estimates of MEP amplitude at a given time point (Chang et al., 2016; Goldsworthy et al., 2016). Further studies are thus needed to determine the optimal number, stimulation intensity, and inter-pulse interval of single TMS pulses for minimizing their cumulative facilitatory effects while still allowing for reliable MEP estimates at given time points following TBS and other TMS protocols.

4.3. *BDNF* and *APOE* polymorphisms *and cTBS-induced plasticity*

In an exploratory analysis, we evaluated the potential association between *BDNF* Met carrier status and cTBS aftereffects, by comparing the cTBS responses between *BDNF* Met+ and Met− participants, regardless of which clusters they were assigned to. The two groups differed significantly in LnMEP at T10, with Met+ and Met− participants showing facilitatory and inhibitory cTBS responses, respectively (Figure 3). Moreover, the *BDNF* status and the AMT (that determined the intensity of cTBS) together accounted for 59% of variability in LnMEP at T10. The *BDNF* status was found to have significant associations with race, verbal IQ, and RMT. Additional analyses of those covariates, however, failed to find significant evidence for confounding of the significant association between *BDNF* status and cTBS response at T10 by race, verbal IQ or RMT.

The results of the present study and previous studies that found associations between *BDNF* polymorphism and measures of cortical plasticity (Cheeran et al., 2008, 2009; Antal et al., 2010; Cirillo et al., 2012; Lee et al., 2013; Chang et al., 2014; Di Lazzaro et al., 2015) but see (Li Voti et al., 2011; Mastroeni et al., 2013), suggest the importance of controlling for *BDNF* polymorphism when comparing M1 cTBS responses between healthy and clinical populations.

The significant association between *BDNF* status and cTBS-induced plasticity may be due to the important *BDNF* role in synaptic plasticity and intracellular signaling (Bramham and Messaoudi, 2005; Numakawa et al., 2010), reduced activity-dependent *BDNF* secretion (Egan et al., 2003), impaired NMDA-dependent LTD (Woo et al., 2005) and/or aberrant GABAergic inhibition in *BDNF* Met carriers (Abidin et al., 2008). However, the relatively small sample size of the present study limits the strength of the conclusions and warrants further replication in larger cohorts. It may also be important to obtain in those cohorts the results for other SNPs that have been found to influence cortical plasticity as measured by TMS, including *catechol-O-methyltransferase* (*COMT*) polymorphism that has been found

to influence M1 cTBS responses (Lee et al., 2014) and to interact with the effect of *BDNF* polymorphism (Witte et al., 2012).

After controlling for *BDNF* status, AMT (or cTBS intensity) was found to have a significant effect on cTBS response at T10; higher AMT values were associated with more negative values, i.e., more suppression or less facilitation of MEPs, at T10. The significant effect of AMT (or cTBS intensity), when considered together with *BDNF* status, on the interindividual variability in cTBS aftereffect at T10 indicates the importance of controlling for AMT or stimulation intensity in studies comparing M1 cTBS responses between healthy and clinical populations.

While there was a hint of more facilitation at T20 in *APOE* ε4+ participants than in *APOE* ε4− participants (Figure 4), the difference did not survive adjustment for multiple comparisons. This result could be due to the fact that, while both the influences of *APOE* ε4 on synaptic plasticity and TBS aftereffects have been found to involve NMDA receptors (Huang et al., 2007; Chen et al., 2010), cTBS-induced plasticity may also involve GABAergic mechanisms (Stagg et al., 2009; Trippe et al., 2009) that are not necessarily affected by the presence of *APOE* ε4 (Andrews-Zwilling et al., 2010).

4.4. Additional considerations

Several factors may limit the generalizability of the present findings. The range of baseline MEP amplitudes was relatively wide and a few participants had average baseline MEP amplitudes smaller than 0.5mV. This was perhaps in part due to the fact that the intensity of single TMS pulses was fixed at 120% of RMT and was not adjusted to obtain any particular MEP amplitude. Since the slope of increase in MEP amplitude with increase in stimulation intensity of single TMS pulses can vary among individuals, it may be beneficial to utilize input-output curves, rather than a fixed proportion of RMT, to determine the stimulation intensity of single pulses. It is also possible that higher intensity of single TMS pulses and/or larger baseline MEP amplitudes would have resulted in different patterns of cTBS aftereffects.

