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Contents

Monthly Volume 10 Number 10 October 19, 2020

REVIEW

ORIGINAL ARTICLE

Observational Study

World Journal of Psychiatry

Monthly Volume 10 Number 10 October 19, 2020

Contents

ABOUT COVER

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REVIEW

Mechanisms of repetitive transcranial magnetic stimulation for anti-depression: Evidence from preclinical studies

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Abstract

This review summarizes the anti-depressant mechanisms of repetitive transcranial magnetic stimulation in preclinical studies, including anti-inflammatory effects mediated by activation of nuclear factor-E2-related factor 2 signaling pathway, anti-oxidative stress effects, enhancement of synaptic plasticity and neurogenesis *via* activation of the endocannabinoid system and brain derived neurotrophic factor signaling pathway, increasing the content of monoamine neurotransmitters *via* inhibition of Sirtuin 1/monoamine oxidase A signaling pathway, and reducing the activity of the hypothalamic-pituitary-adrenocortical axis. We also discuss the shortcomings of transcranial magnetic stimulation in preclinical studies such as inaccurate positioning, shallow depth of stimulation, and difficulty in elucidating the neural circuit mechanism up- and down-stream of the stimulation target brain region.

Key Words: Repetitive transcranial magnetic stimulation; Anti-depressant mechanisms; Nuclear factor-e2-related factor 2; Endocannabinoid system; Monoamine oxidase; Hypothalamic-pituitary-adrenocortical axis; Brain derived neurotrophic factor

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Core Tip: Repetitive transcranial magnetic stimulation (rTMS) is an effective treatment for major depressive disorder. This paper reviews the anti-depressant mechanisms of rTMS that have been found in preclinical studies in recent years and discusses the shortcomings of TMS in preclinical studies.

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INTRODUCTION

Repetitive transcranial magnetic stimulation (rTMS), electroconvulsive therapy (ECT), and vagus nerve stimulation are three physical strategies that have been approved by the United States Food and Drug Administration for the treatment of major depressive disorder (MDD)[1]. Compared with ECT and vagus nerve stimulation, rTMS is more readily accepted by patients with MDD because it does not require anesthesia and minimally invasive surgery with fewer side effects.

Since rTMS is an effective treatment for MDD[2-6], understanding its anti-depressant mechanisms may help to deepen the understanding of depression. This paper focuses on preclinical studies, reviews the underlying mechanisms of rTMS in animal models of depressive-like behavior, and discusses the shortcomings and deficiencies of rTMS in preclinical studies. Preclinical studies have shown that rTMS plays an anti-depressant role through a variety of mechanisms with diverse signaling pathways (Table 1).

REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION ACTIVATES THE ANTI-INFLAMMATORY EFFECTS MEDIATED *VIA* THE NUCLEAR FACTOR-E2-RELATED FACTOR 2 SIGNALING PATHWAY

Inflammation is strongly associated with depression[7-10]. Patients with autoimmune and infectious diseases are more likely to develop depression[11]. Patients with aseptic inflammation in the brain (such as stroke) are more likely to be accompanied by depression[12]. There are few clinical studies on the effects of rTMS on immune inflammation in MDD patients. Langguth *et al*[13] reported the recurrence of rheumatoid arthritis in an elderly female patient with treatment-resistant depression (TRD) comorbid with rheumatoid arthritis after receiving 20 Hz (intensity, 90% motor threshold) rTMS. After the patient received rTMS, the peripheral C-reactive protein and interleukin-6 (IL-6) contents increased (from 6.7 mg/L to 25 mg/L and from 3.4 ng/L to 15 ng/L, respectively), indicating that rTMS enhanced the inflammatory response of the patient. In contrast, Zhao *et al*[14] recruited 58 elderly patients with TRD and 30 healthy controls. The levels of peripheral IL-1β and tumor necrosis factor α (TNFα) in the patients were higher than those in healthy controls. Compared with the non-rTMS treated group, peripheral IL-1β and TNFα levels were markedly reduced in patients who were continuously treated with 10 Hz (intensity, 80 % motor threshold) rTMS for 4 wk. In addition, the levels of peripheral pro-inflammatory cytokines had no observable change in healthy controls after treatment by rTMS, which was consistent with the results of animal studies[15].

Nuclear factor-E2-related factor 2 (Nrf2) is a transcription factor that binds to antioxidant response elements and has anti-inflammatory effects in addition to anti-oxidative stress[16-18]. There was significantly reduced expression of Nrf2 both in the hippocampus and prefrontal cortex (PFC) of depressive-like mice induced by chronic social defeat stress or stress susceptible rats induced by learned helplessness[18,19]. Moreover, autopsy revealed that Nrf2 expression was decreased in the PFC region of MDD patients[19,20]. Tian *et al*[21] found that depressive-like behavior induced by chronic unpredictable mild stress (CUMS) in rats were improved by rTMS (15 Hz/1.26 T) *via* increasing Nrf2 translocation into the nucleus and decreasing the expression of TNFα, inducible nitric oxide synthase, IL-1β, and IL-6 in the hippocampus. When the *Nrf2*

Table 1 Main preclinical findings on antidepressant mechanisms of repetitive transcranial magnetic stimulation

Ref.	Model	rTMS				Main findings
		Frequency (Hz)	Intensity (T)	Duration (d)	Coil size	
Tian *et al*[21], 2020	CUMS	15	1.26	7	Inner diameter 2.5 cm; outer diameter 5 cm (SD rats)	Regulation of Nrf2-induced anti-inflammatory effect in the hippocampus
Yang *et al*[42], 2019	CUS	1	20 mT	14	Not mentioned	Enhancement of synaptic plasticity in the hippocampus
Xue *et al*[45], 2019	CUS	5	1.26	7	Inner diameter 2.5 cm; outer diameter 5 cm (SD rats)	Activation of the ECS in the hippocampus
Zhao *et al*[49], 2018	CUMS	10	50% of the resting motor threshold	15	5 cm in diameter (SD rats)	Decreasing the activity of the HPA axis
Heath *et al*[48], 2018	OB	10	50 mT	20	8 mm in diameter (C57BL/6J mice)	Activation of the BDNF signaling pathway and pro-proliferative in the hippocampus
Fang *et al*[43], 2018	CUMS	15	rTMS device maximum power	7	Not mentioned	Activation of the ECS in the hippocampus
Peng *et al*[68], 2017	CUS	5/10	0.84/1.26	7	Inner diameter 2.5 cm; outer diameter 5 cm (SD rats)	Suppression of Sirt1/MAO-A signaling in the PFC
Chen *et al*[47], 2015	CUS	15	1.26	7	Inner diameter 2.5 cm; outer diameter 5 cm (SD rats)	Activation of the BDNF signaling pathway and pro-proliferative in the hippocampus
Wang *et al*[44], 2014	CUMS	15	rTMS device maximum power	7	Inner diameter 2.5 cm; outer diameter 5 cm (SD rats)	Activation of the ECS and BDNF signaling pathway in the hippocampus
Kim *et al*[78], 2014	CUMS	10	1.4	14	7 cm in diameter (SD rats)	Changing metabolic patterns in the brain
Feng *et al*[46], 2012	CUMS	15	rTMS device maximum power	21	Inner diameter 5 cm; outer diameter 7 cm (SD rats)	Decreasing the activity of the HPA axis, and activation of BDNF signaling pathway in the hippocampus
Tasset *et al*[29], 2010	OB	60	0.7 mT	14	Not mentioned	Anti-oxidative stress effects

