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Interventional strategies for enhancing quality of life and health span in older adults, volume II

Edited by
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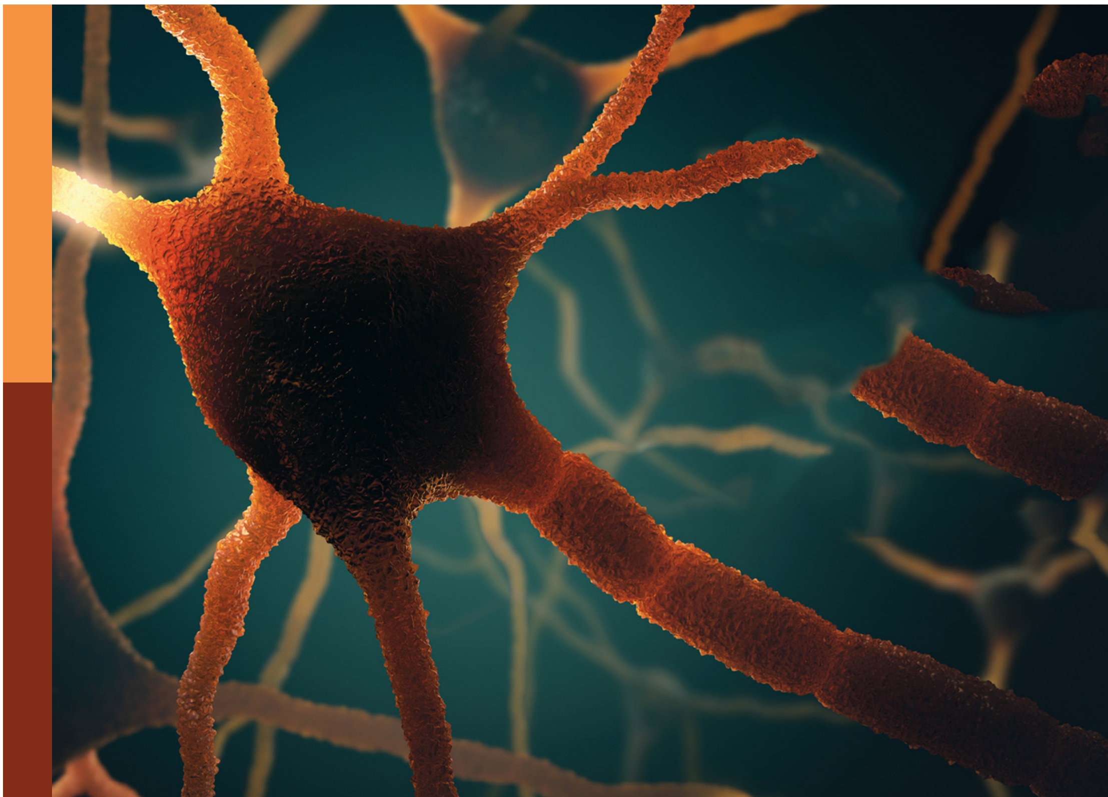

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Interventional strategies for enhancing quality of life and health span in older adults, volume II

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Editorial: Interventional strategies for enhancing quality of life and health span in older adults, volume II

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aging, stroke, cognition impairment, frailty, neuroinflammation, quality of life

Editorial on the Research Topic
Interventional strategies for enhancing quality of life and health span in older adults, volume II

Introduction

Aging is a natural and complex process that starts at conception and finishes at death. Several phenomena occur in individuals across the lifespan that can influence human health and wellbeing (Li et al., 2021). Some changes are related to heredity, nutritional quality and quantity, levels of physical activity, and actions that contribute to mental health, however, other factors are still unknown or poorly understood. Consequently, it is relevant to attempt to stimulate researchers to explore interventional strategies for enhancing quality of life in older adults and discuss diseases that might compromise older individuals.

Normal aging is associated with the accumulation of deleterious and undesirable changes that occur in the body's tissues, cells, and molecules, that can lead to an increased risk of co-occurring diseases and premature mortality. In general, most strategies to lengthen life expectancy have mainly been based in the need for effective interventions that might help offset the deleterious effects of aging. However, the costs associated with aging and a longer life expectancy have still increased over the decades due to the nature and severity of chronic age-related diseases. As a result, there is an urgent need to offer effective pharmacological and non-pharmacological interventions to improve quality of life, wellbeing, and independence in older adults. Therefore, the aim of this special issue is to summarize the most recent and relevant approaches permitting to understand and resume the most important parameters related to the aging process.

The current Research Topic includes nine contributions: two reviews (one systematic review and meta-analysis, one systematic reviews) and seven original articles. These findings were divided into the following sections: stroke, cognition impairment, frailty, and translational research about neuroinflammation and behavior in old rats.

Stroke

Stroke is the second leading cause of death globally, and it is most common in the elderly (Katan and Luft, 2018). Stroke frequently leads to significant alterations in cortical excitability of the primary motor cortex in the affected and unaffected hemispheres and often leads to disability of the individual, with reduced motor function, which can limit participation in normal and simple activities of daily living, such as locomotion, dressing, or eating.

Transcranial direct current stimulation (tDCS) is a non-invasive brain stimulation technique that involves applying a small current to the scalp in an attempt to modulate cortical excitability. Chow et al., through a Systematic Review and Meta-Analysis, evaluated the impact of tDCS applied alone or combined with other therapies on the recovery of motor function after stroke as assessed by common outcome measures such as Barthel Index (BI), the upper and lower extremity Fugl–Meyer Assessment (FMA), and the Modified Ashworth Scale (MAS). The potential benefits of tDCS varied depending on the assessment tool used, the duration of the stroke, and the associated therapies. Their review suggests that mechanistic studies are needed to better understand the potential role of stimulation type and dosage after the stroke and that future studies should carefully conduct studies that utilize group randomization, controls for the duration of the stroke, and report different motor recovery assessment types.

Cerebral edema (CDE) is a common complication in patients with acute ischemic stroke (AIS) and can reduce the benefit of endovascular therapy (EVT). Huang et al. developed a Dynamic Nomogram for 3-Month Prognosis for Acute Ischemic Stroke Patients After Endovascular Therapy that was a Pooled Analysis in Southern China. The aim was to determine whether certain risk factors are associated with a poor prognosis mediated by CDE after EVT. The primary endpoint was a measure of a poor prognosis (modified Rankin Scale score $\geq$ 3) at 3 months assessed in all patients receiving EVT. The least absolute shrinkage and selection operator and multivariate logistic regression were used to select variables for the prognostic nomogram. Based on these variables, the nomogram was established and validated. Furthermore, structural equation modeling was used to explore the pathways that link CDE and a poor prognosis. Seven predictors were identified, namely, diabetes, age, baseline Alberta Stroke Program Early CT score, modified Thrombolysis in Cerebral Infarction score, early angiogenic CDE, National Institutes of Health Stroke Scale score, and collateral circulation. The nomogram consisting of these variables showed the best performance, with a large area under the curve in both the internal and external sets. In addition, CDE served as a significant moderator. A nomogram for predicting a poor prognosis after EVT in AIS patients was established and validated with CDE as a moderator.

Considering the EVT, randomized clinical trials and large stroke registries have demonstrated a time-dependent benefit of the EVT in individuals with acute ischemic stroke due to large vessel occlusion. Zhang Y. et al. evaluated the association of Time to Groin Puncture with Patient Outcome after Endovascular Therapy Stratified by Etiology in a study that aimed to investigate whether this could be applied in different stroke subtypes in a real-world single-center cohort. Consecutive patients with ischemic stroke with large vessel occlusions who presented within 24 h after the onset of the symptom were prospectively registered and retrospectively assessed. Baseline multi-modal imaging was conducted before EVT. Independent predictors of functional independence (90 day modified Rankin scale 0–2) and any incidence of intracranial hemorrhage (ICH) were explored using stepwise logistic regression model in the entire cohort and in stroke subtypes. Individuals were classified as large-artery atherosclerosis (LAA)-related and cardioembolic (CE) subtypes. It was concluded that a faster groin puncture has a more pronounced effect on functional outcome in patients of the CE subtype than in those of the LAA subtype. Reducing the time to groin puncture is of great importance in improving the prognosis of patients after EVT, especially those of the CE subtype, and in reducing the incidence of any ICH in all patients.

