Review Article

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Transcranial Direct Current Stimulation for Global Cognition in Mild Cognitive Impairment

Jenny Jeaeun Chan[1], Yeryeong Cho[2], and Jae-Hon Lee[1,*]

Departments of [1]Psychiatry and [2]Interdisciplinary Medical Science, Schulich Medicine and Dentistry, Western University, London, ON, Canada

Mild cognitive impairment (MCI) is a condition characterized by noticeable deficits in memory retrieval or other cognitive domains than the individuals with the same age but do not significantly interfere with daily functioning. It represents an intermediate stage between normal aging and dementia, and a crucial opportunity for intervention prior to extensive cognitive decline. Transcranial direct current stimulation (tDCS), a non-invasive neuromodulation technique, has shown promise in enhancing global cognition in MCI. Current evidence suggests that tDCS provides short-term cognitive benefits, particularly in memory and attention, with moderate effects observed in processing speed. However, its impact on executive function and language remains inconsistent, highlighting variability in individual responses and study methodologies. While long-term efficacy remains uncertain due to limited longitudinal research and short follow-up periods, safety concerns, especially with self-administered tDCS such as in home-based tDCS, underscore the need for proper training and device innovation. Despite this, tDCS is a promising, portable tool for cognitive enhancement in MCI, with potential to delay progression to dementia. Addressing challenges such as optimizing stimulation protocols, accounting for individual neuroanatomical variability, and establishing long-term effectiveness will be essential for its broader clinical adoption. Future research should focus on standardizing methodologies, incorporating biomarkers to predict treatment response, and conducting large-scale, longitudinal studies to refine its therapeutic application.

Key Words: *Transcranial Direct Current Stimulation; Cognition; Cognitive Dysfunction*

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Corresponding Author:
Jae-Hon Lee
Department of Psychiatry, Schulich Medicine and Dentistry, Western University, 1151 Richmond St, London, ON N6A 5W9, Canada
Tel: +1-519-685-8500 (Ext. 76503)
Fax: +1-519-667-6836
E-mail: jae-hon.lee@lhsc.on.ca

INTRODUCTION

1. Mild cognitive impairment (MCI)

MCI is recognized as a transitional stage between normal cognitive aging and more severe forms of cognitive decline such as dementia.[1] Patients with MCI are characterized by noticeable deficits in memory retrieval or other cognitive domains compared to others their age, but not to the extent of significantly interfering with daily functioning.[1,2] This stage represents a critical window for early detection and intervention, as appropriate management can delay or even reverse progression to dementia.[3]

MCI is a complex condition influenced by multiple factors, including those associated with neurodegenerative diseases such as Alzheimer's disease (AD) and Parkinson's disease.[4,5] A significant proportion of individuals with MCI progress to AD, while others may develop cognitive impairments linked to Parkinsonian syndromes.[6,7] Despite this, MCI is not an inevitable precursor to dementia.[8] Early and effective interventions have the potential to reverse the condition, enhancing the quality of life for individuals and reducing the societal and economic burden of dementia care.[8]

Despite extensive research, managing MCI remains challenging, as pharmacological treatments aimed at improving cognition have failed to show significant benefits or slow progression.[5] These limitations have shifted focus

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toward non-pharmacological approaches like neuromodulation techniques and cognitive training which aim to enhance cognitive resilience and delay progression to dementia.

2. Transcranial direct current stimulation (tDCS)

tDCS, a non-invasive therapeutic neuromodulation technique, applies a low-intensity direct current of 1-2 mA to the scalp through electrodes to modulate neuronal excitability.[9-11] Unlike techniques that induce action potential such as electroconvulsive therapy (ECT), tDCS alters the neuronal resting membrane potential to depolarization or hyperpolarization depending on the electrode placement, thereby enhancing or suppressing neural excitability.[12] This treatment is particularly appealing for its portability and absence of serious adverse effects, making it a promising intervention for cognitive impairments such as those seen in MCI.[13] tDCS has been studied in a variety of applications, including memory enhancement,[14] attention,[15] and processing speed[11] and executive function.[16,17] For individuals with MCI, tDCS may provide a unique opportunity to strengthen neural pathways and alleviate cognitive decline.