BDNF: Brain derived neurotrophic factor; CUS: Chronic unpredictable stress; CUMS: Chronic unpredictable mild stress; ECS: Endocannabinoid system; HPA axis: Hypothalamic-pituitary-adrenocortical axis; MAO-A: Monoamine oxidase A; Nrf2: Nuclear factor-E2-related factor 2; OB: Olfactory bulbectomy; PFC: Prefrontal cortex; rTMS: Repetitive transcranial magnetic stimulation; SD rats: Sprague Dawley rats; Sirt1: Sirtuin 1.

gene was silenced, the anti-depressant effect of rTMS disappeared simultaneously with a decrease of inflammatory factors. The results suggested that rTMS plays an anti-depressant role *via* enhancement of an anti-inflammatory action mediated by the Nrf2 signaling pathway. However, the mechanism by which rTMS exerts its anti-depressant effect through an anti-inflammatory effect has not been fully elucidated. Therefore, more preclinical studies are needed in this respect.

ANTI-OXIDATIVE STRESS EFFECTS

Humans produce reactive oxygen species (ROS) in the process of using O_2 to oxidize glucose to generate adenosine triphosphate. Excessive ROS act on lipids, proteins, and deoxyribonucleic acid, and produce a large number of peroxidation products such as lipid peroxidation products malondialdehyde and 4-hydroxyalkenals, resulting in oxidative stress, which is considered an important factor for disease development. There are two types of anti-oxidative stress systems in the body: One is the enzymatic anti-oxidative stress system including glutathione peroxidase (GSH-Px) and superoxide dismutase; The other is the non-enzymatic anti-oxidative stress system including glutathione (GSH). Several meta-studies have shown increased peroxidation products and decreased anti-oxidative stress agents in MDD patients[22-25]. Durmaz *et al*[26] found that, compared with the value before treatment, the serum content of

thiol, an anti-oxidant organic sulfur, was reduced in TRD patients after treatment with 20 Hz (intensity, 110 % motor threshold) rTMS. However, there are different views on the anti-depressant effect of rTMS through anti-oxidative stress. Aydın *et al*[27] found that there was no difference in serum thioredoxin, a protein with anti-oxidant function, between healthy and TRD patients, or between TRD patients before and after rTMS treatment.

The review of Medina-Fernández *et al*[28] detailed the anti-oxidative stress effects of rTMS in a variety of diseases. In preclinical studies of depression, the mechanism of anti-oxidative stress in rTMS has been poorly studied. Compared with sham rTMS group, rTMS at 60 Hz/0.7 mT increased the decreased contents of GSH, GSH-Px, and superoxide dismutase, and decreased the contents of malondialdehyde, 4-hydroxyalkenals, and caspase-3, a key terminal shear enzyme in apoptosis, in brain tissue homogenate in a rat depression model induced by olfactory bulbectomy[29]. The idea that oxidative stress is one of the causes or characteristics of MDD has not been widely accepted by the academic community. In addition, the anti-depressive role of rTMS through the mechanism of anti-oxidative stress has been controversial in clinical studies, in which the measurement of oxidative stress markers in peripheral blood may not reflect the real situation in the brain truthfully and completely. Unfortunately, only one preclinical study was found to clarify the mechanism of anti-oxidative stress in the anti-depressive effect of rTMS.

ACTIVATION OF ENDOCANNABINOID SYSTEM AND BRAIN DERIVED NEUROTROPHIC FACTOR SIGNALING PATHWAY ENHANCES SYNAPTIC PLASTICITY AND NEUROGENESIS

Cumulative evidence suggests that the endocannabinoid system (ECS) is involved in the physiopathologic mechanism of depression[30-32]. ECS receptors include cannabinoid type 1 receptor (CB1R) and CB2R. ECS ligands include arachidonoyl ethanolamide (AEA), 2-arachidonyloglycerol (2-AG), noladine ether, virodhamine, and N-arachidonoyldopamine. Other endogenous compounds such as palmitoylethanolamide and oleylethanolamide also have affinity for the ECS receptors. AEA and 2-AG are the most important ligands in the ECS. The key proteins in AEA biosynthesis and decomposition are N-acyl phosphatidyl ethanolamine-phospholipase D and fatty acid amide hydrolase, respectively. The key proteins in 2-AG biosynthesis and decomposition are diacylglycerol lipase α (DAGLα) and monoacylglycerol lipase (MAGL), respectively. Endocannabinoids produced in the postsynaptic element activate endocannabinoid receptors located in the presynaptic membrane and perform a number of anti-depressant biological functions including: (1) Reducing the activity of the hypothalamic-pituitary-adrenocortical (HPA) axis; (2) Enhancing hippocampal synaptic plasticity; (3) Promoting the neurogenesis of the hippocampus; and (4) Increasing the expression of brain derived neurotrophic factor (BDNF) in hippocampal tissue[33-36]. BDNF, a key factor affecting multiple signaling pathways in the brain, binds to the receptor TrkB on the membrane and activates the Ras/MAPK, PI3K/Akt, PLCγ, and GTPase signaling pathways to promote neurogenesis and enhance synaptic plasticity[37-41].

One Hz/20 mT rTMS increased the expression of synaptic proteins PSD95 and NR2B in the hippocampus of Wista rats with a depressive-like behavior induced by chronic unpredictable stress (CUS)[42]. rTMS at 15 Hz (intensity, device maximum power) reduced the expression of MAGL and Bax, increased the contents of 2-AG, CB1R, BDNF, and Bcl-2, and promoted neurogenesis in the hippocampus, improving depressive-like behavior induced by CUMS. CB1R antagonist (AM251) counteracts the biological function of the above mentioned rTMS[43,44]. rTMS at 5 Hz/1.26 T improved depressive-like behavior induced by CUS in rats *via* increasing the expression of CB1R, DAGLα, N-acyl phosphatidyl ethanolamine-phospholipase D, PSD95, and synaptophysin, and decreasing the expression of MAGL and fatty acid amide hydrolase in the hippocampus. The anti-depressant effect of rTMS was offset by short hairpin RNA targeting DAGL or CB1R[45]. The above preclinical studies suggested that rTMS plays an anti-depressant role by activating the ECS, which may provide evidence for the development of new anti-depressants targeting ECS.