In 2014, Taiwan's National Health Insurance administration launched a post-acute care (PAC) program for patients to improve their functions after acute stroke. Weng et al., in a Retrospective Multi-Center Cohort in Central Taiwan evaluated the Combined Functional Assessment for Predicting Clinical Outcomes in Stroke Patients After PAC aiming to determine PAC assessment parameters, either alone or in combination, for predicting clinical outcomes. Data were collected on post-stroke patients' functional ability at baseline and after PAC stay. The assessment included the Modified Rankin Scale (MRS), Functional Oral Intake Scale (FOIS), Mini-Nutritional Assessment (MNA), Berg Balance Scale (BBS), Fugl-Meyer Assessment (FMA), Mini-Mental State Examination (MMSE), aphasia test, and quality of life. The above items were assessed first at baseline and again at discharge from PAC. Logistic regression was calculated to determine factors that were associated with PAC length of stay (LOS), 14-day hospital readmission, and 1-year mortality. It was concluded that the physical performance parameters of patients with acute stroke improved after PAC. PAC assessment with multiple parameters better predicted clinical outcomes. These parameters could provide information on rehabilitation therapy for patients with acute stroke receiving PAC.

Cognitive impairment

Accelerated growth in the rate of cognitive impairment is an emerging problem in the senescent population. This could be explained by the fact that the increased prevalence of cerebrovascular and neurodegenerative disorders correlates with age, which is one of the greatest risk factors for late-onset Alzheimer's disease (AD) and other types of dementia. Brain perfusion declines with aging. Physical exercise represents a low-cost accessible form of intervention to increase cerebral blood flow. Renke et al., in a Systematic Review evaluated the Impact of Physical Exercise-Induced Increased Resting Cerebral Blood Flow on Cognitive Functions to provide a state-of-the art review on this subject. The current systematic review does not show a direct link between exercise-induced augmentation of brain perfusion and better cognitive functioning. However, in none of the reviewed studies was such an association the primary study endpoint. It is suggested that carefully designed clinical studies with focus on cognitive and perfusion variables are needed to provide a response to the question whether exercise-induced cerebral perfusion augmentation is of clinical importance.

In aging research, an attempt has been made to detect age-related structural changes in white matter fibers using Diffusion tensor imaging (DTI) indices, including fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD). Then, it would be possible to detect age-related alterations in the white matter microstructure in aging research. DTI is a neuroimaging technique that enables researchers to investigate the properties of white matter *in vivo* by applying a tensor model to the diffusion of water molecules in the brain. In a pilot study Sugimoto and Otake-Matsuura developed a tract-based Spatial Statistics Analysis of Diffusion Tensor Imaging in Older Adults After the Photo-Integrated Conversation Moderated by Robots (PICMOR) Intervention Program. This cognitive intervention program called PICMOR uses one of the most intellectual activities of daily life, conversations. To examine the effects of PICMOR on cognitive function in older adults, a randomized controlled trial was conducted and reported that verbal fluency task scores were improved by PICMOR. Based on these behavioral findings, the aim of the pilot study was to identify candidate structures for white matter microstructural changes induced by PICMOR. The results from tract-based spatial statistics analyses showed that the intervention group, who participated in PICMOR-based conversations, had significantly higher FA values or lower MD, AD, or RD values across various fiber tracts, including the left anterior corona radiata, external capsule, and anterior limb of the internal capsule, compared to the control group, who participated in unstructured free conversations. It is also concluded that larger improvement in verbal fluency task scores throughout the intervention was associated with smaller AD values in clusters, including the left side of these frontal regions.

Reminiscence and conversation between older adults and younger volunteers using past photographs are very effective in improving the emotional state of older adults and alleviating depression. Poor interaction and lack of social participation are among the contributing factors to social isolation that are closely associated with depression, one of the main risk factors for the development of Alzheimer's dementia. Reminiscence and communication about past photographs between older adults and younger volunteers, healthcare workers, or families contributes to encourage positive interaction and social engagement. It is known that the electroencephalogram (EEG) has a strong association with emotion in comparison to other physiological signals. The challenge is to eliminate muscle artifacts in the EEG during speech and to reduce the number of dry electrodes to improve user comfort while maintaining high emotion recognition accuracy. Jiang et al. evaluated EEG signals emotion recognition based on convolutional neural network-recurrent neural network framework with channel-temporal attention (CTA) mechanism for older adults, and was proposed the CTA mechanism into convolutional neural network (CNN) and bidirectional long-short term memory (bi-LSTM) (CTA-CNN-Bi-LSTM) emotion recognition framework. EEG signals of eight channels were first implemented in the multivariate extension of empirical mode decomposition (MEMD)—canonical correlation analysis (CCA) (MEMD-CCA) method on brain regions separately (Frontal, Temporal, Parietal) to remove the muscle artifacts, then were fed into the Channel-Temporal attention module to get the weights of channels and temporal points most relevant to the positive, negative and neutral emotions to recode the EEG data. The CNNs module then extracted the spatial information in the new EEG data to obtain the spatial feature maps which were then sequentially inputted into a Bi-LSTM module to learn the bidirectional temporal information for emotion recognition. In conclusion, it was designed group experiments to demonstrate that the proposed CTA-CNN-Bi-LSTM framework outperforms the previous works. Moreover, the highest average recognition accuracy of the positive, negative, and neutral emotions achieved 98.75%.

Frailty

Frailty is a clinical syndrome in older adults who are easily affected by, and vulnerable to, stress. Physical frailty includes slow gait speed, weakness, self-reported exhaustion, low activity, and body mass loss. Frailty is considered a major public health challenge of the twenty-first century, characterized by the decline of multiform body functions (Wang et al., 2022). Physical activity may be the most effective intervention to delay frailty. Zhang X. et al., throughout a randomized controlled trial protocol, are suggesting evaluating effects of Remotely Supervised Physical Activity on Health Profile in Frail Older Adults, aiming to verify the effect of remotely supervised physical activity on health profile in community-dwelling frail older adults. It would be a multicenter, three-blind, two-arm, and cohort randomized controlled study. An intelligent exercise rehabilitation management system, which is an integrated digital platform that involves evaluation, guidance, monitoring, and feedback, would be used. The primary outcome is physical function, and secondary outcomes include gait parameters, psychology, and cognition measurements. The authors suggest that intervention plays a positive role in delaying frailty and, if the proposed program is effective, it will provide a viable means to promote healthy aging in primary healthcare.

Translational research: Neuroinflammation and behavior in old rats

Translational research is fundamental to the implementation of actions in different fields of the health sciences. In addition, it is critical to the geroscience due to the various and complex aspects related to the aging. Acute cardiac damage can be induced by isoproterenol (ISO) injections in animals. The associated inflammatory response are then manifested in the brain as neuroinflammation, with potential consequences for brain function and behavior. Although cardiac responses are reported to differ based on age and sex, for neuroinflammation and brain function much less is known. Tóth et al., evaluated the sex dimorphism in ISO-induced cardiac damage associated neuroinflammation and behavior in old rats, aiming to compare the cardiac damage and its consequences for neuroinflammation, brain function and behavior in aged male and female rats. Older Wistar rats were treated with ISO, and exploratory behavior and short-term memory were tested. Heart and brain tissues were collected. In male, but not in female rats, ISO induced significant cardiac damage. Accordingly, mortality was higher in males than in females. Baseline hippocampal microglia activity was lower in females, while ISO induced neuroinflammation in both sexes, Hippocampal brain-derived neurotrophic factor expression appeared lower in females, without effects of ISO. In the open field test, ISO-treated males, but not females, displayed anxiety-like behavior. In conclusion, sex dimorphism in effects of ISO was observed for cardiac damage and open field behavior. However, these effects could not be related to differences in hippocampal neuroinflammation or neuronal function.

Conclusions

Putting together the findings described in the current editorial about stroke, cognition impairment, frailty, and translational research about neuroinflammation and behavior in old rats, it is possible to develop and to establish interventional strategies to enhance the quality of life and health span in the elderly. These strategies would be useful to counterbalance the undesirable consequences of aging.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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Conflict of interest

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ORIGINAL RESEARCH
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A Dynamic Nomogram for 3-Month Prognosis for Acute Ischemic Stroke Patients After Endovascular Therapy: A Pooled Analysis in Southern China

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Cerebral edema (CDE) is a common complication in patients with acute ischemic stroke (AIS) and can reduce the benefit of endovascular therapy (EVT). To determine whether certain risk factors are associated with a poor prognosis mediated by CDE after EVT. The 759 patients with anterior circulation stroke treated by EVT at three comprehensive stroke centers in China from January 2014 to October 2020 were analyzed. Patients underwent follow-up for 3 months after inclusion. The primary endpoint was a measure of a poor prognosis (modified Rankin Scale score $\geq$ 3) at 3 months assessed in all patients receiving EVT. Least absolute shrinkage and selection operator and multivariate logistic regression were used to select variables for the prognostic nomogram. Based on these variables, the nomogram was established and validated. In addition, structural equation modeling was used to explore the pathways linking CDE and a poor prognosis. Seven predictors were identified, namely, diabetes, age, baseline Alberta Stroke Program Early CT score, modified Thrombolysis in Cerebral Infarction score, early angiogenic CDE, National Institutes of Health Stroke Scale score, and collateral circulation. The nomogram consisting of these variables showed the best performance, with a large area under the curve in both the internal validation set (0.850; sensitivity, 0.737; specificity, 0.887) and external validation set (0.875; sensitivity, 0.752; specificity, 0.878). In addition, CDE (total path coefficient = 0.24, $P < 0.001$) served as a significant moderator. A nomogram for predicting a poor prognosis after EVT in AIS patients was established and validated with CDE as a moderator.