This literature review aims to synthesize the most current evidence regarding the efficacy of tDCS in MCI for enhancing global cognition, which encompasses overall cognitive functioning and its integration across multiple domains. This review seeks to identify patterns, limitations, and emerging trends in current research regarding the use of tDCS for MCI. Additionally, it will explore the potential implications of these findings for clinical practice, including considerations for integrating tDCS into multidisciplinary approaches for managing MCI. This review is intended to provide clinicians with an up-to-date, comprehensive overview of tDCS for MCI populations.

FACTORS INFLUENCING THE EFFICACY OF tDCS

There are several important factors that influence the strength and focality of the electric field generated by tDCS and, by extension, the treatment response. These factors include individual neuroanatomical differences as well as variations in the tDCS parameters including the current intensity, stimulation duration, the target regions, and electrodes' polarity, size, shape, and configuration.[18] Individual anatomy is an important factor in the intensity and focality of the current delivered to deeper regions of the brain, and thus the electric field strength and focality, as both are decreased with increasing resistance of head tissues (white and grey matter, skull, scalp, skin).[18] Different stimulation parameters can also be adjusted based on individual needs to modulate the electric field strength and focality, and there is growing interest in the use of different biomarkers and neuroimaging techniques to facilitate this process.[19-23]

The location of the electrodes is a critical factor in determining the effectiveness of tDCS, as it dictates which brain regions are stimulated and the resulting therapeutic outcomes. A standard tDCS typically involves the placement of two electrodes on the scalp-an anode (positive electrode) and a cathode (negative electrode) elsewhere to complete the circuit.[24] Researchers carefully select electrode positions based on the desired cognitive or therapeutic effects. For example, to enhance cognitive functions such as memory, attention, and executive functioning in MCI, the anode is often placed over regions like the prefrontal cortex or dorsolateral prefrontal cortex (DLPFC), which are involved in these processes.[25]

The optimal number of sessions of tDCS for MCI remains an area of active research. The session protocols can vary, ranging from as few as one or two sessions, to more extensive programs of five to twenty sessions or more, depending on the severity of MCI and individual responsiveness.[26] The duration of a session varies, usually between 5 and 30 min, with longer sessions associated with more sustained after-effects.[27] No additional benefits appear to be associated with sessions exceeding 30 minutes.[28]

1. Safety and tolerability of tDCS in MCI

Research to date on tDCS treatment in MCI populations has generally supported its short-term safety under controlled conditions, with studies reporting that tDCS is typically well-tolerated, with most adverse effects (AEs) being mild and transient. Based on AEs listed in both studies involving MCI and healthy adult populations, the most common AE is itching, followed by burning sensations, headaches, tingling, sleepiness, difficulty concentrating, mild fatigue, skin redness, and dizziness.[29] Importantly, these effects usually subside within the first few minutes of stimulation, minimizing discomfort for participants.[30] Meanwhile, self-reported measures of fatigue are associated with longer single-session durations,[31] while skin irritation/lesions appear particularly related to improper electrode placement or insufficient prior hydration of electrodes. This is in keeping with how skin lesions as an AE have been mentioned more prevalently in at-home tDCS trials, where treatment is self-administered.[32] These safety concerns are reflected in the results of the home treatment setting trial, a randomized controlled trial (RCT) on home-based tDCS for the treatment of major depressive disorder which was prematurely terminated due to an accumulation of AEs in the form of burns or skin lesions. The safety monitoring in this study was insufficient to detect or prevent AEs within an appropriate time frame.[33] Another recent study by Park et al.[33] showed that while home-based tDCS did show cognitive improvements post-treatment, 3 out of the 19 participants experienced burns. Despite the great potential of at-home tDCS as a convenient and accessible treatment option, the safety issues stemming from improper self-administration highlight critical issues which need to be addressed for self-administered home-based tDCS treatments, including the need for improved safety protocols, monitoring, and safer device designs.[33]

Research thus far has not indicated any major adverse

events directly attributable to tDCS, including a recent RCT in 2023 which reported no serious adverse events in participants of various ages, sexes, and diagnoses for tDCS at various amperages up to 2 mA and different electrode placements.[34] Such findings support the short-term safety and tolerability of tDCS. However, due to the limited duration of tDCS treatment and short follow-up periods in most studies, the long-term safety of tDCS has yet to be firmly established and there remains a gap in systematic studies that examine the cumulative effects of tDCS over longitudinal treatment periods.[35]

