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Short Communication

A Novel Therapeutic and Diagnostic Approach in Depression Related Cognitive Impairment

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DESCRIPTION

MDD (Major depressive disorder) related cognitive impairment is a leading cause of functional decline and morbidity worldwide. Furthermore, evidence suggests a strong link between depression and BDNF (brain-derived neurotrophic factor), a novel pro-cognitive and neuroprotective molecule. Several clinical and pre-clinical studies have shown that Repetitive transcranial magnetic stimulation (rTMS) significantly induces the expression of the hippocampal BDNF that plays a critical role in MDD. Despite these positive findings, there is still no proven non-invasive approach to evaluate the BDNF related synaptic effects of rTMS in humans.

We summarized the underlying mechanisms of the neuroprotective and pro-cognitive effect of BDNF, which is induced by a region-specific rTMS approach. We have also evaluated the role of Magnetic Resonance Spectroscopy in monitoring the BDNF related synaptic and metabolic responses after rTMS application in MDD patients with cognitive dysfunction.

In our review, we have provided strong evidence that hippocampal BDNF could be a key molecule in mediating the neuroprotective and pro-cognitive effects of rTMS, while Magnetic Resonance Spectroscopy might play a crucial role in monitoring the BDNF related metabolic changes after rTMS application in MDD patients. Further specific designed studies are needed to enlighten us on the time-dependent pro-cognitive correlates of the rtMS application.

Major depressive disorder as a cognitive impairment

Depression is a frequent mood disorder characterized by significant dysfunction of neuroplasticity and oxidative balance (Yuluğ B, *et al.*, 2010; Corlier J, *et al.*, 2020; Caglayan B, *et al.*, 2019). This is suggested by several observations that depression leads to decreased volume of the hippocampus, which is a critical region responsible for core memory formation. Thus, rapidly increasing data shows that depression is commonly associated with cognitive dysfunction that significantly reduces the quality of life. Brain-derived neurotrophic factor (BDNF) is a well-known neuroprotective molecule that also exerts some pro-cognitive effects, making it a well-candidate for depression-related cognitive dysfunction (Yuluğ B, *et al.*, 2010; Burak Y, *et al.*, 2016). Thus, there is rapidly increasing evidence showing that altered BDNF levels are associated with depression pathogenesis. Furthermore, decreased BDNF expression in the hippocampal region has been shown to play a critical role in cognitive impairment in MDD (Corlier J, *et al.*, 2020; Yuluğ B, *et al.*, 2009). Since the hippocampus seems the most significant region responsible for the memory impairment, it is of critical importance to induce the BDNF and evaluate the BDNF related hippocampal alterations with non-invasive neuroimaging methods.

rTMS as a BDNF inducer in MDD and related cognitive impairment

There have been several extensive sample studies showing that antidepressant treatment provided no improvement in multiple domains of cognitive function in MDD (Shilyansky C, *et al.*, 2016). Furthermore, even some studies suggested that antidepressant medication might have detrimental effects on cognition (Sneed JR, *et al.*, 2010; Nagane A, *et al.*, 2014). Considering all of these findings, it is not unreasonable to assume an unmet need for efficacious pro-cognitive treatment alternatives in MDD related cognitive impairment. Repetitive transcranial magnetic stimulation (rTMS) is a feasible non-invasive brain-stimulation method shown to be effective on various neurodegenerative diseases and related symptoms (Yuluğ B, *et al.*, 2010; Lapchak PA and Zhang JH, 2017). However, despite its beneficial clinical effects, it is still unclear how rTMS acts at the molecular level. Studies have suggested that rTMS might alter the electrophysiological correlations such as Long-Term Potentiation (LTP) or long-term depression leading to critical alterations in hippocampal synaptic connectivity (Yuluğ B, *et al.*, 2010; Yulug B, *et al.*, 2018). Animal studies indicated that rTMS treatment-related cognitive improvements were strongly associated with BDNF expression at mRNA and protein levels (Yulug B, *et al.*, 2016; Luftu H, *et al.*, 2016). These results are also consistent with studies showing that BDNF has significant pro-cognitive effects (Yuluğ B, *et al.*, 2009).

Beyond that, several studies in humans suggested that rTMS application leads to an antidepressant effect and increases cognitive functions by improving the regional cerebral blood flow, glucose metabolism, and electrophysiological responses (Yulug B, *et al.*, 2018; Yuluğ B, *et al.*, 2009). However, it is worth mentioning that most rTMS methods chosen for MDD treatment were applied to the left Dorsolateral Prefrontal Cortex (DLPFC), which is easy to stimulate. These studies finally have shown that DLPFC targeted rTMS was a safe and efficacious treatment for depression (George MS, *et al.*, 2010; Carpenter LL, *et al.*, 2012).