Moreover, several preclinical studies have observed that rTMS increased the content of BDNF in the hippocampus and PFC, and promoted hippocampal neurogenesis in rodent CUMS, CUS, and olfactory bulbectomy depression models[44,46-49]. However, there are inconsistencies between the results of preclinical and clinical studies. BDNF

may be involved in hippocampal neurogenesis and synaptic plasticity as a neurotrophic factor, but the existence of a neuro-regenerative disorder hypothesis for depression is controversial. As compared with normal controls, the serum BDNF level markedly decreased in MDD patients, and significantly negatively correlated with the severity of depressive symptoms. In addition, in TRD patients carrying a homozygous BDNF Val/Val allele, the BDNF levels increased after treatment by rTMS[50,51]. However, the results of treatment effect were controversial in TRD patients, and it can be confirmed to be a predictor of treatment response in TRD patients. We included five relevant articles and conducted a mini meta-analysis using Review Manager 5.3 software[14,52-55]. It was found that serum BDNF levels in TRD patients increased after rTMS treatment (Figure 1A). Considering the issue of high heterogeneity, we applied the leave-one-out method to analyze the results[56], and found that after removing the study of Zhao *et al*[14], the heterogeneity decreased from 96% to 11%, and the conclusion that rTMS treatment had no effect on serum BDNF content in TRD patients was reached, which was consistent with the study results of Brunoni *et al*[57] (Figure 1B). BDNF is a macromolecular protein that does not easily cross the blood-brain barrier, which may be responsible for the inconsistency between the results of the above preclinical and clinical studies.

SUPPRESSION OF SIRTUIN 1/MONOAMINE OXIDASE A SIGNALING PATHWAY

Certain monoamine oxidase (MAO) inhibitors are used to treat patients with MDD, which include phenelzine, brofaromine, toloxatone, isocarboxazide, tranylcypromine, and moclobemide. MAO includes MAO-A and MAO-B subtypes in the brain, where MAO-A is involved in the metabolism of 5-hydroxytryptamine, norepinephrine, and dopamine, and MAO-B metabolizes dopamine, benzylamine, and phenethylamine[58-60]. Moreover, MAO-A produces ROS during the process of metabolizing monoamine neurotransmitters, which promotes neuronal apoptosis[61,62]. The expression of MAO-A is regulated by the transcription factors NHLH2, KLF11, R1, and FOXO1. Among them, NHLH2 and FOXO1 need to be deacetylated by Sirtuin 1 (Sirt1) to play the role of transcription factors[63-67]. Injection of Sirt1 inhibitor EX527 into the PFC of CUS rats improved depressive-like behavior. Further, the 5-hydroxytryptamine concentration in the PFC was increased by reducing the expression of Sirt1 and MAO-A and the activity of MAO, and the depressive-like behavior in CUS rats was improved after treatment by rTMS at 5 Hz/0.84 T, 5 Hz/1.26 T, 10 Hz/0.84 T, and 10 Hz/1.26 T[68]. MAO inhibitors take several weeks to demonstrate anti-depressant efficacy[69,70], whereas rTMS is not only effective in patients with TRD but also works faster than anti-depressants. Therefore, the Sirt1/MAO-A signaling pathway may not be a key mechanism for anti-depressant therapy in rTMS, especially for patients with TRD.

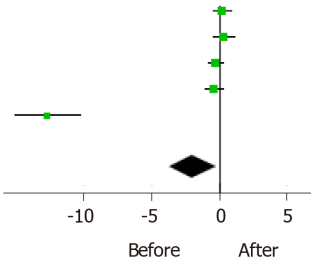
DECREASING THE ACTIVITY OF THE HYPOTHALAMIC-PITUITARY-ADRENOCORTICAL AXIS

Hyperactivity of the HPA axis may be one of the pathophysiological mechanisms of depression[71-73]. Both preclinical and clinical studies have found increased activity of the HPA axis either in depressive-like animal models or in MDD patients. However, the results were contradictory, especially in clinical studies. There are many interfering factors for hormone levels, such as changes in circadian rhythm[74]. Drugs targeting the HPA axis have not been successful in clinical trials[70]. As a result, it has not been possible to use HPA related measurements in the diagnosis of MDD, and there may be many mechanisms that have not been clarified. rTMS at 10 Hz (intensity, 50 % of the resting motor threshold) and 15 Hz (intensity, device maximum power) reduced the levels of adrenocorticotropic hormone and cortisol in peripheral blood of depressive-like rats induced by CUMS[46,49]. There are few preclinical and clinical studies supporting that rTMS exerts an anti-depressant effect by reducing the activity of the HPA axis, and the current evidence is still insufficient.

A

Study or subgroup	Before mean	Before SD	Before Total	After mean	After SD	After Total	Weight	Std. mean difference IV, random, 95%CI
Gedge 2012	10.05	5.134	18	8.9	4.327	18	21.2%	0.24 [-0.42, 0.89]
Lang 2006	13.041	3.899	14	11.204	5.776	14	21.0%	0.36 [-0.39, 1.11]
Yukimasa 2006	2.53	2.01	26	3.11	2	26	21.4%	-0.28 [-0.83, 0.26]
Zanardini 2006	29.73	8.02	16	32.63	7.59	16	21.1%	-0.36 [-1.06, 0.34]
Zhao 2019	4.24	1.12	29	14.74	0.28	29	15.3%	-12.69 [-15.14, -10.24]
Total (95%CI)			103			103	100.0%	-1.95 [-3.69, -0.21]

Heterogeneity: Tau^2 = 3.62, Chi^2 = 104.09, df = 4 (P < 0.00001); I^2 = 96%
Test for overall effect: Z = 2.19 (P = 0.03)



B

Study or subgroup	Before mean	Before SD	Before Total	After mean	After SD	After Total	Weight	Std. mean difference IV, fixed, 95%CI
Gedge 2012	10.05	5.134	18	8.9	4.327	18	24.5%	0.24 [-0.42, 0.89]
Lang 2006	13.041	3.899	14	11.204	5.776	14	18.8%	0.36 [-0.39, 1.11]
Yukimasa 2006	2.53	2.01	26	3.11	2	26	35.2%	-0.28 [-0.83, 0.26]
Zanardini 2006	29.73	8.02	16	32.63	7.59	16	21.5%	-0.36 [-1.06, 0.34]
Total (95%CI)			74			74	100.0%	-0.05 [-0.38, 0.27]

Heterogeneity: Tau^2 = 3.37, df = 4 (P = 0.34); I^2 = 11%
Test for overall effect: Z = 0.32 (P = 0.75)

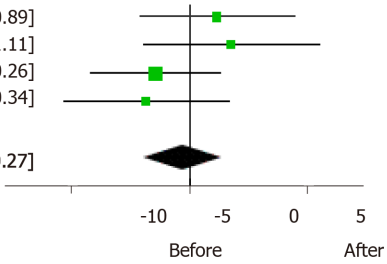


Figure 1 Forest plots of serum brain derived neurotrophic factor levels in treatment-resistant depression patients before and after repetitive transcranial magnetic stimulation treatment.