Keywords: ischemic stroke, endovascular therapy, prognosis, nomogram, risk factor

INTRODUCTION

Endovascular therapy (EVT) has been recognized as the standard treatment for acute ischemic stroke (AIS) and is suitable for certain patients with anterior circulation infarction with large-vessel occlusion (Hill and Goyal, 2018). However, a significant proportion of AIS patients do not clinically improve despite timely EVT, successful revascularization of the occluded arteries, and reperfusion of the ischemic areas. Even after successful EVT, a high degree of variability in clinical outcomes remains among AIS patients; therefore, predicting functional outcomes may have important implications for the clinical management of these patients. The reasons for the lack of improvement in these cases are still not fully understood. Although five randomized EVT trials were performed recently to analyze factors affecting the 3-month prognosis (Goyal et al., 2016), most findings from these trials focused on the severity of stroke, site of occlusion, estimated time from symptom onset to treatment, and method of treatment, while few studies incorporated cerebral edema (CDE), especially in Chinese Han ethnics (Chen et al., 2019; Han et al., 2020). Most patients with AIS die from CDE, which can lead to reduced cerebral blood flow, increased intracranial pressure and neuronal death. Moreover, CDE is the second major pathomorphological feature of stroke, and it can be attributed to the focus of the infarct. In large cerebral infarctions, progressive ischemic edema can lead to serious complications and mass effects, with a mortality rate of up to 80% (Berrouschot et al., 1998), unless treated with early recanalization (Thoren et al., 2020). Thus, CDE may be a crucial modulator of clinical prognosis; However, the role of baseline patient characteristics and treatment modalities, among others, in modulating clinical prognosis during ischemic injury through the mediating effect of CDE has also not been established yet.

We hypothesized that certain risk factors are associated with a poor prognosis mediated by CDE in AIS patients after EVT. For example, other known risk factors for a poor prognosis after EVT include the stroke severity, as measured by the National Institutes of Health Stroke Scale (NIHSS), the recanalization status, and the baseline Alberta Stroke Program Early CT score (ASPECTS) (Yeo et al., 2016; Khan et al., 2017; Stracke et al., 2020). However, their impact on the prognosis of AIS after EVT remains uncertain; the predictive accuracy of individual variables is limited, and multivariate risk prediction tools based on demographic, clinical and neuroimaging characteristics may be more practical.

This study was performed to determine factors of a poor prognosis in patients with AIS despite the use of EVT to develop a dynamic nomogram for predicting a poor prognosis in such patients, and to explore the moderating role of CDE.

MATERIALS AND METHODS

Participants

To ensure the generalizability of the study results, patients with anterior circulation infarction treated with EVT were pooled from 3 comprehensive stroke centers (Jinling Hospital from January 2014 to December 2018, Yijishan Hospital from July 2015 to October 2020 and the Second Affiliated Hospital of Fujian Medical University from January 2016 to December 2019). The uniform inclusion criteria were as follows: (1) age $\geq$ 18 years; (2) prestroke modified Rankin Scale (mRS) score $<$ 2; and (3) occlusion of the internal carotid artery (ICA) or middle cerebral artery (MCA) (M1/M2) confirmed on preoperative imaging. The treatment options and methods have been previously described (Huang et al., 2021).

The collaborators collected datasets with the same clinical and imaging characteristics used in an external validation cohort from three other stroke centers, namely, the No.1 People's Hospital of Yulin, Quanzhou First Hospital, and Shengli Clinical Medical College of Fujian Medical University, to validate the nomogram. Data were collected from a cohort of consecutive AIS patients admitted to these three hospitals from January 2017 to October 2020.

Data Collection

All consecutive patients with anterior circulation AIS were prospectively documented. Baseline characteristics included demographics, vascular risk factors, medical history (diabetes mellitus, hypertension, and atrial fibrillation), Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classification, stroke severity (measured by NIHSS), pre- and post-treatment imaging features, type of treatment, and complications.

The operational parameters included the estimated time from onset to puncture (OTP), time from stroke onset to reperfusion (OTR), location of occlusion, EVT approach (stent-first/aspiration-first/angioplasty-first), remedial treatment, and collateral circulation. Recanalization after EVT was evaluated by the interventional physician according to the modified Thrombolysis in Cerebral Infarction (mTICI) scoring system. Successful recanalization was defined as an mTICI score of 2b or 3. The collateral circulation was evaluated based on the retrograde contrast opacity of the vessels within the occluded region on delayed pretreatment digital subtraction angiography (DSA). The collateral circulation was scored as follows (Christoforidis et al., 2005) grade 0 if there was little or no significant reconstruction of the occluded vascular region or if the collaterals reached less than 1/3 of the occluded region; grade 1 if the collaterals reached less than 2/3 of the occluded region; and grade 2 if the side branches reached more than 2/3 of the region or the proximal main vessel. Neuroradiologists evaluated the severity of brain edema 24–72 h after EVT. Early angiogenic CDE was classified based on the published literature (Cheripelli et al., 2016), as follows: no swelling, 0 point; effacement of the lateral ventricle, 1 point; effacement of the lateral ventricle and third ventricle, 2 points; and midline shift, 3 points.

Primary Outcome

The primary endpoint consisted of the functional outcome as assessed with the mRS in all patients 3 months after stroke. Good functional recovery was defined as an mRS score of 0–2, and poor functional recovery was defined as an mRS score $\geq$ 3.

Statistical Analysis

R version 3.5.1, SPSS version 25.0 and AMOS 24.0 were used to perform the statistical analyses. Continuous variables are presented as the means $\pm$ standard deviation (SD) or as the median and interquartile range (IQR), and categorical variables are expressed as frequencies or percentages. First, to avoid case deletion due to missing baseline data in the multivariate analysis, a regression-switching approach was used to multiply impute the missing data (**Supplementary Figure 1**). The imputation model consisted of variables from the analytical model, imputed incomplete variables and complete variables that served as predictors. Second, to predict a poor prognosis in patients, the original data were randomly divided into two subsets, namely, the training set (70%) and the internal validation set (30%), in R. The data from the training set were analyzed using the least absolute shrinkage and selection operator (LASSO) regression method. LASSO regression is a method of data dimensional reduction that can be used to select predictors associated with the primary endpoint. Third, in the current study, patients were divided into good and poor prognosis groups based on neurological recovery (mRS score). Binary logistic regression was used to analyze the associations of factors with the 3-month prognosis. Moreover, a nomogram was constructed on the basis of the binary logistic regression analysis results to visualize the probability of a combination of factors affecting the prognosis. Fourth, Harrell's concordance index (C-index) was used to quantify the performance of the nomograms. The imputed data were randomly divided into a training set (70%) and an internal validation set (30%) (**Supplementary Figure 2**). All data from the internal validation set were used for internal validation of the model. The nomogram was also externally validated using external validation sets from three other stroke centers. Discrimination and calibration were assessed using a bootstrapping method with 1,000 iterations. Additionally, decision curve analysis (DCA) was performed to independently evaluate the clinical value of the model based on the calculation of the patient's net benefit at each threshold probability. The model was compared to the strategies of selecting all and selecting none; the strategy with the highest calculated net benefit was considered optimal, and the random forest algorithm was used to evaluate the importance of the predictors. Finally, an ordinal logistic regression analysis was performed to explore the factors influencing CDE, using CDE classification as the dependent variable and the related factors as independent variables. Then, structural equation modeling (SEM) was used to explore the pathways linking CDE and a poor prognosis. The structural impairments were assessed by the collateral status and the admission ASPECTS and NIHSS. Four parameters were used to evaluate model fitting: the root-mean-square-error of approximation (RMSEA), goodness-of-fit index (GFI), adjusted goodness-of-fit index (AGFI), and Akaike information criterion (AIC). Two-sided $P < 0.05$ was considered statistically significant.

