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専　　攻　　名	生体制御学専攻
学位論文題名	Possible Facilitative effects of repeated anodal Transcranial Direct current stimulation on Functional Outcome 1 Month later in schizophrenia: an Open Trial (統合失調症の機能的アウトカムに対する反復アノーダル経頭蓋直流電気刺激の１ヶ月後の促進効果：オープン試験)
論文審査委員	委員長　教　授　宇賀　貴紀 委　員　准教授　新藤　和雅 委　員　准教授　北間　敏弘

学位論文内容の要旨

Aim of the present study: Schizophrenia patients elicit psychotic symptoms, mood symptoms, and cognitive impairment. Specifically, cognitive function, such as learning memory, working memory, executive function, verbal fluency, and attention/information processing are impaired in patients with the illness. Transcranial direct current stimulation (tDCS) is a feasible and safe method, using weak and direct electrical current to the brain through electrodes. The dorsolateral prefrontal cortex (DLPFC) has been a target for studies investigating tDCS on cognitive function in schizophrenia. Although some studies indicate the facilitative effect of tDCS over the DLPFC on some domains of cognitive function, there is still little information on whether tDCS would improve a higher level of functional outcome in schizophrenia. We hypothesized that tDCS may also be effective in improving functional capacity in schizophrenia, since this level of functional outcome is associated with cognitive function. To our knowledge, no study has been attempted to determine whether tDCS directly improves functional capacity, or the improvement on other symptoms, such as psychosis, depression, would indirectly improves it. Based on these considerations, we aimed to determine whether repetitive tDCS is efficacious in improving determinants of outcome, such as cognitive function, daily-living skills, and depressive mood in patients with schizophrenia.

Methods: Inpatients or outpatients treated at National Center Hospital, National Center of Neurology and Psychiatry, were enrolled. Participants were recruited by psychiatrists' referrals.

They provided written informed consent before starting the trial. Twenty-eight patients underwent tDCS (2 mA x 20 min) two times per day for five consecutive days. The anodal electrode was placed over the left dorsolateral prefrontal cortex while the cathodal electrode was placed over the right supraorbital region. Antipsychotics taken by participants were as follows: risperidone (eight patients), paliperidone, quetiapine, aripiprazole (seven for each), olanzapine (six), haloperidol (three), chlorpromazine, levomepromazine, zotepine (two for each), perospirone, blonanserin, sulpiride (one for each). No medication was modified during the study period. No severe side effect was observed throughout the trial. All participants tolerated the treatment well.

Results: One month after the last stimulation, there was a significant improvement on cognitive function, measured by the Brief Assessment of Cognition in Schizophrenia (BACS) ($d = 0.49$). Significant effects were also shown on daily-living skills (functional capacity), measured by the UCSD Performance-based Skills Assessment-Brief (UPSA-B) ($d = 0.70$). Depressive symptoms, measured by the Calgary Depression Rating Scale (CDSS), as well as psychotic symptoms measured by on the Positive and Negative Syndrome Scale (PANSS) Positive and General Psychopathology subscales also responded to the treatment ($d = 0.38$, $d = 0.48$ and $d= 0.50$, respectively). No significant correlation was noted between baseline values and their changes from baseline of BACS and UPSA-B scores. In contrast, significant negative correlations were demonstrated between baseline values vs. their changes from baseline of PANSS Positive subscales ($r = -0.65$, $p < 0.001$), Negative subscales ($r = -0.56$, $p < 0.002$), General Psychopathology subscales ($r = -0.64$, $p < 0.001$), and CDSS total scores ($r = -0.66$, $p < 0.001$). No significant correlation was found between chlorpromazine equivalent dose of antipsychotics vs. changes from baseline of BACS, UPSA-B, PANSS, and CDSS scores. The same applied to correlations between change from baseline of UPSA-B scores vs. changes from baseline of BACS, PANSS, and CDSS scores.

Discussion: To our knowledge, this study was the first to suggest the ability of tDCS to improve daily-living skills linked to cognition, as well as depressive symptoms in patients with schizophrenia. Also, this study was the first to indicate improvement of functional capacity after five-day administration of tDCS, which was not correlated with the change of cognition, psychosis, and depression. At the same time, tDCS was found to enhance cognition in these subjects. Inclusion of a sham-controlled group could have provided a definitive conclusion. Accordingly, we are initiating a randomized sham-controlled trial with a larger sample.

Conclusion: The results of the present study suggest the efficacy of tDCS on cognition, daily-living skills, and depression. These results may add to the concept that tDCS provides a strategy to enhance functional outcomes in patients with schizophrenia.

論文審査結果の要旨

本学位論文は、統合失調症の機能的能力に対する反復経頭蓋直流電気刺激の促進効果のパイロット試験に関するものである。

統合失調症患者は、精神病症状や気分障害の他、作業記憶、実行機能、言語機能、注意機能などの認知機能の障害を呈する。一方、経頭蓋直流電気刺激（transcranial direct current stimulation: tDCS）は、脳機能への安全で簡便な介入を可能としており、様々な精神神経疾患への適用が考えられている。これまでの先行研究により、統合失調症患者の背外側前頭前野に tDCS 介入を行うと、作業記憶や注意機能などの認知機能が改善することが報告されてきた。しかし、背外側前頭前野への tDCS 介入効果が、より高次な機能的能力（日常生活技能）まで波及するかは不明であった。

そこで本研究では、28 名の統合失調症患者に対し、背外側前頭前野への tDCS 介入を行い、機能的能力を改善するかを検証した。国立精神神経医療研究センター病院の 20〜60 歳の入院あるいは外来患者を独自にリクルートし、同意が得られた患者に対し、1 回 2mA・20 分、1 日 2 回、連続 5 日間の tDCS 介入を施行した。先行研究に倣い、陽性電極を左背外側前頭前野に、陰性電極を右眼窩上に設置し、背外側前頭前野の機能が促進されるよう工夫した。そして、機能的能力を含む統合失調症病態の指標として、標準的に用いられている BACS、UPSA-B、PANSS、CDSS を計測し、刺激前と刺激 1 カ月後の機能を比較した。

その結果、UPSA-B で計測された金銭出納やコミュニケーションなどの機能的能力に改善が見られたほか、BACS で計測された言語性記憶や言語流暢性などの認知機能にも改善が見られた。また、CDSS で計測されたうつ症状の改善も見られた。これらのデータは統計学的に処理されており、信頼性があると判定できた。以上の結果から、tDCS の統合失調症患者での機能的能力への効果が示され、これらの成果は英文原著論文として報告された。一方で、効果検証を確実なものにするためには、コントロールとの対比が必要と考えられたが、現在、RCT を試行中であり、プロトコールを英語原著論文として報告済みである。

本研究は、統合失調症の機能的能力に着目し、tDCS の効果を検証した点が新規かつ独創的である。また、統合失調症新規治療法の確立に向けた基礎データを提供した点で意義が高く、博士（医学）の学位に値する。