FUTURE PERSPECTIVES

This review summarizes several newly discovered anti-depressant mechanisms of rTMS in preclinical studies, including: (1) Anti-inflammatory effects mediated by activation of the Nrf2 signaling pathway; (2) Anti-oxidative stress effects; (3) Enhancement of synaptic plasticity and neurogenesis *via* activation of the ECS and BDNF signaling pathway; (4) Increasing the content of monoamine neurotransmitters *via* inhibition of the Sirt1/MAO-A signaling pathway; and (5) reducing the activity of the HPA axis.

Preclinical research has an incomparable huge advantage in obtaining brain specimens compared to clinical research. In the future preclinical research on rTMS mechanism, the following issues can be appropriately considered:

(1) The efficacy of rTMS is closely related to parameters, treatment time, and experimental protocol[75,76], and there is no unified treatment protocol in preclinical studies although it is available in clinical practice;

(2) Epidemiological studies show that the morbidity of females is higher than that of males for MDD[70,77]. However, all the studies in Table 1 used male rodents, which may be inappropriate or incomplete to elucidate the anti-depressant mechanisms of rTMS in animals;

(3) Different intensity of 10 Hz rTMS affects the metabolic patterns in the brain and periphery of the depression models[48,78]. rTMS at 1.4 T reduced the level of γ-amino butyric acid in the hippocampus and PFC regions of CUMS rats[78]. rTMS at 1 T increased the content of α-amino butyric acid and reduced the content of 3-methylhistidine in peripheral blood of mice suffering from olfactory bulbectomy[48]. Recently, proteomics and metabolomics techniques are gradually used to explore the anti-depressant mechanism of rTMS to focus on screening candidate biomolecule or biomarkers, which may provide a clue for further elucidating the relevant mechanisms;

(4) Preclinical studies have mostly focused on the hippocampus in animal models of depressive-like behavior. However, an increasing amount of evidence indicates that, other core brain regions are also closely associated with the development and progression of depression, such as the PFC, amygdala, cingulate gyrus, habenula, and

visual cortex[79-81], which should be considered in future studies. In addition, deep brain stimulation plays an important anti-depressant role in patients with MDD[82-85], suggesting that neural circuit dysfunction may be one of the mechanisms of depression[86]; however, there is no animal research to probe the regulation of neural circuits related to the anti-depressant effect of rTMS, which may be one of the future research directions;

(5) The shortcomings of TMS include inaccurate positioning and shallow depth of stimulation, which cause the difficulty to elucidate the neural circuit mechanism of up- and down-stream of the stimulation target region in animal models.

The left and right dorsolateral PFC of MDD patients have asymmetric low and high activity, respectively[87]. In clinical practice, high and/or low frequency rTMS are commonly used to stimulate the left and/or right side, respectively, to obtain anti-depressant effects. However, in preclinical studies, as shown in Table 1, due to the relatively large diameter of the coils of the rTMS device, it is not possible to accurately stimulate a specific brain region in rodents, and instead a large range of a hemisphere or even the whole brain is stimulated. This may be detrimental to the elucidation of the potential anti-depressant mechanism of rTMS. The development of rTMS devices for rats and mice with appropriate size and precise focus may be more conducive to exploring the mechanism of the anti-depressant effect of rTMS.

Another unavoidable defect of TMS is the problem of depth of stimulation, that is, TMS can only stimulate the superficial cerebral cortex, but has no stimulation effect on the subcortical brain regions[88]. Deep TMS can stimulate relatively deep brain regions compared to other TMS, but it may cause the superficial regions to be strongly stimulated[89]. In addition, TMS has energy consumption in non-target tissues such as the scalp, skull, and cerebrospinal fluid, which can reduce the energy occupancy rate of target tissues.

The application of a smaller size rTMS coil can achieve precise positioning, but the efficacy of the stimulation is insufficient and the therapeutic effect is affected. Exhilaratingly, enhancing the therapeutic effect by using magnetic nanoparticles may be in a creative way. Kong *et al*[90] found that magnetic nanoparticles could pass through the blood-brain barrier in mice. Furthermore, Li *et al*[91] intravenously injected magnetic nanoparticles with a core of Fe_3O_4 in rats, which can enhance the therapeutic effect of TMS. Our research team constructed a novel superparamagnetic Fe_2O_3 nanoparticle, accurately injected it into the left prelimbic cortex of CUMS mice treated by rTMS at10 Hz/0.1 T for 5 d, and significantly improving the depressive symptoms of these mice[92].

CONCLUSION

In conclusion, fully elucidating the anti-depressant mechanisms of rTMS will increase the chances of discovering new therapeutic strategies.

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ORIGINAL ARTICLE

Observational Study

Development of a depression in Parkinson's disease prediction model using machine learning

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Abstract

BACKGROUND

It is important to diagnose depression in Parkinson's disease (DPD) as soon as possible and identify the predictors of depression to improve quality of life in Parkinson's disease (PD) patients.

AIM

To develop a model for predicting DPD based on the support vector machine, while considering sociodemographic factors, health habits, Parkinson's symptoms, sleep behavior disorders, and neuropsychiatric indicators as predictors and provide baseline data for identifying DPD.

METHODS

This study analyzed 223 of 335 patients who were 60 years or older with PD. Depression was measured using the 30 items of the Geriatric Depression Scale, and the explanatory variables included PD-related motor signs, rapid eye movement sleep behavior disorders, and neuropsychological tests. The support vector machine was used to develop a DPD prediction model.

RESULTS

When the effects of PD motor symptoms were compared using "functional weight", late motor complications (occurrence of levodopa-induced dyskinesia) were the most influential risk factors for Parkinson's symptoms.

CONCLUSION

It is necessary to develop customized screening tests that can detect DPD in the early stage and continuously monitor high-risk groups based on the factors related to DPD derived from this predictive model in order to maintain the emotional health of PD patients.