The present work tested the utility of cluster analysis with the complete-linkage method, previously used in an rTMS study (Gangitano et al., 2002), for identifying subpopulations of healthy participants with distinct patterns of cTBS response. There are other methods of hierarchical and nonhierarchical cluster analysis, including single-linkage, average-linkage, centroid, median, Ward's method, *k*-means, etc., each with their own advantages and disadvantages (Kaufman and Rousseeuw, 2009; Rencher and Christensen, 2012). It remains to be investigated which methods of cluster analysis are the most sensitive and robust in identifying natural clusters within post-TBS MEP data.

Besides the method of clustering, choosing which time points to include in the cluster analysis of post-TBS data may also influence the composition of the resultant clusters. Because of the exploratory nature of the present work, and to avoid any bias in the selection of the time points, we included all available time points from T5 through T50 in the cluster analysis. It may be the case that choosing certain time points instead of the whole dataset can improve the sensitivity or robustness of the cluster analysis. One option may be to

choose T5, previously found to be the most reliable time point for measuring MEP changes following cTBS (Vernet et al., 2014) and/or T10 to capture the peak effect of TBS, including for participants whose MEPs return rapidly to baseline levels, and perhaps one of the later time points, e.g., T40 and/or T50, to use their discriminatory power for classifying the cTBS aftereffects (present results) and for capturing the differential time of return of post-TBS MEP amplitudes to baseline levels between healthy and clinical populations (Oberman et al., 2010, 2012, 2014, 2016; Freitas et al., 2011b; McClintock et al., 2011).

Finally, the type of post-TBS MEP data may also influence the results of cluster analysis. In the present work, we chose LnMEP as a measure of TBS-induced MEP modulation that is normalized to each participant's baseline MEP amplitude and log-transformed to achieve a near-normal distribution. It is possible that conducting the cluster analysis with other types of post-TBS MEP data, e.g., area-under-the-curve, absolute deviation from the baseline amplitude, or time of return to the baseline, can improve the results of cluster analysis.

5. Conclusions

The large interindividual variability in cTBS response among healthy individuals should be considered when utilizing cTBS as an index of the mechanisms of cortical plasticity. Relying only on grand-average results can obscure important interindividual differences in cTBS response within each group of participants. Data-driven cluster analyses can identify subpopulations of individuals with distinct patterns of cTBS response. *BDNF* polymorphism had a significant effect on MEP changes at 10 minutes after cTBS. Moreover, *BDNF* status and AMT (or cTBS intensity) accounted for a large portion of interindividual variability in cTBS responses at T10. Changes in MEPs at T10 and T40 had the most discriminatory power for categorizing the cTBS responses. When considered together, MEP changes at T10 and at T40 accounted for a large portion of interindividual variability in cluster assignment. Considering these factors can improve the utility of cTBS as index of cortical plasticity and can increase the power of studies that examine differences in cTBS response between healthy and clinical populations.

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Highlights

- Cluster analysis can identify subpopulations in healthy adults with distinct cTBS responses.
- MEP changes at 10 and 40 minutes post-cTBS best predicted the results of the cluster analysis.
- Variability in cTBS response after 10 min was influenced by *BDNF* polymorphism and cTBS intensity.