RESULTS

This study involved 759 AIS patients, comprising 452 (59.6%) male participants and 307 (40.4%) female participants from three stroke centers in China. The mean age of all participants was 66.9 ± 11.5 years. Among the risk factors for stroke, hypertension was identified in 67.5% (512/759) of the patients, atrial fibrillation was identified in 48.2% (366/759), and diabetes was identified in 19.0% (144/759). The median time from onset to sheath insertion and the median duration of the operative procedure was 270 (IQR: 213–330) minutes and 73 (IQR: 50–109) minutes, respectively. Revascularization was achieved in

TABLE 1 | Baseline clinical features and radiographic characteristics.

	Training set *n* = 531	Internal validation set *n* = 228	External validation set *n* = 219
Demographics			
Female, n (%)*	209 (39.4)	98 (43.0)	86 (39.3)
Age, years, mean (SD)*	67.1 (11.3)	66.5 (11.8)	64.7 (12.0)
Medical history			
Hypertension, n (%)	366 (68.9)	146 (64.0)	
Diabetes mellitus, n (%)*	105 (19.8)	39 (17.1)	51 (23.3)
Atrial fibrillation, n (%)	259 (48.8)	107 (46.9)	
Clinical characteristics			
Baseline SBP, mmHg, mean (SD)	147.1 (24.2)	145.0 (25.1)	
Baseline DBP, mmHg, mean (SD)	82.2 (13.8)	82.2 (16.2)	
Admission NIHSS, median (IQR)*	16 (13–20)	16 (12–19)	16 (13–20)
Baseline ASPECTS, n (%)*			
<8	126 (23.7)	60 (26.3)	38 (17.4)
≥8	405 (76.3)	168 (73.7)	181 (82.6)
OTP, min, median (IQR)	270 (210–330)	270.0 (215.8–332.3)	
OTR, min, median (IQR)	349 (286–445)	360 (286–420)	
Collateral status, n (%)*			
Grade 0	105 (19.8)	51 (22.4)	64 (29.2)
Grade 1	192 (36.2)	84 (36.8)	99 (45.2)
Grade 2	234 (44.1)	93 (40.8)	56 (25.6)
mTICI score > 2b, n (%)	404 (76.1)	169 (74.1)	185 (84.5)
First treatment, n (%)			
Stent retriever	399 (75.1)	165 (72.4)	
Contact aspiration	77 (14.5)	35 (15.4)	
Angioplasty	55 (10.4)	28 (12.3)	
Tandem, n (%)	67 (12.6)	27 (11.8)	
Occlusion site, n (%)			
ICA	224 (42.2)	107 (46.9)	
MCA (M1)	269 (50.7)	106 (46.5)	
M2 and beyond	38 (7.2)	15 (6.6)	
CDE*			
0 point	357 (67.2)	156 (68.4)	169 (77.2)
1 point	51 (9.6)	20 (8.8)	5 (2.3)
2 points	6 (1.1)	2 (0.9)	2 (0.9)
3 points	117 (22.0)	50 (21.9)	43 (19.6)
Remedial treatment, n (%)	89 (16.8)	50 (21.9)	
TOAST classification, n (%)			
Atherosclerotic	173 (32.6)	75 (32.9)	
Cardioembolic	299 (56.3)	126 (55.3)	
Others	59 (11.1)	27 (11.8)	

**For the external validation set, only those variables used in the nomogram were included.*

572 (75.4%) patients. Over the 3-month follow-up, 331 (43.6%) patients recovered well.

Risk Factors and Risk Model Development

The patient dataset was randomly divided into a training set ($n = 531$ patients) and an internal validation set ($n = 228$ patients) (**Table 1**). There were 322 males (60.6%), 390 (73.4%) patients over 60 years old, and 228 with a good 3-month prognosis (42.9%) in the training set. The internal validation set, comprised 130 male patients (57.0%) and 98 female patients (43.0%). Within the validation set, 170 (74.6%) patients were older than 60 years, and 103 patients (45.2%) had a good 3-month prognosis. For external validation, the collaborators provided data only for the variables in the nomogram. The detailed demographic and clinical characteristics are shown in **Table 1**.

After the selection of variables through LASSO regression models, age, ASPECTS, mTICI score, sex, remedial treatment, hypertension, diabetes, atrial fibrillation, location of occlusion, CDE, NIHSS, and collateral circulation were identified as the best subset of risk factors to include in the model for predicting a poor prognosis (**Supplementary Figure 3** and **Supplementary Table 1**). **Figure 1A** shows the multiple logistic