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Core Tip: When the effects of Parkinson's disease (PD) motor symptoms were compared using "functional weight", the occurrence of levodopa-induced dyskinesia was the most influential risk factor in the diagnosis of depression in Parkinson's disease (DPD). These results can be used as baseline information to prevent DPD and establish management strategies. It is necessary to develop customized screening tests that can detect DPD patients in the early stage and continuously monitor high-risk groups based on the factors related to DPD derived from this predictive model in order to maintain the emotional health of PD. It is also necessary to develop customized programs for managing depression from the onset of PD.

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INTRODUCTION

Parkinson's disease (PD) is a typical degenerative disease of the elderly with the second-highest incidence rate after Alzheimer's disease. The incidence rate of PD increases worldwide as the population ages. The Health Insurance Research and Assessment Service (2017)[1] reported that the number of patients with PD increased from 39265 in 2004 to 96499 in 2016, a 2.5-fold increase over 13 years, in South Korea. If the current trend in the aging population continues, the number of patients with PD will increase even further.

Although the primary symptom of PD is dyskinesia such as rigidity, it is highly likely that non-motor symptoms such as depression or cognitive impairment develop as PD progresses[2]. Among these symptoms, depressive symptoms are the most common non-motor symptoms of PD and previous studies[3-6] have reported that 35% to 75% of patients with PD suffer from depression, which is much higher than the prevalence of depression in adults in the local community (< 10%)[7]. Depression is known to adversely affect the quality of life in PD patients[8], and Parkinson's patients with depression have significantly higher anxiety symptoms, pessimism, suicidal thoughts, and self-condemnation compared to Parkinson's patients without depression[4,9]. Lee *et al*[10] analyzed 4362 patients with PD and reported that the elderly with PD had a 2-fold higher risk of suicide compared to healthy elderly. Even though patients with PD frequently experience depression[6,11], only 1% of them recognize that they have depression. These results suggest that it is necessary to diagnose depression in PD (DPD) as soon as possible[7,8]. Depression induced by PD requires social management and should not be considered a personal matter. As the symptoms of depression deteriorate as PD progresses, these symptoms, together with cognitive impairment, not only increase direct costs such as examinations and treatment but also raise indirect costs such as job loss due to disability and the care burden of supporting family members[12,13]. Ultimately, it causes unnecessary social expenditure at the national level. However, there are few studies on the characteristics and related factors of depression, a non-motor symptom of PD, compared to the motor symptoms of PD. Many medical practitioners are still more interested in the motor symptoms of PD than the non-motor symptoms. Moreover, depression is often misdiagnosed due to the non-motor and motor symptoms associated with PD[5]. It is important to diagnose depression in PD patients as soon as possible and identify predictors of depression to improve quality of life in PD patients.

It has been reported that the duration of PD, Hoehn and Yahr phase, age, activities of daily living, low cognitive function, and sleep behavior disorder affect DPD[5,14,15]. Depression frequently occurs during the early stages of PD[16]. Previous studies suspected that PD might cause depression along with dyskinesia due to dopamine

deficiency[6,17]. However, other studies showed that the administration of L-dopa (levodopa), a Parkinson's treatment, did not improve depression symptoms indisputably[18]. Therefore, it cannot be determined that depression is simply due to the effect of dopamine deficiency. On the other hand, many recent scholars have argued that depression in PD patients was caused by the complex interactions of multiple factors, rather than a single cause[19,20]. However, these previous studies[5,16,17] are limited in determining a risk factor, while considering multiple risk factors as each study used different confounding factors or covariates and used regression models to predict a risk factor, although they were effective in exploring individual risk factors. Additionally, regression analysis requires data which satisfy many assumptions such as normality, linearity, and homoscedasticity, and disease data are highly likely to violate these assumptions.

Recent studies have used various machine learning classifiers such as the support vector machine (SVM) and decision tree as statistical classification methods to identify multiple risk factors for diseases such as depression[21]. Of these, the SVM divides data into two groups linearly and explores the optimal boundary. SVM can be used for classifying nonlinear data, it has less probability of overfitting than the decision tree model, and it has high prediction accuracy even for small sample sizes[22,23]. The objectives of present study were to develop a model for predicting DPD based on the SVM, while considering sociodemographic factors, health habits, Parkinson's symptoms, sleep behavior disorders, and neuropsychiatric indicators as predictors and to provide baseline data for identifying DPD.

MATERIALS AND METHODS

Subjects

The present study was conducted by analyzing the Parkinson's Disease Epidemiology (PDE) Data provided by the National Biobank of Korea, the Centers for Disease Control and Prevention (CDC), and Republic of Korea (No. KBN-2019-005). This study was approved by the Research Ethics Review Board of the National Biobank of Korea (No. 2019-005) and the Korea-CDC (No. 2019-1327). The goal of the National Biobank and the structure of the data were described by Lee *et al*[24]. The PDE data used in this study were collected at 14 university hospitals from January to December, 2015, under the supervision of the Korea CDC. The PDE data consisted of health behaviors, sociodemographic factors, motor characteristics related to PD, disease history, neuropsychological test results and sleep behavior disorders. PD was diagnosed according to the idiopathic Parkinson's disease diagnosis criteria of the United Kingdom Parkinson's disease Society Brain Bank[25]. This study analyzed 223 of 335 patients who were 60 years or older with PD, after excluding 112 subjects who had a least one missing value in the Geriatric Depression Scale (GDS)[26], a depression screening test.

Measurement

Depression was measured using the 30 items of the GDS[26], and the threshold point of depression was 10 points. Explanatory variables included PD-related motor signs (*e.g.*, late motor complications, bradykinesia, tremor, postural instability, and rigidity), rapid eye movement (REM) and sleep behavior disorders, the Korean Mini Mental State Examination score[27], Korean Montreal Cognitive Assessment score[28], global Clinical Dementia Rating score (CDR)[29], Korean Instrumental Activities of Daily Living score (K-IADL)[30], Untitled Parkinson`s Disease Rating total score (UPDRS)[31], UPDRS motor score[32], Hoehn and Yahr staging (H and Y staging)[33], and the Schwab and England Activities of Daily Living scale (Schwab and England ADL)[34].

SVM was used to develop a DPD prediction model. SVM is a MLalgorithm that finds an optimal decision boundary, in other words, a linear separation dividing the hyperplane (H-plane) optimally, by converting training data to a higher dimension through nonlinear mapping[35]. For example, A = [b, e] and B = [c, f] are non-linearly (non-lin) separable in two dimensions. When they are mapped in three dimensions, they have linearly separable characteristics. Therefore, when appropriate non-lin mapping is conducted at sufficiently large dimensions, data with two classes can always be separated in H-plane[23].