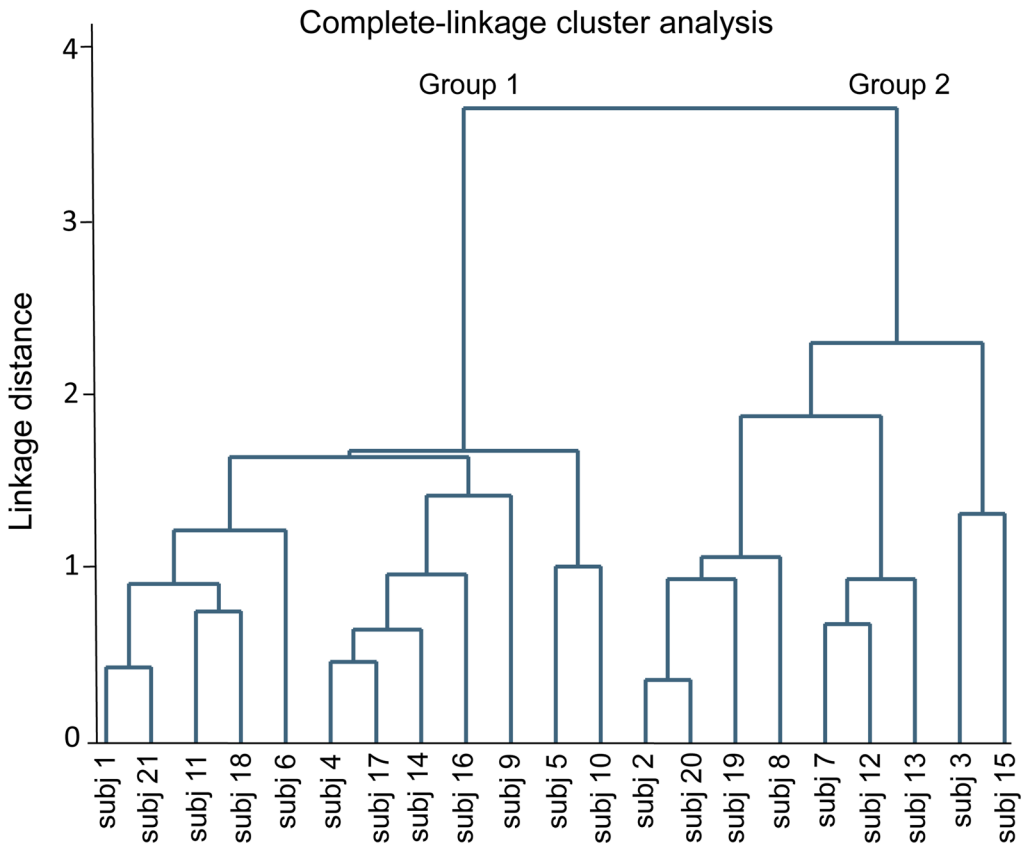

Figure 1.

Dendrogram (cluster tree) summarizing the results of complete-linkage cluster analysis of natural log-transformed, baseline-corrected amplitudes of motor evoked potentials at 5 to 50 minutes following continuous theta-burst stimulation (cTBS) of the left primary motor cortex in healthy individuals. The numbers on the abscissa indicate the subject numbers. Linkage distance is defined as the Euclidean distance between the farthest observations in each of the two linked subgroups. The tree structure illustrates two distinct patterns of response to cTBS by 12 individuals in Group 1 and nine individuals in Group 2.