EFFECTS OF tDCS ON GLOBAL COGNITION IN MCI

Studies examining the cognitive impacts of tDCS have largely used two specific outcome measures, the Addenbrooke's Cognitive Examination-Revised (ACE-R) and Mini-Mental State Examination (MMSE), as markers of global cognition. In this review, more focus was placed on ACE-R given that previous studies have indicated its superiority over the MMSE in detecting cognitive deficits in MCI.[36] ACE-R accesses the global cognition by evaluating 5 cognitive domains: memory, orientation/attention, verbal fluency, and language.[36,37] Among these domains, executive function, which encompasses abilities such as planning, cognitive flexibility, and inhibitory control, is particularly vulnerable in individuals with MCI due to its reliance on prefrontal cortex activity.[38]

Studies examining the efficacy of tDCS on global cognition have yielded somewhat mixed results. One study reported systematic review highlighted variability in outcomes, and a study involving twice-daily tDCS sessions for five consecutive days found no significant improvements in cognition, based on Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog) and MMSE results.[39] Conversely, a systematic review suggested that anodal tDCS might serve as an effective adjunct therapy for MCI patients.[40] Similarly, One study reported that applying tDCS over the DLPFC at 2 mA for 20 minutes per day for 10 days improved general cognition and immediate memory in older adults with MCI as measured by MMSE.[41] Based on the above, it appears that despite initially mixed findings in older studies[39] more recent research does trend towards supporting the notion that tDCS improves global cognition in MCI.[40,41]

1. tDCS on memory

tDCS has shown potential to enhance memory in individuals with MCI by modulating brain networks and improving synaptic plasticity.[4,5] Studies have focused on various memory domains, which include episodic working and semantic domains. In terms of episodic memory, tDCS is thought to modulate the hippocampus and associated cortical networks, and working memory, which involves short-term storage and manipulation of information.[42] Semantic memory, though less frequently studied, has also been shown to benefit from tDCS in some studies.[39] These effects are thought to arise from tDCS' ability to strengthen neural connectivity and plasticity, making it a promising approach for addressing memory deficits in MCI.

2. tDCS on attention and processing speed

Recent research suggests that tDCS can effectively improve attention and processing speed in individuals with MCI by targeting key brain regions such as the DLPFC and parietal cortex, which are involved in attentional control and cognitive processing. By increasing cortical excitability and promoting neuroplasticity, tDCS enhances neural networks responsible for these functions, leading to improved processing efficiency.[15] These findings highlight the potential of tDCS as a promising intervention for addressing attention and processing speed deficits in MCI.

3. tDCS on executive function & language ability

Research indicates that tDCS shows limited efficacy in improving executive function and language abilities in individuals with MCI, particularly as cognitive decline progresses. While anodal tDCS targeting the DLPFC has demonstrated potential in enhancing information updating, its effects on other executive skills, such as inhibition and set-shifting, remain inconsistent. For example, a 3-day anodal tDCS protocol improved phonological fluency in healthy elderly individuals but failed to yield similar benefits for MCI patients, suggesting that tDCS may lose effectiveness as cognitive impairments become more pronounced.[16] Current research therefore does not appear to support using tDCS for improving executive function and language deficits specifically in MCI.

4. Short-term effects of tDCS on cognitive functions in MCI

tDCS has demonstrated promising short-term benefits for cognitive functions in individuals with MCI. Immediately following tDCS sessions, studies often report enhancements in memory, attention, and executive function.[35] These effects are attributed to increased cortical excitability and the transient facilitation of neuroplasticity.[27] By selectively stimulating specific brain regions, tDCS can temporarily improve cognitive performance in MCI populations.[40] However, sustaining these cognitive gains over time remains a significant challenge. Factors such as stimulation frequency, protocol design, and the integration of complementary interventions like cognitive training play a critical role in determining the durability of these improvements.[43]

5. Long-term effects and challenges

The long-term efficacy of tDCS in MCI populations remains less conclusive, with studies presenting mixed results. Some research indicates that cognitive improvements persist up to about a month after intervention, while others report a regression of benefits once stimulation ceases.[43] Variability in study methodologies, inconsistent follow-up durations, and differing stimulation protocols

complicate the evaluation of sustained effects. Addressing these inconsistencies through well-designed longitudinal studies is essential to understand the full therapeutic potential of tDCS and to determine optimal protocols, including session frequency, intensity, and duration. Although tDCS holds promise for promoting cognitive resilience, the precise mechanisms and protocols required for sustained efficacy remain areas of active research.

