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

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HIGHLIGHTS

- Cluster analysis can identify subpopulations in healthy adults with distinct cTBS responses.
- MEP changes at 10 and 40 min 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.

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 min 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 < 0.006), and Group 2 ($n = 9$) that showed significant suppression at T5–T15 (p's < 0.022). LnMEPs at T10 and T40 were best predictors of, and together accounted for 80% of, cluster assignment.
Results: 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 ($p = 0.025$). *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 > 0.32).
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.

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

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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 50 Hz bursts of three TMS pulses repeated every 200 ms (at 5 Hz), for a total of 600 pulses, in one of two protocols: (1) a 2-s on, 8-s off intermittent TBS (iTBS) pattern for 190 s, which in most individuals increases MEP amplitude by approximately 35% for up to 60 min, or (2) a continuous TBS (cTBS) pattern for 40 s, 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.