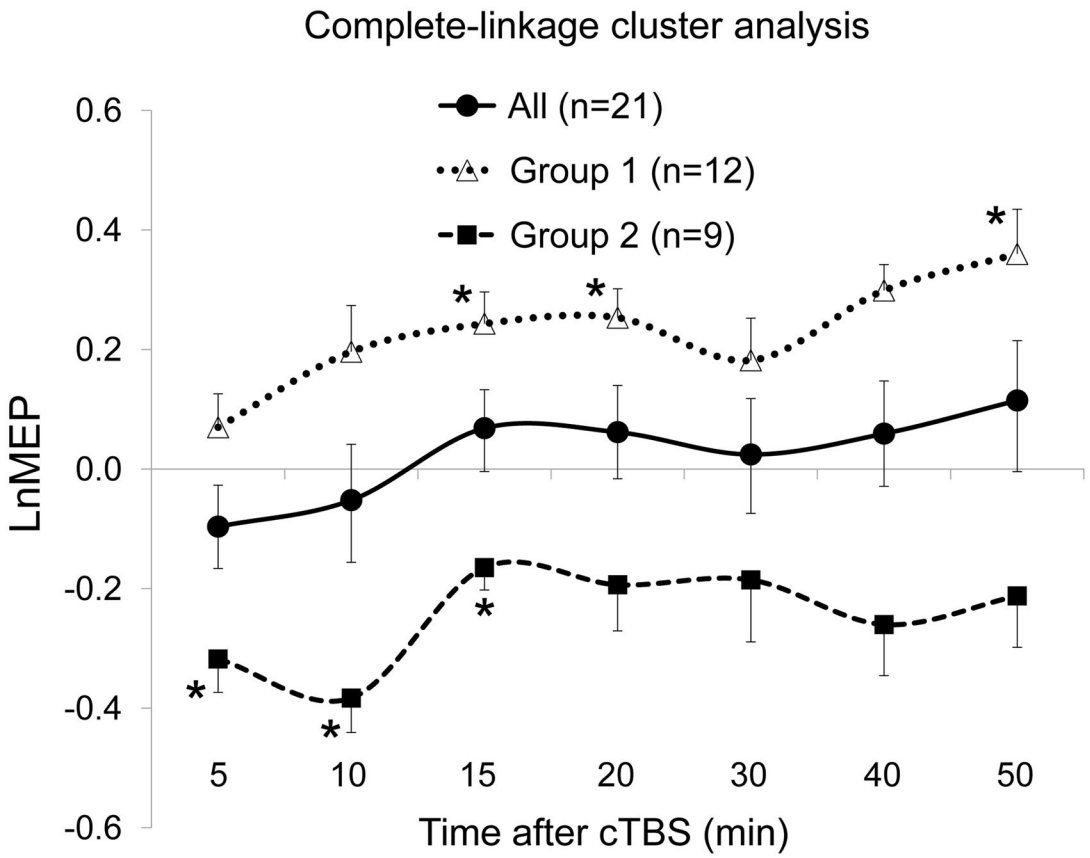

Figure 2.

Effects of continuous theta-burst stimulation (cTBS) of the left primary motor cortex in all participants and in two subgroups (Groups 1 and 2) identified by complete-linkage cluster analysis of natural log-transformed, baseline-corrected amplitudes of motor evoked potentials (LnMEP) at 5 to 50 minutes following cTBS. The overall results ('All') did not show a significant MEP modulation at any of the seven time points. Groups 1 and 2 were significantly different from each other at all time points except at T30. Values that were significantly different from zero are marked by *. All *p*-values were adjusted for multiple testing using false discovery rate. Error bars represent standard error of the mean.