FUTURE DIRECTIONS

1. Integration with other therapies

Several studies have examined whether combined tDCS and cognitive training (CT) yields any synergistic effects on cognitive improvements in MCI populations, with mixed results. One study in MCI patients found that CT-tDCS yielded significantly larger improvements in global cognitive functioning and verbal fluency versus both CT or tDCS alone, whereas there was no significant inter-group difference in verbal short-term memory and visuospatial memory.[44] However, other studies comparing CT-tDCS and CT alone in MCI populations have found that although both groups reported significant cognitive improvements post-intervention and at follow up, there was no significant difference between groups.[45,46] However, previous studies focused on healthy older adults have shown that CT-tDCS resulted in greater working memory outcome improvements.[47,48] A recent systematic review on CT combined with various types of non-invasive brain stimulation (NIBS) on improving cognition in patients with MCI and AD concluded that CT-tDCS was noted to improve language function, but not global cognition.[49] Meanwhile, a recent RCT comparing cognitive improvements after Interactive Computerized Cognitive Training (ICCT) alone versus in combination with tDCS showed no significant difference in cognition between the groups.[50] However, ICCT-tDCS did significantly improve dual-task gait performance including increased gait speed, reduced gait variability, and dual-task costs which may have clinical implications in reducing falls risk in elderly MCI patients.[51,52] Larger RCTs in MCI populations are therefore needed to examine whether CT-tDCS would be a superior therapeutic intervention versus CT or tDCS alone. Recent studies continue to explore whether there are any synergistic effects in combination therapy with tDCS and other non-pharmaceutical therapies currently utilized in the treatment of MCI, such as cognitive training[53] or exercise.[54] The results of these studies will provide valuable insight into how tDCS could potentially be incorporated in various multidisciplinary treatment strategies for MCI patients.

2. Precision medicine

Given the advantages of tDCS in the ability to fine-tune various parameters to suit individual needs, there has been interest in its applicability to precision medicine. Recent evidence highlights the potential of biomarkers in both gaining further insight into the neuromodulation mechanisms of tDCS for research purposes as well as in predicting responses to tDCS in MCI populations and designing treatment parameters.[20-23,55,56]

3. Imaging biomarkers

A key contributor to the challenges in determining optimal tDCS treatment protocols is that neuroanatomical differences including cortical thickness and conductivity differences have significant impact on the intensity and focality of the current reaching target brain regions in tDCS treatment.[19] One study estimated that up to 75% of the tDCS current applied to rodents and human cadavers was shunted by the scalp, subcutaneous tissue and muscle.[57] Such findings highlight the role of combining neuroimaging with tDCS which may help predict individual response variability to tDCS and determine optimal parameters. Several studies have proposed various human neuroimaging techniques to accomplish this, such as electroencephalogram (EEG)[55] position emission tomography (PET)[19], and functional magnetic resonance imaging (fMRI).[20]

4. Electroencephalogram (EEG)-tDCS

Studies have shown that tDCS-induced changes in cortical excitability show variability in the resultant behavioural effects, with several reasons to explain this variability: fMRI and EEG studies have shown that although tDCS acts predominantly on the cortex underlying the target stimulation area, it also has more widespread effects in distant neural networks.[55,58] Thus simultaneous EEG monitoring in conjunction with tDCS could provide real-time data on the impact of tDCS on cortical excitability across the brain. The advantage of this over other neuroimaging techniques is that while EEG has poorer spatial resolution than fMRI or PET, it has superior temporal resolution and can more accurately reflect the timing of neuronal activity throughout tDCS.[55] Additionally, certain EEG abnormalities in AD patients have been shown to predict cognitive response to pharmacological treatment–namely increased delta and theta activity, and decreased posterior alpha and beta activity in frontal and temporo-parietal regions.[59] This appears to align with predicting response to tDCS as well. In a recent clinical trial by Andrade et al.[56], a machine learning model identified five EEG channels located within four brain regions as being predictive of post-tDCS cognitive improvements in AD patients: FC1, F8, CP5, Oz, and F7. The brain regions these channels are in are as follows: the frontal cortex, which is critical for cognitive functions like memory, attention, and executive function; the parietal cortex, a region associated with spatial processing and attention; the occipital cortex which is responsible for visual processing; and the frontal-temporal junction, which is involved in various cognitive tasks. These specific brain regions align with known neurodegenerative changes in AD and the results of this study highlight these channels as predictors for assessing tDCS response in AD populations.[56]

