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Impact of Transcranial Direct Current Stimulation on Cognitive Function, Brain Functional Segregation, and Integration in Patients with Mild Cognitive Impairment According to Amyloid-Beta Deposition and *APOE* ε4-Allele: A Pilot Study

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Abstract: Anodal transcranial direct current stimulation (anodal-tDCS) is known to improve cognition and normalize abnormal network configuration during resting-state functional magnetic resonance imaging (fMRI) in patients with mild cognitive impairment (MCI). We aimed to evaluate the impact of sequential anodal-tDCS on cognitive functions, functional segregation, and integration parameters in patients with MCI, according to high-risk factors for Alzheimer's disease (AD): amyloid-beta (Aβ) deposition and *APOE* ε4-allele status. In 32 patients with MCI ([^{18} F] flutemetamol-: n = 10, [^{18} F] flutemetamol+: n = 22; *APOE* ε4-: n = 13, *APOE* ε4+: n = 19), we delivered anodal-tDCS (2 mA/day, five times/week, for 2 weeks) over the left dorsolateral prefrontal cortex and assessed the neuropsychological test battery and resting-state fMRI measurements before and after 2 weeks stimulation. We observed a non-significant impact of an anodal-tDCS on changes in neuropsychological battery scores between MCI patients with and without high-risk factors of AD, Aβ retention and *APOE* ε4-allele. However, there was a significant difference in brain functional segregation and integration parameters between MCI patients with and without AD high-risk factors. We also found a significant effect of tDCS-by-*APOE* ε4-allele interaction on changes in the functional segregation parameter of the temporal pole. In addition, baseline Aβ deposition significantly associated negatively with change in global functional integrity of hippocampal formation. Anodal-tDCS might help to enhance restorative and compensatory intrinsic functional changes in MCI patients, modulated by the presence of Aβ retention and the *APOE* ε4-allele.

Keywords: amyloid beta deposition; *APOE* ε4-allele; mild cognitive impairment; transcranial direct current stimulation

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1. Introduction

Alzheimer's disease (AD) is a leading cause of dementia and imposes a marked social and economic burden. Mild cognitive impairment (MCI), a prodromal AD stage, involves subjective and objective decline in cognitive function, but preservation of the independent daily living ability [1]. Since 10–15% of MCI patients convert to dementia annually, various attempts have been made to delay or prevent the transition to dementia at this stage [2]. Although therapeutic attempts, such as cognitive intervention [3], regular physical exercise [4], and dietary intervention have shown some positive results for changes in cognitive function and biomarkers [5], additional evidence is needed for these interventions to be