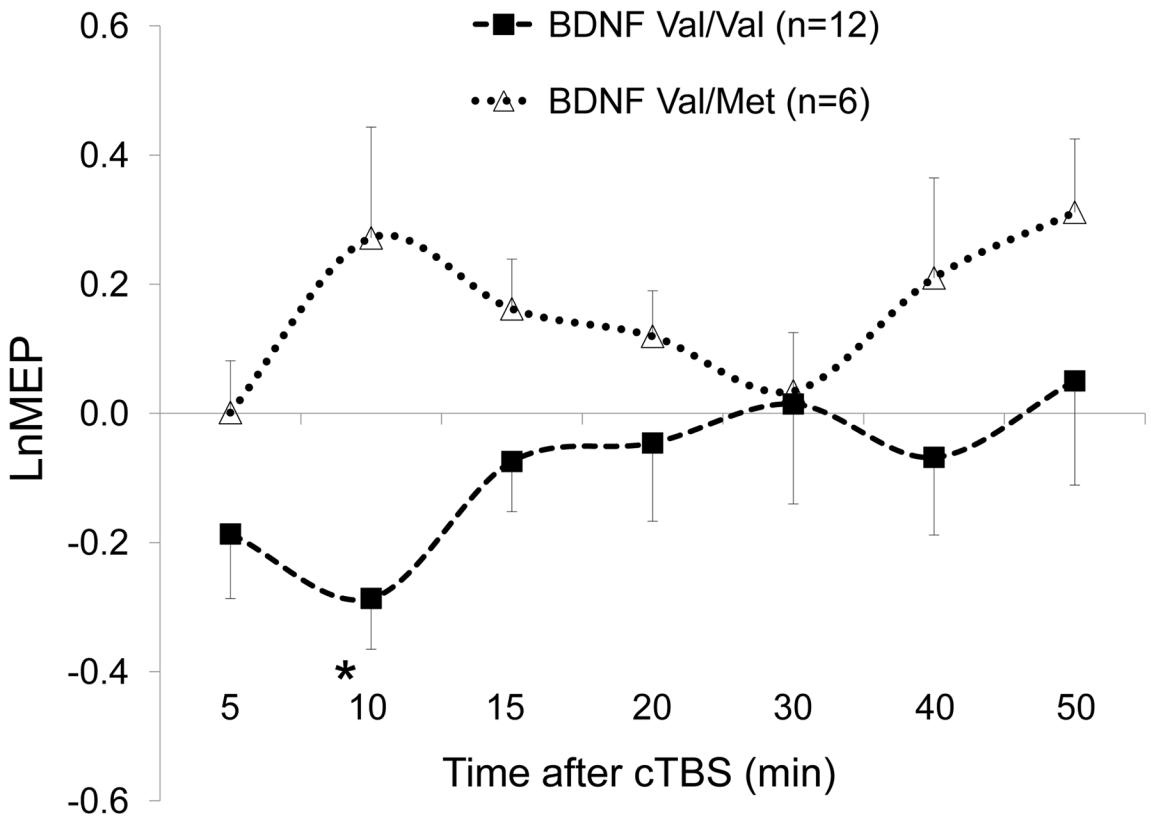

Figure 3.

Effects of continuous theta-burst stimulation (cTBS) of the left primary motor cortex at 5 to 50 minutes following cTBS in *BDNF* Val66Val (Val/Val) and *BDNF* Val66Met (Val/Met) participants. * LnMEPs were significantly different between the two groups at 10 minutes post-cTBS. All *p*-values were adjusted for multiple testing using false discovery rate. Error bars represent standard error of the mean. *BDNF*, brain-derived neurotrophic factor; LnMEP, natural log-transformed, baseline-corrected amplitudes of motor evoked potentials.