5. Positron emission tomography (PET)-tDCS

PET imaging is one viable option in this regard, as the nature of PET imaging imparts the unique advantage of being able to examine the effects of tDCS within the central nervous system in vivo including cerebral metabolism, neuroreceptor occupancy, and neurotransmitter activity. As PET imaging can image the whole brain, one is also able to investigate the effects of tDCS in both target brain regions being stimulated as well as other remote or functionally connected brain areas. Conversely, inherent disadvantages of PET include radiation exposure and high costs, which are barriers to large-scale applications especially when considering the medical vulnerabilities of often elderly MCI populations. In a systematic review examining the potential role of PET in tDCS research, fludeoxyglucose-18f-PET (FDG-PET) and [15O] water PET were identified as highly suitable biomarkers for testing whether tDCS counteracts cognitive impairments and motor dysfunction in the human brain. [11C] alfentanil and [11C] raclopride PET were additionally identified as receptor agents that could provide key insights into studying the neuroprotective and restorative effects of tDCS. Overall, PET radiotracers could provide another way to characterize functional processes as well as receptor binding related to tDCS-induced cognitive changes.[19]

6. Functional magnetic resonance imaging (fMRI)-tDCS

fMRI technology is the most widely used neuroimaging technique for investigations of the neural mechanisms underlying cognition and motor functions, including the effects of tDCS.[60] This is due to the many benefits of fMRI – excellent spatial precision, whole-brain imaging capabilities, and sufficient temporal resolution. fMRI has the particular benefit of providing both whole-brain temporal resolution and high-resolution structural imaging data within the same imaging session, enabling verification of electrode positioning on the scalp, realistic current modelling based on individual head and brain anatomy, and precise localization of potential stimulation effects.[61,62] Previous studies have shown that tDCS administered in conjunction with resting state fMRI allowed for identification of widespread changes in whole-brain functional connectivity in addition to stimulation-induced changes in brain activity at the stimulation site.[20]

7. Molecular biomarkers

Recent studies have explored the use of pivotal blood biomarkers known to be associated with cognitive decline in neurodegenerative diseases in predicting therapeutic outcomes from tDCS.[21,22] For instance, a recent pilot study involving mild AD patients with amyloid PET positivity showed that in addition to significant improvements post-tDCS in cognitive domains including language abilities, verbal memory, attention span and frontal lobe functions, the active-tDCS group showed marked reduction in post-intervention plasma Aβ oligomerization tendency level, an AD-associated biomarker.[21] Another study focused on vascular endothelial growth factor (VEGF), an angiogenesis biomarker associated with memory decline in neurodegenerative diseases, with higher VEGF levels associated with optimal brain aging, lower age-related cognitive decline and higher hippocampal volume.[63] In a recent pilot study involving MCI and mild AD patients, lower pre-treatment serum concentrations of VEGF predicted greater recall memory improvements in participants treated with 5 weeks of an exercise only, tDCS only, or a combined exercise and tDCS treatment regimen.[22] These findings underline the growing potential of integrating various neurophysiological and molecular biomarkers to personalize tDCS interventions in MCI patients and help stratify patients into likely responders versus non-responders to help guide clinicians in their treatment planning.