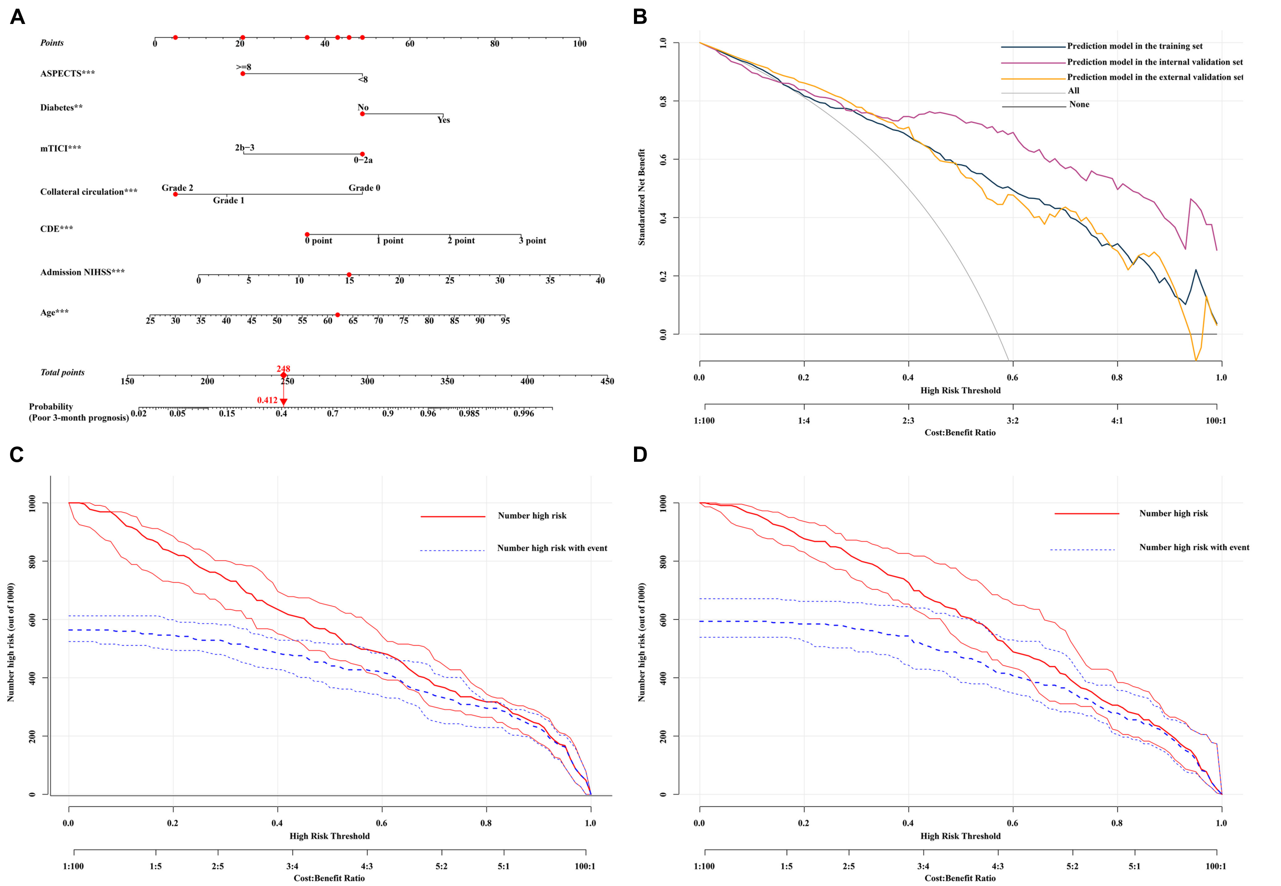

FIGURE 1 | (A) Nomogram for the prediction of a poor 3-month prognosis. Scores were based on the ASPECTS, age, mTICI score, diabetes, CDE, NIHSS, and collateral circulation status by drawing a line from the corresponding value upward to the "score line." The "total score" was calculated as the sum of the individual scores for each of the 7 variables included in the nomogram. For example, we will consider a 62-year-old diabetic patient had an mTICI score of 0-2a with a CDE grade of 0 points, a collateral circulation grade of 2, an NIHSS of 15, and an ASPECTS of $\geq$ 8. Thus, the sum of the total risk points was 248, and a vertical line can be drawn down to the "3-month poor prognosis probability" axis. For this patient, the prognostic probability was 41.2%. **(B)** Decision curve analysis (DCA) of the nomogram in the validation set. The *x*-axis shows the threshold probability. The *y*-axis shows the net benefit. The gray line shows the net benefit of the treatment strategy for all patients. The black line shows the net benefit of the strategy for patients without treatment. The yellow, dark green, and purple lines represent the nomogram. This nomogram was used to assess the probability of a poor prognosis in a specific patient with AIS treated with EVT. Patients with a higher risk of a poor prognosis after EVT may require further treatment, such as decompressive craniectomy, while patients with a lower risk of mortality may not require further treatment. The distinction between patients with a high and low risk of mortality is the main purpose of this figure. In this study, the reference risk was calculated by assuming that all patients required further treatment to prevent adverse events, whereas zero net benefit was defined as no patients requiring further treatment. The threshold probability is defined at the point where the expected benefit of further treatment equals the expected benefit of avoiding further treatment. For any given probability threshold, the nomogram with the largest net benefit would be the most ideal model (**(C)** for internal validation and **(D)** for external validation). The clinical impact curve of the nomogram of a high risk of a poor prognosis, in which the predicted high-risk probability coincides well with the actual high-risk probability and has a superior standardized net benefit, including 95% confidence intervals (CIs). NIHSS, National Institutes of Health Stroke Scale; CDE, early angiogenic CDE score.

regression analysis for a poor prognosis within 3 months (the higher the total score, based on the sum of points assigned to each predictor in the nomogram, the higher the risk of a poor prognosis). In addition, to make the model more accessible to clinicians, a dynamic web-based version of the nomogram was created. The interface of this web version is shown in **Supplementary Figure 4**. On the right side of the interface, the 3-month prognostic probability and 95% confidence interval (CI) can be obtained by entering the appropriate patient data and then clicking the button at the bottom of the page. The predicted probabilities of the online tool are consistent with those of the static nomogram.[1]

DCA can be used to estimate the net benefit of a model based on the difference between true-positive and false-positive results and is widely used to assess whether nomogram-assisted decision-making improves patient outcomes. DCA showed that the nomogram could be easily applied and used to make valuable and useful judgments (**Figure 1B**). The red curve (number at high risk) represents the number of people classified as positive (high risk) by the model at each threshold probability; the blue curve (number at high risk with the outcome) represents the number of true positives at each threshold probability (**Figures 1C,D**). The C-index (95% CI) and area under the receiver operating characteristic (ROC) curve (AUC) for the model was 0.903 (0.883–0.924) and 0.903 in the internal validation set and 0.831 (0.804–0.858) and 0.831 in the external validation set, respectively. In addition, the nomogram model performed well, with a high AUC in both the internal validation set (sensitivity, 0.856; specificity, 0.874) and external validation set (sensitivity, 0.615; specificity, 0.888) (**Supplementary Figures 5A,B**). According to the calibration plot, the mean absolute error for a poor 3-month prognosis in the internal and external validation sets were 0.018 and 0.029, respectively (**Supplementary Figures 5C,D**). Among the included variables, statistically significant prognostic predictors were severe neurological deficits [odds ratio (OR), 1.092; 95% CI, 1.050–1.135], age (OR, 1.049; 95% CI, 1.031–1.067), diabetes (OR, 2.087; 95% CI, 1.286–3.386), CDE (OR, 1.925; 95% CI, 1.550–2.390), collateral circulation (OR, 0.476; 95% CI, 0.363–0.625), ASPECTS (OR, 0.329; 95% CI, 0.200–0.541), and recanalization status (OR, 0.338; 95% CI, 0.210–0.546). A variable importance measure was used to evaluate the impact of each variable. The order of importance of the variables was as follows (highest to lowest): age, NIHSS, CDE, collateral circulation, mTICI score, ASPECTS, and diabetes (**Figure 2A**).

Path Analysis of the Effects of Cerebral Edema on Poor Prognosis

After adjusting for confounders in the ordinal regression model, it was found that patients with higher diastolic blood pressure (DBP) (OR = 1.012, 95% CI: 1.001–1.022, $P = 0.028$), severe neurological deficits (OR = 1.053, 95% CI: 1.029–1.078, $P < 0.001$), a lower ASPECTS (OR = 1.997, 95% CI: 1.528–2.611, $P < 0.001$) and a poor collateral circulation had more severe CDE (**Table 2**). The significant linking pathways from CDE to a poor prognosis in the SEM model are displayed in **Figure 2B**. In this SEM model, collateral status and the admission ASPECTS and NIHSS were not only directly (standardized beta estimates −0.22, −0.13, and 0.19, respectively, all $P < 0.001$) but also indirectly linked with a poor prognosis. CDE (total path coefficient = 0.24, $P < 0.001$) served as a significant mediator.

TABLE 2 | Ordered logistic regression analysis of factors affecting the grading of brain edema after treatment in patients with acute ischemic stroke.

Factors	OR (95% CI)	*P*-value
Age, years	0.990 (0.977–1.003)	0.135
Sex		
Male	0.964 (0.727–1.280)	0.800
Female	Ref.	
Baseline SBP, mmHg	1.000 (0.994–1.006)	0.985
Baseline DBP, mmHg	1.012 (1.001–1.022)	0.028
Admission NIHSS	1.053 (1.029–1.078)	<0.001
Hypertension		
No	0.730 (0.537–0.994)	0.046
Yes	Ref.	
Diabetes mellitus		
No	0.793 (0.579–1.086)	0.148
Yes	Ref.	
Atrial fibrillation		
No	1.436 (0.998–2.067)	0.051
Yes	Ref.	
Tandem		
No	0.966 (0.620–1.506)	0.879
Yes	Ref.	
Baseline ASPECTS		
<8	1.997 (1.528–2.611)	<0.001
≥8	Ref.	
Collateral status		
Grade 0	4.126 (2.819–6.040)	<0.001
Grade 1	2.497 (1.742–3.580)	<0.001
Grade 2	Ref.	
TOAST classification		
Atherosclerotic	0.754 (0.474–1.201)	0.235
Cardioembolic	1.081 (0.645–1.812)	0.767
Others	Ref.	
Occlusion site		
ICA	3.249 (1.601–6.592)	0.001
MCA (M1)	1.496 (0.730–3.064)	0.271
M2 and beyond	Ref.	

DISCUSSION

The main finding of our study is that a poor prognosis in AIS patients with anterior circulation occlusion was associated with the following clinical and imaging determinants: age, diabetes, collateral circulation, CDE, NIHSS, ASPECTS at baseline, and mTICI score. After random forest model training, the variables were, in descending order of importance, age, NIHSS, CDE, collateral circulation, mTICI score, ASPECTS, and diabetes. In