In contrast, there is relatively preliminary data showing that rTMS could also improve cognitive functions in MDD (Kuroda Y, *et al.*, 2006; Fitzgerald PB, *et al.*, 2009; Wajdik C, *et al.*, 2014; Höppner J, *et al.*, 2003; O'Connor MG, *et al.*, 2005; O'Connor MG, *et al.*, 2016; Moser DJ, *et al.*, 2002; Salagre E, *et al.*, 2017), that could be related to the fact that hippocampus, a critical region responsible for core memory formation, cannot be altered *via* superficial stimulation approaches. In this respect, since the hippocampus is difficult to stimulate with conventional rTMS methods due to its deep location, current regimens focusing on superficial brain regions showing high connectivity with the hippocampus (Wang JX, *et al.*, 2014) confirmed that the stimulation of the hippocampus was associated with significant improvement in memory functions. However, although these studies revealed that inducing deeper located brain regions resulted in acute pro-cognitive effects; future

studies involving MDD patients with cognitive pathology are needed.

Magnetic resonance spectroscopy as a non-invasive imaging tool for hippocampal metabolic alterations

The Magnetic Resonance (MR) metabolites NAA/Cr, NAA/Cho, and Cho/Cr provide powerful information. Several studies have shown that Magnetic Resonance spectroscopy is sensitive during neurodegenerative diseases characterized by altered synaptogenesis and BDNF levels. For instance, decreased NAA during the progressive neurodegenerative phase reflecting altered neuronal metabolism. Since NAA (N-Acetyl Aspartate) is a well-known neuronal survival marker reflecting an intact mitochondrial oxidative phosphorylation (Jenkins BG, *et al.*, 2000) and synaptic integrity (Maier M, *et al.*, 1995), detecting the effect of BDNF on the synaptogenesis in humans through measuring N-Acetyl Aspartate (NAA) levels by Magnetic Resonance Spectroscopy (MRS) (Jenkins BG, *et al.*, 2000; Maier M, *et al.*, 1995) might be a novel approach for evaluating the rTMS-induced hippocampal effects in MDD. Furthermore, while the only possibility to detect the acute neuroprotective response after rTMS application is an invasive histopathological examination, Magnetic Resonance Spectroscopy (MRS) may provide critical information regarding the pro-cognitive and neuroprotective effects of rTMS on the hippocampus. To the best of our knowledge, there is still no neuroimaging method that could detect the BDNF response in the brain parenchyma (i.e., BDNF labelled imaging) after rTMS application.

CONCLUSION

Beyond suggesting the pivotal role of BDNF in MDD and related cognitive impairment, our study indicates that BDNF may also be a potential non-invasive treatment option in MDD. However, different hippocampal oriented rTMS treatment protocols combined with MRS studies are crucial to understanding the underlying metabolic correlates of the pro-cognitive, antidepressant and neuroprotective effect of rTMS in MDD.