SVM is very accurate as it can model complex nonlinear decision-making domains and tends to be overfitting less than other models, which is a major advantage of this method[36]. This study used R version 3.6.1 for statistical analyses. The prediction performance (accuracy) of eight SVM models was compared using four algorithms [

i.e., a radial basis function (Gauss function), a linear algorithm, a sigmoid algorithm, and a polynomial algorithm] and two types of SVM [C-SVM (C parameter) and Nu-SVM (Nu parameter)]. The prediction performance of the models was evaluated by considering overall accuracy, sensitivity, and specificity.

RESULTS

General characteristics of the 223 study subjects with PD were analyzed and are shown in Table 1. The mean age of the subjects was 71.7 years (SD = 6.1). The initial age at diagnosis of PD was 70.8 years (SD = 6.3) and the training period was 7.5 years (SD = 5.3). The percentage of non-smokers was 79.7%, right-handed subjects was 96.0%), and subjects without a family history of PD was 82.5%. It was found that 22.5% of the subjects had diabetes, 41.3% had hypertension, and 13.3% had hyperlipidemia. In terms of cognitive characteristics, 30.9% of the subjects had PDD, 61% had Mild Cognitive Impairment in Parkinson's disease (PD-MCI), and 8.1% of them had Parkinson's disease with cognitive impairment (PD-NC). The results of the GDS confirmed that 41.7% of the patients had depression. The distribution of neuropsychological test results is presented using a density plot (Figure 1).

Table 1 shows the general characteristics of the study subjects with depression and the related potential factors (influencing factors) of DPD. The results of the chi-square test showed that PD patients with depression and PD patients without depression were significantly different as assessed by the Korean Mini Mental State Examination, Korean Montreal Cognitive Assessment, Global CDR score, total score of UPDRS, sum of boxes in CDR, K-IADL, motor score of UPDRS, H and Y staging, and Chwab and England ADL ($P < 0.05$).

Comparing the accuracy of the DPD prediction model according to the SVM classification algorithm

The fit of the model varies by the kernel type of SVM. Therefore, our study compared the prediction accuracy of eight SVM models [(C-SVM or Nu-SVM) × (Gaussian kernel, linear, polynomial, or sigmoid algorithm)] to examine the performance of the models according to various kernel types (Table 2). The results of model fitting showed that the Gaussian Kernel-based Nu-SVM had the highest sensitivity (96.0%), specificity (93.3%), and mean overall accuracy (95%). On the other hand, although the polynomial-based C-SVM had the highest sensitivity (100%), it had the lowest specificity (20%) and the lowest mean overall accuracy (70%).

This study determined that the Gaussian algorithm-based Nu-SVM model, which had the highest sensitivity and overall accuracy, was the optimal model for predicting DPD and analyzed the importance of variables. The Gaussian algorithm-based Nu-SVM model utilized 34 support vectors and the "functional weight (importance of variables)" is presented in Table 3. Even though the functional weight of SVM is not a value simply for comparing the magnitudes of variables' influence or ranking the importance of variables, it is possible to compare the influence within the level of factors (*e.g.*, comparing the influence of gender) using it. It is also possible to understand whether the relationship between predictors and outcome variables is a risk factor or a preventive factor. The DPD prediction model revealed that the global CDR score, the sum of boxes in CDR, K-IADL, total UPDRS, motor UPDRS, age (≥ 75 years old), gender (female), education level (high school graduate or above), PD family history, smoking (21-40 packs per year), exposure to pesticides, postural instability, late motor complications (occurrence of levodopa-induced dyskinesia), late motor complications ("levodopa-induced dyskinesia" and occurrence of "wearing OFF"), and REM sleep behavior disorders were risk factors for depression. When the effects of PD motor symptoms were compared using "functional weight", late motor complications (occurrence of levodopa-induced dyskinesia) were the most influential risk factors for DPD.

DISCUSSION

Our study developed a depression prediction model using SVM for PD patients. This study used the hospital registry data and found that 41.7% of PD patients suffered from depression. Although it is difficult to compare directly, the results of this study were similar to the results of previous studies[4-6], showing that one in two PD patients

Table 1 General characteristics of the subjects with depression, *n* (%)

Characteristics	Depression		*P* value
	No (*n* = 130)	Yes (*n* = 93)	
Age			0.918
60-74 yr	83 (58.0)	60 (42.0)	
≥ 75 yr	47 (58.8)	33 (41.3)	
Sex			0.183
Male	62 (63.3)	36 (36.7)	
Female	68 (54.4)	57 (45.6)	
Education level			0.158
Middle school graduate and below	76 (54.7)	63 (45.3)	
High school graduate and above	54 (64.3)	30 (35.7)	
Handness			0.905
Right	125 (58.4)	89 (41.6)	
Left	2 (66.7)	1 (33.3)	
Both hands	2 (50.0)	2 (50.0)	
Family PD history			0.921
No	108 (58.7)	76 (41.3)	
Yes	9 (60.0)	6 (40.0)	
Pack year (smoking)			0.666
1-20 pack year	6 (42.9)	8 (57.1)	
21-40 pack year	5 (62.5)	3 (37.5)	
41-60 pack year	1 (50.0)	1 (50.0)	
61+ pack year	118 (59.3)	81 (40.7)	
Traumatic brain injury			0.852
No	118 (60.8)	76 (39.2)	
Yes	7 (63.6)	4 (36.4)	
Diabetes			0.214
No	103 (60.9)	66 (39.1)	
Yes	25 (51.0)	24 (49.0)	
Hypertension			0.246
No	71 (55.5)	57 (44.5)	
Yes	57 (63.3)	33 (36.7)	
Hyperlipidemia			0.220
No	114 (60.3)	75 (39.7)	
Yes	14 (48.3)	15 (51.7)	
Tremor			0.630
No	17 (54.8)	14 (45.2)	
Yes	107 (59.4)	73 (40.6)	
Rigidity			0.342
No	8 (72.7)	3 (27.3)	
Yes	120 (58.3)	86 (41.7)	
Bradykinesia			0.962