[1] https://odywong.shinyapps.io/PredictingpPrognosis/

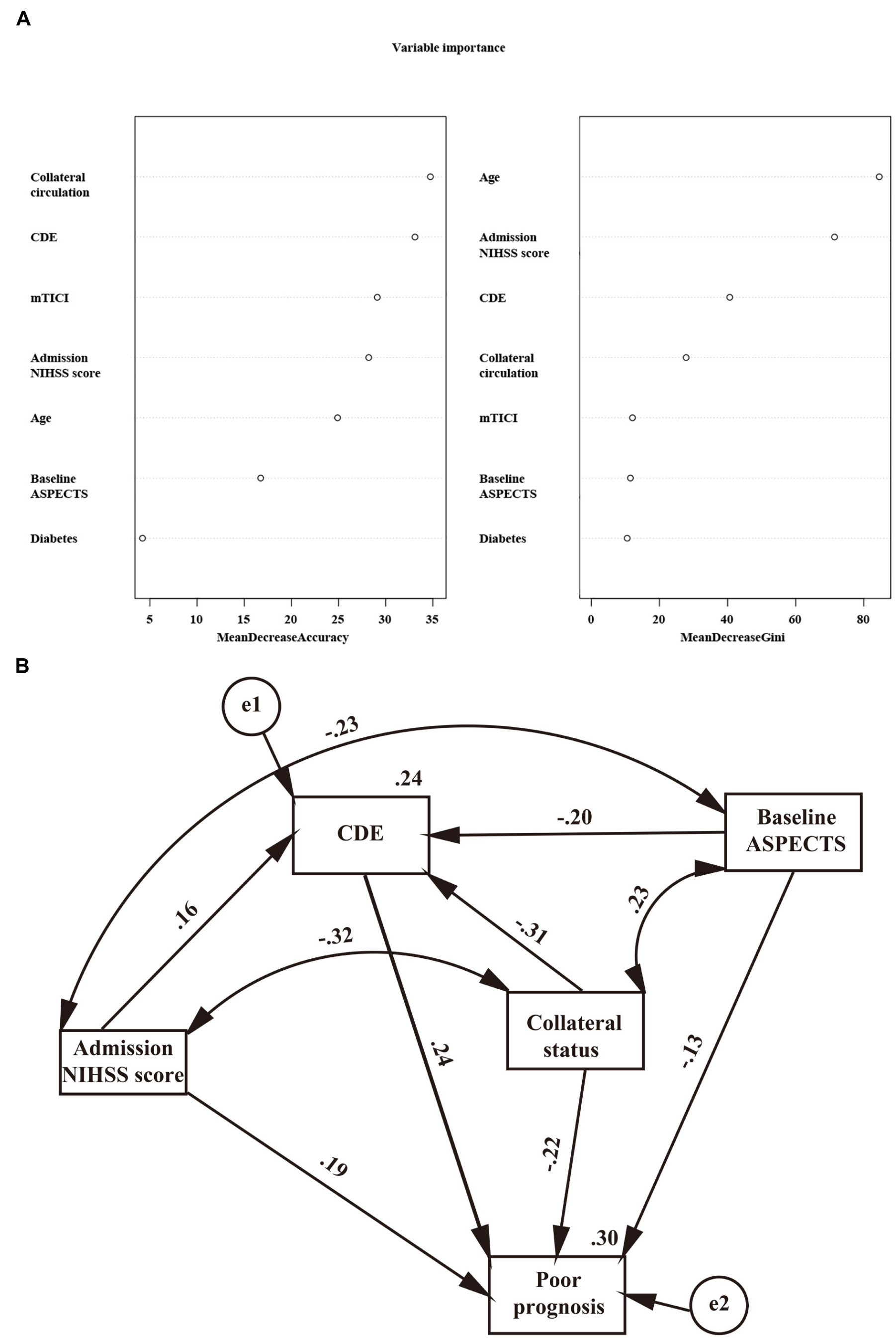

FIGURE 2 | (A) Importance values of clinical variables. MeanDecreaseAccuracy indicates a decrease in accuracy after variable substitution; MeanDecreaseGini indicates a decrease in the Gini coefficient after variable substitution. A higher value indicates that the variable is more important. **(B)** Regressions from the structural equation model on the relationship of the admission NIHSS, baseline ASPECTS, collateral status, and CDE with a poor prognosis. Standardized coefficients are presented; all $P < 0.001$.

the present study, CDE served as an important mediator of a poor prognosis in AIS patients.

We found that older patients had significantly higher rates of a poor 3-month prognosis than younger patients. We also found that the presence of diabetes, a higher NIHSS on admission and a poor collateral circulation were independent predictors of a poor 3-month prognosis. First, many studies have examined the results of EVT in older adults (Lima et al., 2016; Sallustio et al., 2017). Overall, our findings are consistent with the findings of these studies, with higher rates of a poor prognosis in the elderly population. Advanced age is well known to be associated with insufficient collateral circulation in multiple tissues, increasing the severity of ischemic injury (Faber et al., 2011). Second, a poor pretreatment collateral circulation may reduce the rates of recanalization and reperfusion in EVT for AIS (Leng et al., 2016). If the collateral circulation is poor and the ischemic core lesion is located in a critical brain region, such as the motor areas, patients are usually left with severe disability even after early reperfusion. These patients may present with severe clinical symptoms hours after symptom onset but experience complete neurological recovery after reperfusion (Yassi et al., 2015). Third, the angiographic collateral score (mTICI score) obtained during EVT is used to predict which patients are most likely to achieve successful revascularization and is associated with increased infarction and the clinical outcome (Marks et al., 2014). Fourth, previous studies have suggested that despite successful revascularization, a high NIHSS in patients is associated with a poor postoperative prognosis (Linfante et al., 2016) because higher NIHSS are associated with increased rates of ineffective recanalization and hemorrhagic transformation (Hussein et al., 2010; Kuntze Soderqvist et al., 2014).

To our knowledge, few studies have been conducted to investigate the relationship of ischemic edema with functional outcomes using CDE as a simple and practical metric in AIS patients after EVT. These findings may have important clinical implications in several areas, including patient selection for interventions, prognostic evaluation, and decision-making regarding adjuvant regimens with antiedematous agents in patients with a poor collateral circulation. First, the influence of the collateral circulation on the prognosis of ischemic stroke is well established (Vagal et al., 2018). The influence of a poor collateral circulation on the clinical prognosis may be due not only to increased lesion growth but also to an increase in ischemic CDE (Galego et al., 2018). Significant CDE with progressive tissue fluid uptake may lead to increased interstitial pressure after the occlusion of a large vessel. This may lead to increased resistance of collateral arterioles and downstream perforating arterioles in the low-perfusion area after cerebral infarction. Subsequently, ischemic edema may worsen, leading to a poor prognosis even after successful EVT. Thus, patients with minimal or no early brain edema may maintain an adequate collateral circulation and may be relatively likely to benefit from EVT. However, patients with an initially poor collateral circulation may rapidly progress to severe CDE. In these patients, the impact of the formation of pronounced early edema on clinical outcomes may be more time-sensitive (Marks et al., 2014). In conclusion, CDE may serve as a predictor of functional outcomes. Second, the development of edema is the result of multiple factors; persistent occlusion is an important cause, as are the size of the ischemic lesion, the collateral circulation status, and the size of the occluded artery, as reflected by the NIHSS and the size of the infarct core. Third, at the tissue level, edema is caused by a gradual increase in blood-brain barrier permeability and disruption (Paciaroni et al., 2012; Horsch et al., 2016; Fredriksson et al., 2017; Shi et al., 2018). Ischemia and hypoxia cause damage to brain tissue, followed by the depletion and failure of ATP-dependent ion pumps, leading to the dysfunction of neuronal electrical function and energy metabolism (Kulik et al., 2008). In addition, cerebral capillary dysfunction caused by ischemia, hypoxia, and reperfusion leads to the progressive deterioration of blood-brain barrier permeability, resulting in cytotoxic edema, ionic edema, vasogenic edema, and hemorrhagic transformation (Simard et al., 2007). In summary, the development and progression of CDE must be closely monitored and controlled after EVT in AIS patients.

Our research has certain limitations. First, this was a retrospective analysis of a small sample of data from three centers. Hence, our results need to be validated in a large-scale prospective multicenter study. Second, CDE was assessed by measuring CDE, which was based on a morphometric analysis and an indirect measure of the mass effect, rather than a direct calculation of the fluid content. Third, there was a lack of external validation across different ethnicities and a relatively small sample size in the validation model. Therefore, future multicenter prospective studies including participants of different ethnicities and larger sample sizes should be conducted to validate the accuracy of the model. Fourth, measuring CDE at 24 h may not capture the maximum values of CDE which generally peaks between day 2–4 after stroke, especially in patients with persistent arterial occlusion who may have been suffering infarct growth beyond 24-h. At the same time, different treatments such as mannitol may influence edema.

Nevertheless, one advantage of the present study is the relatively large cohort of AIS patients treated with EVT from multicenter; compared with nomograms, dynamic nomograms often provide more tailored risk predictions that facilitate management-related decisions. Importantly, the overall predictive performance and clinical utility of our model were also well validated in external cohorts. In addition, we created a prognostic dynamic nomogram in an online webserver. Without the need to install specific software, clinicians can access can access nomogram calculators online anywhere anytime. This will undoubtedly simplify the application and facilitate its use in clinical practice. Also, this paper provides a new insight to clinicians for predicting the probability of 3-month prognosis in AIS patients undergoing EVT, supporting therapeutic decision in this clinical setting.