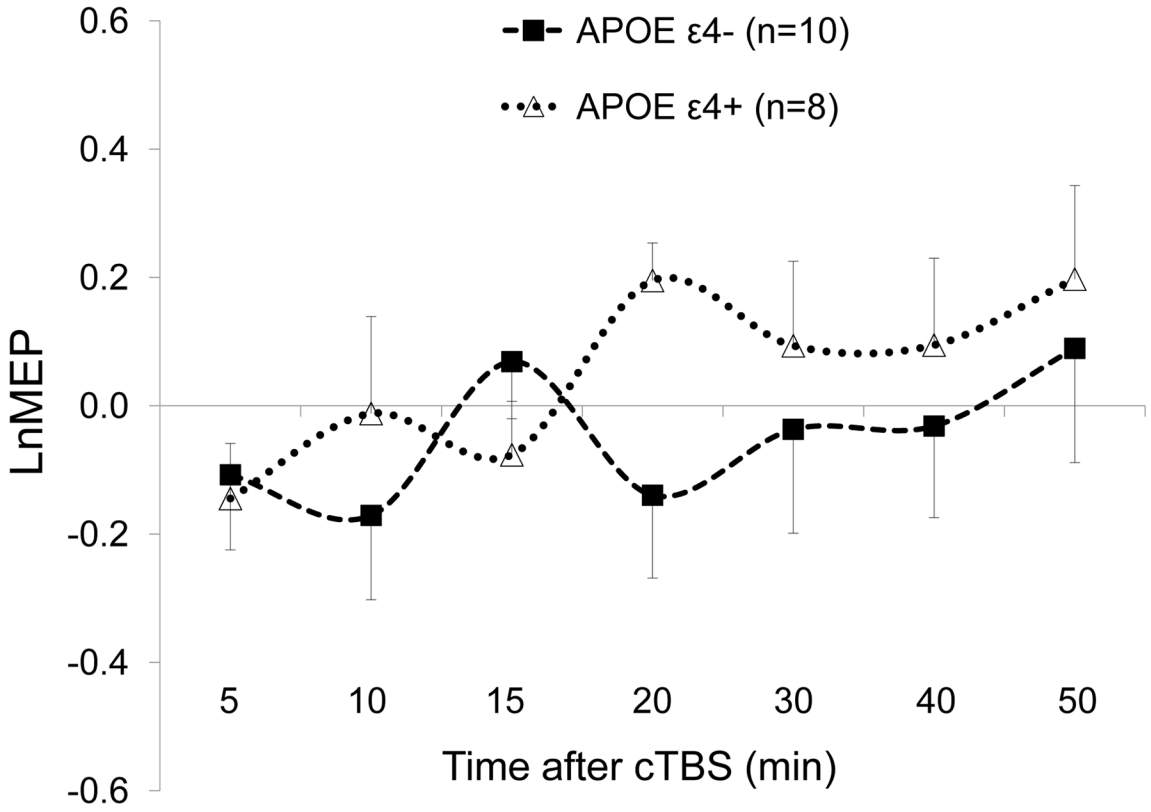

Figure 4.

Effects of continuous theta-burst stimulation (cTBS) of the left primary motor cortex at 5 to 50 minutes following cTBS in *APOE* ε4+ (ε3/ε4) and *APOE* ε4− (ε2/ε3 or ε3/ε3) participants. LnMEP at T20 was significantly more positive in in *APOE* ε4+ participants than in in *APOE* ε4− participants ($p = .046$), but the p-value did not survive adjustment for multiple comparisons (FDR-adjusted $p = .32$). LnMEPs were not significantly different between the two groups at other time points. Error bars represent standard error of the mean. *APOE*, apolipoprotein E; LnMEP, natural log-transformed, baseline-corrected amplitudes of motor evoked potentials.

Table 1

Participants' demographics, single-nucleotide polymorphisms, and neuropsychological measures.

	Age (yr)	Gender	Race	Ethnicity	Education* (yr)	*BDNF* †	*APOE* †	MMSE	Abbreviated Stanford-Binet IQ	Verbal KN	Nonverbal FR
Participant 01	24	M	Asian	non-Hispanic	16	Val/Met	ε3/ε3	30	100	10	10
Participant 02	26	M	Other	non-Hispanic	19	Val/Val	ε3/ε4	30	121	17	10
Participant 03	23	M	Multiracial	Hispanic	16	Val/Val	ε3/ε3	30	106	11	11
Participant 04	56	F	African-American	non-Hispanic	14	-	-	30	97	9	10
Participant 05	47	M	White	non-Hispanic	20+	Val/Val	ε3/ε3	30	133	17	14
Participant 06	21	M	Asian	non-Hispanic	16	-	-	30	94	8	10
Participant 07	53	M	White	non-Hispanic	16	Val/Val	ε3/ε4	30	106	13	9
Participant 08	51	M	White	non-Hispanic	16	Val/Val	ε3/ε3	30	115	14	11
Participant 09	62	M	White	non-Hispanic	16	Val/Met	ε3/ε4	30	118	12	14
Participant 10	21	M	White	Hispanic	15	Val/Val	ε3/ε4	30	109	14	9
Participant 11	22	M	White	Hispanic	17	Val/Val	ε2/ε3	30	112	10	14
Participant 12	32	M	White	non-Hispanic	19	Val/Val	ε3/ε3	29	100	9	11
Participant 13	28	M	White	Hispanic	-	Val/Val	ε3/ε3	30	115	13	12
Participant 14	50	F	African-American	non-Hispanic	12	-	-	30	97	10	9
Participant 15	23	M	White	non-Hispanic	17	Val/Val	ε2/ε3	30	127	16	13
Participant 16	24	M	Multiracial	Hispanic	17	Val/Met	ε2/ε3	28	115	12	13
Participant 17	22	M	Asian	non-Hispanic	17	Val/Met	ε3/ε4	30	103	9	12
Participant 18	47	M	African-American	non-Hispanic	18	Val/Met	ε3/ε3	30	88	9	7
Participant 19	32	M	Asian	non-Hispanic	20+	Val/Met	ε3/ε4	30	103	8	13
Participant 20	65	M	Asian	non-Hispanic	20+	Val/Val	ε3/ε4	30	124	15	13
Participant 21	46	M	White	non-Hispanic	13	Val/Val	ε3/ε4	30	88	9	7