No	7 (58.3)	5 (41.7)	
Yes	121 (59.0)	84 (41.0)	
Postural instability			0.187
No	66 (64.1)	37 (35.9)	
Yes	59 (55.1)	48 (44.9)	
REM and RBD			0.081
No	58 (63.7)	33 (36.3)	
Yes	55 (51.4)	52 (48.6)	
Late motor complications			0.140
Only ON-OFF/Wearing OFF	12 (54.5)	10 (45.5)	
Only levodopa-induced dyskinesia	2 (22.2)	7 (77.8)	
Both ON-OFF/Wearing OFF and levodopa-induced dyskinesia are present	13 (59.1)	9 (40.9)	
Both ON-OFF / Wearing OFF and levodopa-induced dyskinesia are absent	99 (61.1)	63 (38.9)	
K-MMSE, mean ± SD	24.2 ± 4.6	21.5 ± 6.1	< 0.001
K-MoCA, mean ± SD	18.2 ± 6.1	13.9 ± 6.7	< 0.001
Global CDR score, mean ± SD	0.5 ± 0.3	0.8 ± 0.7	< 0.001
Sum of boxes in CDR, mean ± SD	2.3 ± 3.1	3.3 ± 4.0	0.041
K-IADL, mean ± SD	1.3 ± 3.0	3.2 ± 5.6	0.003
Total score of UPDRS, mean ± SD	34.5 ± 17.1	53.2 ± 26.1	< 0.001
Motor score of UPDRS, mean ± SD	22.7 ± 10.9	30.0 ± 13.5	< 0.001
H and Y staging, mean ± SD	2.2 ± 0.6	2.6 ± 0.9	0.002
Schwab and England ADL, mean ± SD	80.1 ± 14.5	67.3 ± 21.5	< 0.001

CDR: Clinical Dementia Rating; K-MMSE: Korean Mini-Mental State Examination; K-MoCA: Korean-Montreal Cognitive Assessment; K-IADL: Korean Instrumental Activities of Daily Living; UPDRS: Untitled Parkinson`s Disease Rating total score; H and Y: Hoehn and Yahr; ADL: Activities of Daily Living.

Table 2 Comparing the accuracy of depression in Parkinson's disease prediction model, %

Type of algorithm	Overall accuracy	Sensitivity	Specificity
C-SVM: Linear	92.5	92.0	93.3
C-SVM: Polynomial	70.0	100	20.0
C-SVM: Gaussian	87.5	96.0	73.3
C-SVM: Sigmoid	85.0	88.0	80.0
Nu-SVM: Linear	90.0	92.0	86.6
Nu-SVM: Polynomial	92.5	92.0	93.3
Nu-SVM: Gaussian	95.0	96.0	93.3
Nu-SVM: Sigmoid	82.5	92.0	66.6

SVM: Support vector machine.

had depression. Despite the frequent occurrence of depression among patients with PD, the Global Parkinson's Disease Survey Steering Committee (2002)[8] reported that only 1% of patients with PD recognized that they had depression. These results imply that, even though PD patients frequently experience depression, it is highly likely that many PD patients, their caregivers, and their medical practitioners do not find

Table 3 Functional weight (importance of variables)

Variables	Functional weight
K-MMSE	-1.454
K-MoCA	-4.499
CDR (Global CDR score)	2.643
CDR (sum of boxes)	2.607
K-IADL	4.919
Total UPDRS	5.302
Motor UPDRS	0.978
H and Y staging	-2.190
Schwab and England ADL	-5.055
Age (60-74)	-3.638
Age (75+)	3.638
Gender (female)	0.345
Education (high school graduate and above)	1.150
Family PD history (yes)	0.232
Pack year (21-40)	0.032
Pack year (41-60)	0.000
Pack year (61+)	-1.032
Coffee (yes)	1.006
Pesticide exposure (currently not exposed but exposed previously)	-1.000
Pesticide exposure (currently exposed to pesticide)	2.264
Tremor (yes)	0.000
Rigidity (yes)	-1.000
Bradykinesia (yes)	0.675
Postural instability (yes)	1.117
LMC (levodopa-induced dyskinesia)	3.000
LMC (Both Wearing OFF and levodopa-induced dyskinesia are present)	0.264
LMC (Both Wearing OFF and levodopa-induced dyskinesia are absent)	-4.715
REM sleep behavior disorders	1.261
Number of support vectors: 34	

CDR: Clinical Dementia Rating; K-MMSE: Korean Mini-Mental State Examination; K-MoCA: Korean-Montreal Cognitive Assessment; K-IADL: Korean Instrumental Activities of Daily Living; UPDRS: Untitled Parkinson`s Disease Rating total score; H and Y: Hoehn and Yahr; ADL: Activities of Daily Living; REM: Rapid eye movement; PD: Parkinson's disease.

depression symptoms in the patients or treat them as symptoms due to aging, and, consequently, the patients do not receive appropriate evaluation or treatment. Therefore, it is necessary to develop an education program in order to manage depression from the onset of PD so that PD patients and their caregivers can receive the correct information regarding depression and receive effective treatments. The results of this study showed that the global CDR score, the sum of boxes in CDR, K-IADL, total UPDRS, motor UPDRS, age (≥ 75 years old), gender (female), education level (≥ high school graduate), PD family history, smoking (21-40 packs per year), exposure to pesticides, postural instability, late motor complications (occurrence of levodopa-induced dyskinesia), late motor complications (occurrence of "wearing OFF" and "levodopa-induced dyskinesia"), and REM sleep behavior disorders were the major predictors of DPD. A number of studies[5,14,15] exploring the risk factors for DPD reported that daily living ability, sleep behavior disorders, cognitive level, and Hoehn