CONCLUSION

In conclusion, a newly developed nomogram for predicting a poor prognosis at 3 months showed that an older age, diabetes, a higher NIHSS, a poor collateral circulation, a lower ASPECTS at baseline, a lower mTICI score, and in particular, a higher level of CDE were associated with a poor prognosis in AIS patients eligible for EVT. Remarkably, for the first time to our knowledge, CDE was also found to be an important mediator of a poor prognosis in AIS patients. Future multicenter prospective studies are needed to validate the findings in different ethnic groups.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

This retrospective study was approved by the local ethics committee and conducted in accordance with the relevant guidelines. The requirement for informed consent was waived. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

Z-XH and X-JH: guarantors of integrity of entire study. Z-XH, X-JH, Y-KL, and S-ZL: literature research. Z-XH, X-JH, Y-KL, S-ZL, Q-LH, Q-KC, and Y-FH: clinical studies. Z-XH and YC: statistical analysis. Z-XH, X-JH, Y-KL, and S-ZL: manuscript editing. All authors: study concepts and study design or data acquisition or data analysis and interpretation, manuscript drafting or manuscript revision for important intellectual content, approval of final version of submitted manuscript, and agreed to ensure any questions related to the work are appropriately resolved.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2021.796434/full#supplementary-material

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A Systematic Review of the Impact of Physical Exercise-Induced Increased Resting Cerebral Blood Flow on Cognitive Functions

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Brain perfusion declines with aging. Physical exercise represents a low-cost accessible form of intervention to increase cerebral blood flow; however, it remains unclear if exercise-induced amelioration of brain perfusion has any impact on cognition. We aimed to provide a state-of-the art review on this subject. A comprehensive search of the PubMed (MEDLINE) database was performed. On the basis of the inclusion and exclusion criteria, 14 studies were included in the analysis. Eleven of the studies conducted well-controlled exercise programs that lasted 12–19 weeks for 10–40 participants and two studies were conducted in much larger groups of subjects for more than 5 years, but the exercise loads were indirectly measured, and three of them were focused on acute exercise. Literature review does not show a direct link between exercise-induced augmentation of brain perfusion and better cognitive functioning. However, in none of the reviewed studies was such an association the primary study endpoint. Carefully designed clinical studies with focus on cognitive and perfusion variables are needed to provide a response to the question whether exercise-induced cerebral perfusion augmentation is of clinical importance.

Keywords: aging, cerebral perfusion, cognition, dementia prevention, exercise

INTRODUCTION

Accelerated growth of the rate of cognitive impairment is an emerging problem of the senescent population. This might be explained due to the fact that the increased prevalence of cerebrovascular and neurodegenerative disorders correlates with age, which is one the greatest risk factors of late-onset Alzheimer's disease (AD) and other types of dementia (Hebert et al., 2010, 2013; Alzheimer's Association, 2019). The population aged over 65 years is constantly growing and is expected to be three times higher in 2050 than 2010, reaching 1.5 billion (WHO et al., 2011) and similarly, the number of patients suffering from AD (24 million cases in 2018) is estimated quadruple in 2050 (Dos Santos Picanco et al., 2016). These statistics may have gross social and economic implications, considering that the annual cost of care per patient with dementia is on average 3.5 times higher than for a person without any type of dementia (Hebert et al., 2013; Alzheimer's Association, 2018).

Cerebral Blood Flow

Cerebral blood flow (CBF) is one of the most commonly used parameters of brain function. It is defined as the rate of blood delivered by the arteries to the capillary bed in brain tissue and is calculated as the volume of blood in milliliters per 100 g of the cerebral tissue per minute (Bertsch et al., 2009). The local neuronal metabolism and activity are strongly correlated with CBF and this relationship is referred to as neurovascular coupling (Kisler et al., 2017). The rate of CBF is known to be diminished in several neuropsychiatric conditions, for example, mild cognitive impairment (MCI), Alzheimer's disease, vascular dementia and Huntington's disease (Ferris et al., 1980; Berent et al., 1988; Stirling Meyer et al., 1988; Alexander et al., 1997). Several studies exist that have shown the correlation between the rate of CBF and the clinical state of the patient, specifically, the cognitive functioning level. Monitoring CBF is often simpler and more reliable in clinical conditions than assessing cognitive functions, especially in older individuals (Lacalle-Aurioles et al., 2014). Various imaging techniques, such as positron emission tomography (PET), magnetic resonance imaging (MRI) with contrast (DSC-MRI), arterial spin labeling MRI (ASL-MRI), and Doppler ultrasonography, are used to assess the rate of CBF. Assessment of neuronal activity is moreover allowed through the blood oxygen level-dependent (BOLD-MRI) signal and can also be achieved by near-infrared spectroscopy (NIRS).

CBF and Aging

In healthy aging, the decrement in mental abilities is not primarily caused by hypoperfusion; on the contrary, the level of CBF is more than sufficient compared to the demand of neurons (Stefanovic et al., 2004; Pasley et al., 2007; Hutchison et al., 2013; Nealon et al., 2017). The rate of CBF decreases constantly, typically 0.35–0.45% per year, for subjects who are middle-aged and older (Leenders et al., 1990; Parkes et al., 2004). Simultaneously, the risk of developing mild cognitive impairment grows due to gradual loss in cognitive functions (Wolters et al., 2017). The reason for the decline of CBF associated with aging is not entirely clear; however, it could be explained by the changes in the density and elasticity of cerebral blood vessels, and neuronal degeneration, as well as the reduced activity of pericytes (Kalaria, 1996; Zhang et al., 2017).

Physical Activity, Cerebral Blood Flow, and Cognitive Functions

Chronic physical exercise is believed to have a multifactorial impact on cerebral function (Barnes, 2015), including the elevation of perfusion levels (Gligoroska and Manchevska, 2012). Moreover, physical activity is a low-cost accessible form of intervention. These effects could potentially be applied in dementia and cognitive decline prevention programs (Daviglus et al., 2010). The effect of exercise on resting CBF, and consequently, on cognitive functions, has been tested in various groups of patients, however, such findings have not yet been systematically reviewed.

It has been shown that physical exercise modulates CBF (Querido and Sheel, 2007; Smith and Ainslie, 2017). Acute aerobic, mild-to-moderate intensity exercise could increase CBF, whereas high-intensity exercise (above anaerobic threshold) leads to CBF decline (Smith and Ainslie, 2017). Moreover, a study evaluating acute resistant/strength exercise effects has demonstrated a reduction in CBF (Perry and Lucas, 2021). With regard to chronic exercise, the studies conducted thus far suggest an improvement in CBF as well as cerebrovascular reactivity (Ainslie et al., 2008; Murrell et al., 2013). These beneficial changes may result from the post-physical training brain vascularization development that is associated with brain metabolic changes, as well as changes in the blood vessels themselves (Ainslie et al., 2008; Steventon et al., 2018). Therefore, type, intensity, time and duration of physical exercise could evoke different responses in CBF (Ainslie et al., 2008; Smith and Ainslie, 2017; Perry and Lucas, 2021).

A lower rate of resting CBF is known to correlate with a worsened neuropsychological outcome, whereas the commonly observed amelioration of cognitive functions (executive functions, working memory) are usually explained by post-exercise synthesis/release of brain-derived neurotrophic factor (BDNF) concentration and central catecholamine synthesis (Chang et al., 2012; Mcmorris and Hale, 2012). Whether a permanent increase of CBF attained by regular training is typically followed by ameliorated cognitive functioning has not yet been well proved. In this systematic review, we aimed to provide a state-of-the-art summary of the current knowledge regarding the relationship between physical exercise, resting CBF and cognition.

MATERIALS AND METHODS

The literature analyzed in this article was selected by a comprehensive search of the PubMed (MEDLINE) database. All the trials published up until the 17th of July 2021 were taken into account. Pubmed (MEDLINE) database was chosen because it represents an unfiltered source of primary literature comprising all different kinds of publication types occurring in academic journals.

To include all the research on the effects of regular physical activity on CBF and cognitive functions, the following search term was composed of the relevant key words ("fitness" or "exercise" or "physical activity" or "training") and ("cerebral blood flow" or "CBF" or "MRI" or "ASL" or "PET" or "NIRS" or "SPECT" or "Doppler" or "BOLD") and ("cognitive function" or "cognitive testing" or "cognition").

The results were filtered to show only clinical trials and then manually searched and further qualified for the study by 2 independent blinded reviewers.