All participants were right-handed. *APOE*, apolipoprotein E; *BDNF*, brain-derived neurotrophic factor; FR, fluid reasoning; IQ, intelligence quotient; KN, knowledge; MMSE, Mini-Mental State Examination. Racial and ethnic categories were defined based on the National Institutes of Health policy and guidelines on the inclusion of women and minorities as subjects in clinical research (NIH Office of Extramural Research, 2001).

*Education data were available for 20 participants.

†*BDNF* and *APOE* data were available for 18 participants.

Table 2

Participants' demographics, single-nucleotide polymorphisms, neuropsychological tests, and baseline neurophysiological measures.

	All (N = 21)	Group 1 (n = 12)	Group 2 (n = 9)	*p*
Age (yr, mean ± *SD*)	36.9 ± 15.2	36.8 ± 15.8	37.0 ± 15.3	0.98
Sex (M : F)	19 : 2	10 : 2	9 : 0	0.49
Race (White : non-White)	10 : 11	5 : 7	5 : 4	0.67
Ethnicity (Hispanic : non-Hispanic)	5 : 16	3 : 9	2 : 7	1.00
Education (yr, mean ± *SD*)*	16.8 ± 2.5	16.0 ± 2.4	18.1 ± 2.2	–
BDNF (Met− : Met+)†	12 : 6	4 : 5	8 : 1	–
APOE (ε4− : ε4+)†	10 : 8	5 : 4	5 : 4	–
Handedness (Right : Left)	21 : 0	12 : 0	9 : 0	1.00
MMSE score (mean ± *SD*)	29.9 ± 0.5	29.8 ± 0.6	29.9 ± 0.3	0.80
Abbreviated Stanford-Binet IQ (mean ± *SD*)	108.1 ± 12.4	104.5 ± 13.4	113.0 ± 9.7	0.12
Verbal KN score (mean ± *SD*)	11.7 ± 2.9	10.8 ± 2.6	12.9 ± 3.1	0.10
Nonverbal FR score (mean ± *SD*)	11.0 ± 2.2	10.8 ± 2.6	11.4 ± 1.4	0.47
RMT (% MSO, mean ± *SD*)	36.1 ± 7.7	36.8 ± 6.6	35.1 ± 9.4	0.63
AMT (% MSO, mean ± *SD*)	26.1 ± 5.2	25.8 ± 5.0	26.4 ± 5.8	0.80
Baseline MEP amplitude (mV, mean ± *SD*)	1.4 ± 1.2	1.2 ± 1.0	1.6 ± 1.3	0.50

AMT, active motor threshold; *APOE*, apolipoprotein E; *APOE* ε4+, ε2/ε4 or ε3/ε4 genotype; *APOE* ε4−, ε2/ε3 or ε3/ε3; *BDNF*, brain-derived neurotrophic factor; *BDNF* Met−, Val66Val; *BDNF* Met+, Val66Met; FR, fluid reasoning; IQ, intelligence quotient; KN, knowledge; MEP, motor evoked potential; MMSE, Mini-Mental State Examination; MSO, maximum stimulator output; RMT, resting motor threshold; *SD*, standard deviation. Racial and ethnic categories were defined based on the National Institutes of Health policy and guidelines on the inclusion of women and minorities as subjects in clinical research (NIH Office of Extramural Research, 2001). Groups 1 and 2 were identified by complete-linkage cluster analysis of natural log-transformed, baseline-corrected MEP amplitudes at 5 to 50 minutes post-cTBS. Comparisons of proportions were conducted with Fisher's exact test. *p* values were not adjusted for multiple comparisons. Education and single-nucleotide polymorphisms were not statistically compared between the two groups because the data were not available for the total sample.

*Education data were available for 12 participants in Group 1 and eight participants in Group 2.

†*BDNF* and *APOE* results were available for 18 participants.