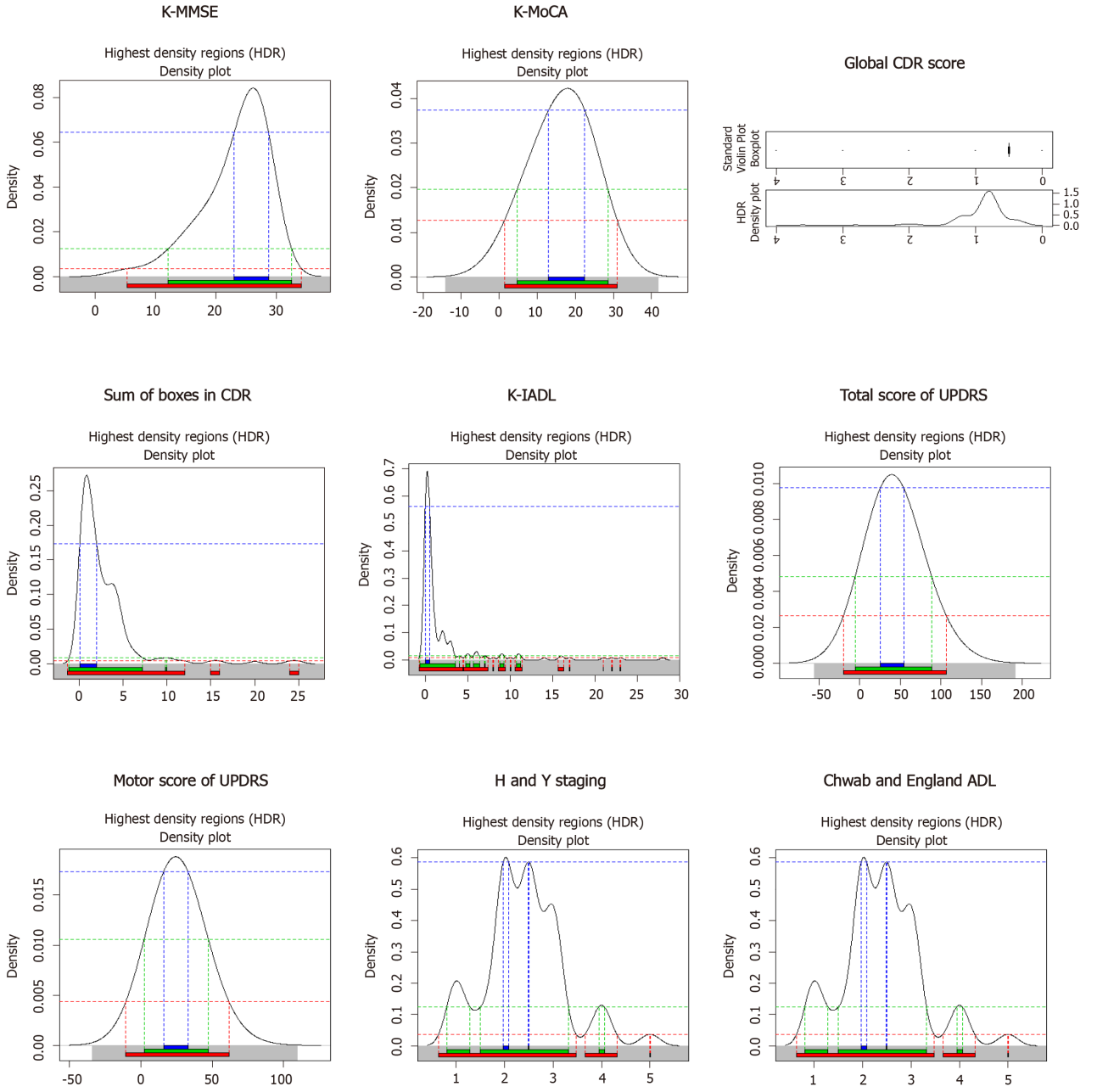

Figure 1 The distribution of neuropsychological tests. CDR: Clinical Dementia Rating; K-MMSE: Korean Mini-Mental State Examination; K-MoCA: Korean-Montreal Cognitive Assessment; K-IADL: Korean Instrumental Activities of Daily Living; UPDRS: Untitled Parkinson`s Disease Rating total score; H and Y: Hoehn and Yahr; ADL: Activities of Daily Living.

and Yahr[33] stages, as well as environmental factors (*e.g.*, social stigma and social participation), were key influencing factors of depression and these results supported the results of our study. In particular, sleep behavior disorder is known to be the most representative factor for predicting the risk of depression[37] and has a high correlation with depression[38]. It is known that sleep behavior disorders are caused by dysfunction in the autonomic nervous system of patients with PD[39]. Bae *et al*[40] evaluated factors related to DPD using structural equation modeling, and reported that a sleeping issue best predicted DPD.

ADL, indicating the limitation of physical functions, is also related to early depression[41], as social relations can decrease due to limited ADL resulting in depression[42]. If depression persists, the quality of life in PD patients is highly likely to decrease[43] and they have a high risk of suicide[10]. Therefore, it is necessary to develop customized screening tools that can detect high-risk groups sensitively and conduct continuous monitoring in order to prevent depression and maintain emotional health.

Another finding of our study was that the prediction accuracy of the Gaussian kernel-based Nu-SVM was the highest when comparing eight SVM classification

algorithms [(C-SVM or Nu-SVM) × (Gaussian kernel, linear, polynomial, or sigmoid algorithm)]. The performance of non-lin SVM is affected by the kernel function and the parameters constituting it[44]. Of these, the Gaussian kernel is an algorithm that maps in a specific space with infinite dimension and it had high predictive accuracy in a previous study[25]. The results of this study suggest that, in the case of binary disease data with a small sample size, developing a prediction model using Gaussian kernel-based Nu-SVM will have higher predictive accuracy than SVM models based on other algorithms.

The present study was meaningful because it developed an SVM-based DPD prediction model using national Parkinson's registry data while considering sociodemographic factors, health habits, Parkinson's symptoms, and sleep behavior disorders as predictors in addition to neuropsychological indicators. The limitations of this study are as follows. First, it is difficult to generalize the results of this study as hospital registry data collected using convenience sampling was used. Future studies are needed to apply systematic sampling at the stage of recruiting subjects to minimize selection bias. Secondly, the sample size was small. Thirdly, causality could not be identified because it was a cross-sectional study. Additional longitudinal studies are required to prove causality. Fourthly, biomarkers and Parkinson's treatments related to depression were not investigated. In order to predict depression more sensitively, it is necessary to develop a predictive model including biomarkers in addition to cognitive tests and neuropsychological tests.

CONCLUSION

The results of our study can be used as baseline information to prevent DPD and establish management strategies. It is necessary to develop customized screening that can detect DPD in the early stage and continuously monitor high-risk groups based on the factors related to DPD derived from this predictive model in order to maintain the emotional health of PD patients. It is also necessary to develop customized programs for managing depression from the onset of PD.

ARTICLE HIGHLIGHTS

Research background

It is important to diagnose depression in Parkinson's disease (PD) patients as soon as possible and identify predictors of depression to improve the quality of life in PD patients.

Research motivation

It has been reported that the duration of PD, Hoehn and Yahr phase, age, activities of daily living, low cognitive function, and sleep behavior disorder affect depression in PD. However, these previous studies are limited in determining a risk factor, while considering multiple risk factors as each study used different confounding factors or covariates and used regression models to predict a risk factor, although they were effective in exploring individual risk factors.

Research objectives

The objectives of our study were to develop a model for predicting depression in Parkinson's disease (DPD) based on the support vector machine while considering sociodemographic factors, health habits, Parkinson's symptoms, sleep behavior disorders, and neuropsychiatric indicators as predictors and to provide baseline data for identifying DPD.

Research methods

The data used in this study was collected at 14 university hospitals from January to December, 2015, under the supervision of the Korea Centers for Disease Control. The data consisted of health behaviors, sociodemographic factors, motor characteristics related to PD, disease history, neuropsychological test results and sleep behavior disorders.

Research results

When the effects of PD motor symptoms were compared using "functional weight", late motor complications (occurrence of levodopa-induced dyskinesia) were the most influential risk factors for DPD.

Research conclusions

It is necessary to develop customized screening that can detect DPD in the early stage and continuously monitor high-risk groups based on the factors related to DPD derived from this predictive model in order to maintain the emotional health of PD patients.

Research perspectives

It is also necessary to develop customized programs for managing depression from the onset of PD.

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