8. Challenges and limitations in existing research

Despite the promising potential of tDCS in treating MCI populations, recent reviews in this field have noted highly variable outcomes within and between studies, highlighting substantial variability in methodology as well as tDCS protocol and outcome measures, as well as small sample sizes and an overall high degree of heterogeneity between studies[64,65] – all of which limit the generalizability of study findings and translation to clinical practice and make it difficult to determine what specifically is the optimal tDCS treatment protocol.[19,61]

Participant characteristics and electrode drift are two practical factors contributing to the heterogeneity of tDCS findings. Individual differences in neuroanatomy critically impact how much current reaches the target brain regions[57], creating variability in this aspect even if the induced current is held constant. Meanwhile, tDCS itself involves passing weak electrical current through electrodes encased in saline-soaked sponges, which are held in place on the head with elastic straps. Electrodes can physically drift from their original placements over the course of a tDCS session.[66] Electrode drift in tDCS can result in current flow variations and potentially contribute to variability in tDCS effects, highlighting the need for future studies to implement methods to both improve electrode positioning and minimize electrode displacement and verify electrode positioning both before and after treatment and/or neuroimaging.[66,67] In addition to the above, outcome measures rely on proxy measures of brain function such as behavioural performance parameters which can be significantly impacted by many internal and external factors. For instance, significant practice effects were evident in cognitive performances across repeat cognitive training sessions.[68]

Much of existing tDCS research continues to be limited by small sample sizes and significant methodological variability. With regards to the latter, the various parameters influencing tDCS protocols such as electrode polarity, current intensity and target region result in a lack of studies with similar protocols, making it difficult to compare results and draw more robust conclusions about the clinical benefits of tDCS or optimal parameters for treatment.

Therefore, there continues to be a need for larger-scale studies and increased diversity of samples. Meinzer et al.[61] suggest the establishment of large-scale consortia as a solution to this issue to facilitate participant recruitment from multiple sources and coordinate tDCS research, of which there are two currently ongoing-one in Germany and another through the International Network of Neuroimaging Neuromodulation (INNN).[61] The data obtained from these consortia will be a valuable addition to existing tDCS research in exploring its applicability to larger, more diverse sample populations. Lastly, most existing tDCS studies involve limited total duration of tDCS treatments and short follow up evaluation periods. For instance, among tDCS studies in 2024, interventions typically ranged from 3 to 15 sessions over a one- to two-week period, with stimulation intensities of around 2 mA delivered for 20-30 minutes per session.[15,16,23,32,33,50] A systematic review of tDCS in MCI and AD populations found tDCS treatment durations to be largely 12 weeks or shorter, with only two studies having longer interventions lasting 24 and 32 weeks respectively.[65] In terms of follow up periods, another similar systematic review from 2023 showed that included studies generally had a 1 month follow up period, with one study including an 8 week follow up at most.[35] There appears to be limited data on more longitudinal follow up post-intervention to date. Overall, it is evident that there remains a lack of data on long-term effects of tDCS over longitudinal treatment periods.[35]

CONCLUSIONS

MCI is increasingly recognized as a transitional stage between normal cognitive aging and more severe forms of decline, such as dementia. The early stage of MCI offers a critical "window of opportunity" for intervention as there remains enough cognitive function at this stage for targeted interventions to have meaningful effects, unlike in dementia where extensive neural damage has already occurred. Intervening during this stage not only improves quality of life for individuals but may also reduce the long-term burden of dementia on healthcare systems. tDCS is a non-invasive brain stimulation treatment which has shown potential as a treatment for improving cognition in MCI, especially given its portability and accessibility. Recent studies show that despite initially mixed results in its cognitive-enhancing effects in MCI populations, tDCS has been increasingly shown to impart improvements in several cognitive domains including global cognition, memory, and attention and processing speed. Less evidence has been shown for executive function and language deficits. Studies continue to note variability in findings between and within studies, of which one key factor is inter-individual differences in neuroanatomy. Increasing research into biomarkers, including neuroimaging findings, are expected to address this problem by identifying predictive factors in determining an individual's cognitive response to tDCS treatment.

There are also ongoing challenges with determining the longitudinal effects of tDCS and in determining the optimal treatment parameters, including duration and number of sessions. Further research with larger, more diverse samples and longitudinal follows up is needed to fill these gaps in current knowledge and to increase the generalizability of study findings. There are also safety concerns associated with improper electrode usage in self-administered home-based tDCS which highlight the need for thorough user training, monitoring, and further safety-centred developments in device design. Despite these challenges, studies continue to support tDCS as a promising treatment modality for improving cognition in MCI populations.

CONFLICT OF INTEREST STATEMENT

None declared.

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