REFERENCES

1. Yuluğ B, Ozan E, Kilic E. Brain-derived neurotrophic factor polymorphism as a genetic risk for depression? A short review of the literature. J Neuropsychiatry Clin Neurosci. 2010.
2. Corlier J, Burnette E, Wilson AC, Lou JJ, Landeros A, Minzenberg MJ, *et al.* Effect of repetitive transcranial magnetic stimulation (rTMS) treatment of major depressive disorder (MDD) on cognitive control. J Affect Disord. 2020; 265: 272-277.
3. Caglayan B, Kilic E, Dalay A, Altunay S, Tuzcu M, Erten F, *et al.* Allyl isothiocyanate attenuates oxidative stress and inflammation by modulating Nrf2/HO-1 and NF-κB pathways in traumatic brain injury in mice. Mol Biol Rep. 2019; 46(1): 241-250.
4. Yulug B, Lutfu H, Elmir K, Ozge DA, Burcu P, Taha H, *et al.* Beyond the therapeutic effect of rTMS in alzheimer's disease: A possible neuroprotective role of hippocampal BDNF? : A minireview. Mini Rev Med Chem. 2018; 18(17): 1479-1485.
5. Yuluğ B, Ozan E, Gonul AS, Kilic E. Brain-derived neurotrophic factor, stress and depression: A minireview. Brain Res Bull. 2009; 78(6): 267-269.
6. Shilyansky C, Williams L, Gyurak A, Harris A, Usherwood T, Etkin A. Effect of antidepressant treatment on cognitive impairments associated with depression: A randomised longitudinal study. Lancet Psychiatry. 2016; 3(5): 425-435.
7. Sneed JR, Culang ME, Keilp JG, Rutherford BR, Devanand DP, Roose SR. Antidepressant medication and executive dysfunction: A deleterious interaction in late-life depression. Am J Geriatr Psychiatry. 2010; 18(2): 128-135.
8. Nagane A, Baba H, Nakano Y, Maeshima H, Hukatsu M, Ozawa K, *et al.* Comparative study of cognitive impairment between medicated and medication-free patients with remitted major depression: Class-specific influence by tricyclic antidepressants and newer antidepressants. Psychiatry Res. 2014; 218(1-2): 101-105.
9. Lapchak PA, Zhang JH. Neuroprotective therapy for stroke and ischemic disease. Springer. 2017.
10. Yulug B, Luftu H, Tavli MA, Nesrin YH, Ertugrul K. The brain protective effect of rTMS (Repetitive Transcranial Magnetic Stimulation) in depression: A mini-review in animal studies. Med Chem. 2016; 12(6): 500-505.
11. Luftu H, Yulug B, Ertugrul K, Burcu P, Wolf RS. The neuroprotective role of repetitive transcranial magnetic stimulation (rTMS) for neurodegenerative diseases: A short review on experimental studies. Mini Rev Med Chem. 2016; 16(16): 1269-1273.
12. George MS, Lisanby SH, Avery D, McDonald WM, Durkalski V, Pavlicova M, *et al.* Daily left prefrontal transcranial magnetic stimulation therapy for major depressive disorder: A sham-controlled randomized trial. Arch Gen Psychiatry. 2010; 67(5): 507-516.
13. Carpenter LL, Janikak PG, Aaronson ST, Boyadjas T, Brock DG, Cook AI, *et al.* Transcranial magnetic stimulation (TMS) for major depression: a multisite, naturalistic, observational study of acute treatment outcomes in clinical practice. Depress Anxiety. 2012; 29(7): 587-596.
14. Kuroda Y, Motohashi N, Ito H, Ito S, Takano A, Nishikawa T, *et al.* Effects of repetitive transcranial magnetic stimulation on [11C] raclopride binding and cognitive function in patients with depression. J Affect Disord. 2006; 95(1): 35-42.
15. Fitzgerald PB, Hoy K, Daskalakis ZJ, Kulkarni J. A randomized trial of the anti-depressant effects of low-and high-frequency transcranial magnetic stimulation in treatment-resistant depression. Depress Anxiety. 2009; 26(3): 229-234.
16. Wajdik C, Claypoole KH, Fawaz W, Holtzhiemer PE, Neumaier J, Dunner DL, *et al.* No change in neuropsychological functioning after receiving repetitive transcranial magnetic stimulation treatment for major depression. J ect. 2014; 30(4): 320-324.
17. Höppner J, Schulz M, Irmisch G, Mau R, Schlafke D, Richer J. Antidepressant efficacy of two different rTMS procedures. High frequency over left versus low frequency over right prefrontal cortex compared with sham stimulation. Eur Arch Psychiatry Clin Neurosci. 2003; 253(2): 103-109.
18. O'Connor MG, Edwin R, Beth J, Cornelia B, Elif O, Pascual LA. The effects of repetitive transcranial magnetic stimulation (rTMS) on procedural memory and dysphoric mood in patients with major depressive disorder. Cogn Behav Neurol. 2005; 18(4): 223-227.
19. Naim-Feil J, Bradshaw JL, Sheppard DM, Rosenberg O, Levkovitz Y, Dannon P, Fitzgerald PB, *et al.* Neuromodulation of attentional control in major depression: A pilot deepTMS study. Neural Plast. 2016; 2016: 5760141.
20. Moser DJ, Jorge RE, Manes F, Paradiso M, Benjamin L, Robinson G. Improved executive functioning following repetitive transcranial magnetic stimulation. Neurology. 2002; 58(8): 1288-1290.
21. Salagre E, Tomioka Y, Sole B, Fernandes BS, Mazzei HD, Garriga M, *et al.* Treatment of neurocognitive symptoms in unipolar depression: A systematic review and future perspectives. J Affect Disord. 2017; 221: 205-221.

22. Wang JX, Rogers LM, Gross EZ, Ryals AJ, Dokucu ME, Brandstatt KL, *et al.* Targeted enhancement of cortical-hippocampal brain networks and associative memory. Science. 2014; 345(6200): 1054-1057.

23. Jenkins BG, Klivnyi P, Kustermann E, Andreassen OA, Ferrante RJ, Rosen BR, *et al.* Nonlinear decrease over time in N-acetyl aspartate levels in the absence of neuronal loss and increases in glutamine and glucose in transgenic Huntington's disease mice. J Neurochem. 2000; 74(5): 2108-2119.

24. Maier M, Ron MA, Barker GJ, Tofts PS. Proton magnetic resonance spectroscopy: An *in vivo* method of estimating hippocampal neuronal depletion in schizophrenia. Psychol Med. 1995; 25(6): 1201-1209.