A two-step approach was used to select articles: (1) titles and abstracts of all search results were screened for the following characteristics (a) original article published in English, (b) case studies and children studies were excluded; (2) full-text articles were obtained from the selected studies and were reviewed on the following inclusion criteria: (a) physical exercise intervention,

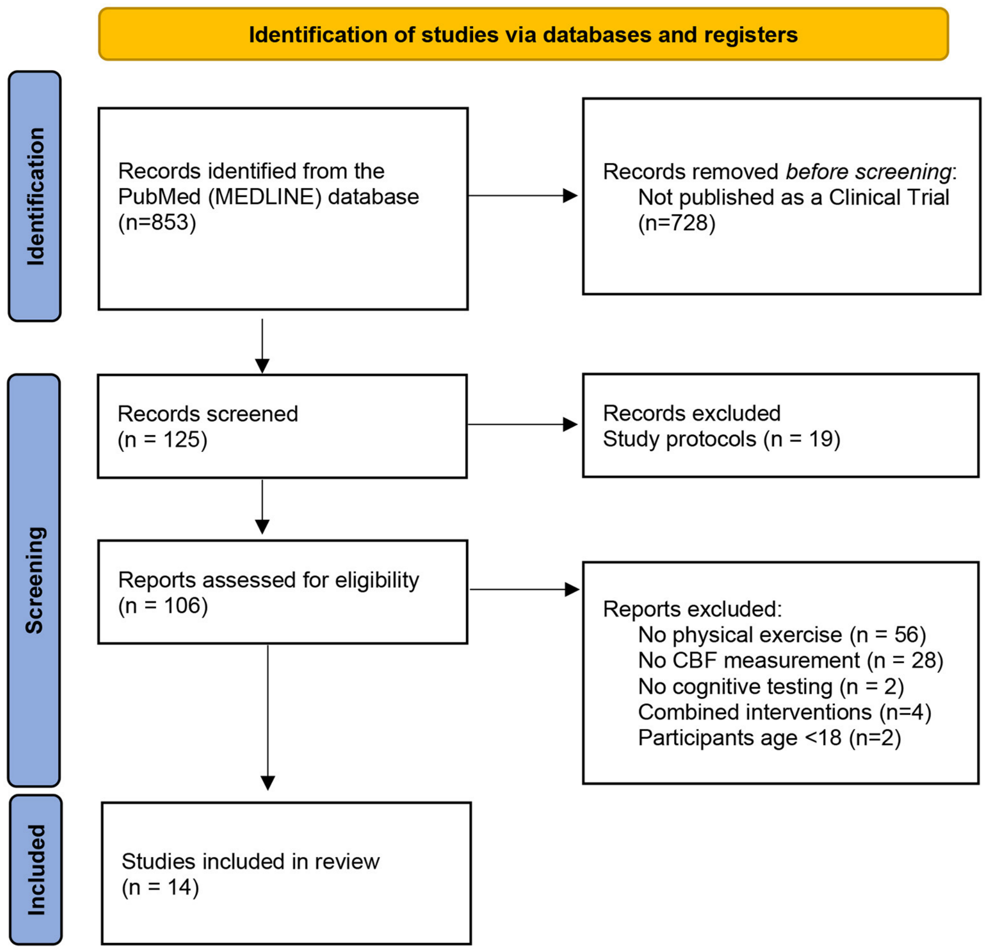

FIGURE 1 | PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow chart showing literature selection. From Page et al. (2021).

(b) measurement of the CBF rate, (c) cognitive functioning assessment. All the included studies matched the focus of our review, which included an investigation of the effects of a long-term physical exercise intervention on adults, measurement of perfusion after the training period and preferably, before the training period, and the assessment of cognitive function and its referral to CBF.

RESULTS

As a result of the search phrase, 125 results were shown in the PubMed database; however, several papers were excluded for the following reasons: (1) no physical exercise intervention in the study or physical exercise was solely a means to achieve some physiological state, for example, dehydration ($n = 56$), (2) 19 of the search results were study protocols, which shows that this area might be planned for future investigation, (3) no measurement of the CBF rate ($n = 21$), (4) no cognitive testing ($n = 2$), and (5) the cognitive results were not conducted after the physical exercise or did not match the area of CBF examination because those measurements were not the main focus of the study (6) participants under the age of 18 ($n = 2$) (Davis et al., 2011; Cho et al., 2017). Four of the studies combined physical exercise with cognitive training, indicating a possible next step in the interventions of cognitive impairment, although they cannot be easily compared with the studies included.

A total of 14 studies matched the search criteria and the three main points of the focus of our analysis (**Figure 1**). All the articles analyzed described longitudinal clinical trials. Nine of the studies (Stanek et al., 2011; Moore et al., 2015; Castellano et al., 2017; Shimizu et al., 2018; Stringuetta Belik et al., 2018; Cho and Roh, 2019; Northey et al., 2019; Guadagni et al., 2020; Lehmann et al., 2020) conducted well-controlled exercise programs that lasted 12–19 weeks for 10–40 participants and two studies (Rosano et al., 2010; Espeland et al., 2018) were conducted in much larger groups of subjects for more than 5 years; however, the amount of exercise was indirectly measured, and three studies (Decroix et al., 2016; Lefferts et al., 2016; Olivo et al., 2021) were focused on acute exercise. Three were pilot studies. The experiments were conducted on various patient samples, including older women, patients undergoing haemodialysis and cardiac rehabilitation, patients with diabetes mellitus, female breast cancer survivors, patients recovering after stroke, and patients suffering from mild AD and MCI.

The rate of perfusion was measured using transcranial Doppler ultrasound examination ($n = 6$) (Stanek et al., 2011; Lefferts et al., 2016; Stringuetta Belik et al., 2018; Cho and Roh, 2019; Northey et al., 2019; Guadagni et al., 2020), functional NIRS (fNIRS) ($n = 2$) (Decroix et al., 2016; Shimizu et al., 2018) and MRI ($n = 5$) (Rosano et al., 2010; Moore et al., 2015; Espeland et al., 2018; Lehmann et al., 2020; Olivo et al., 2021), including both ASL and BOLD studies. BOLD studies were included as they represent changes of deoxyhaemoglobin concentration, which are related to blood supply mechanisms (Wang et al., 2021). In addition, one PET study (Castellano et al., 2017) was included, as brain glucose metabolism closely follows perfusion rate (Baron et al., 1982).

Cognitive functions were assessed by suitable tests that could be compared with the perfusion measurement results. Because of the variety of the used tests, they will be described in detail in the paragraphs dedicated to specific studies.

A summary of the intervention study designs is provided in **Tables 1–3**.

Long-Term Lifestyle Interventions

Intensive Lifestyle Intervention and Cerebral Blood Flow in Diabetes Mellitus Patients

Diabetes mellitus may impair CBF through mechanisms that include vessel stiffness, poor vascular function and lumen narrowing (Nealon et al., 2017). In order to investigate the possibility of slowing these processes down, an intensive lifestyle intervention (ILI) was performed in a long-term study by Espeland et al. (2018) as a part of the Look AHEAD (Action for Health in Diabetes) multicentre, randomized controlled clinical trial (Ryan et al., 2003). Patients diagnosed with diabetes were randomly assigned into two groups. The ILI group ($n = 157$) underwent a process that included diet modification and physical activity (goal was more than 175 min of activity per week) to induce and maintain an average weight loss ≥ 7%. During the first 6 months, the participants were evaluated weekly and then three times per week for the following 6 months. In the following years, actions were taken in order to encourage the maintenance of the lifestyle change in the patients. The participants in the second group ($n = 153$) received a control condition of diabetes support and education (DSE), which included three group sessions each year, however, no specified diet, activity or weight goals. CBF was measured using ASL MRI at the 10–12-year anniversary of Look AHEAD enrolment for each subject. Cognitive testing was focused on verbal learning and memory (Rey Auditory Verbal Learning Test), processing speed and working memory [Digit Symbol Substitution Test (DSST)], executive functions [Modified Stroop Color and Word Test (SCWT) and the Trail-Making Test Part B (TMT B)], and global cognitive function [Modified Mini-Mental State Examination (MMSE)]. The ASL-MRI results showed a significant improvement in CBF level in the ILI group compared to the DSE group ($p = 0.04$) and the level of CBF was 6–7% higher in all regions for the ILI participants, compared to DSE, with minor interregional differences between

TABLE 1 | Summary of long-term lifestyle interventions.

References	Sample description and size (mean age)	Description of the method	Duration of intervention	Aim for weekly activity	CBF measurement	CF measurement	Statistically significant imaging results	Statistically significant cognitive results
Espeland et al. (2018)	Patients diagnosed with diabetes 157 EXP (57.5 ± 6.3) 153 CON (58.5 ± 6.6)	Intensive lifestyle intervention	10–12 years	>175 min/week	MRI	Rey auditory verbal learning test, digit symbol coding Test, SCWT, MMSE	CBF level ($p < 0.05$)	Digit symbol coding, SCWT, TMT part B ($p < 0.05$)
Rosano et al. (2010)	Older patients, PA—active and after PE intervention, SA—not active after no PE intervention 20 EXP (81.45); 10 CON (80.8)	Walking, follow-up 2 years after intervention, after maintaining active/not active lifestyle	26+ weeks	150 min/week	fMRI while DSST	fDSST, MMSE	Activation was higher in EXP group, $p = 0.04$	fDSST: more widely distributed network that included ECF regions within the dorsolateral prefrontal, posterior parietal, and anterior cingulate cortices compared with the regions active in the CON group

CBF, cerebral blood flow; EXP, experimental group; CON, control group; MRI, magnetic resonance imaging; SCWT, Stroop Color and Word Test; MMSE, Mini-Mental State Examination; TMT, Trial Making Test; PE, physical exercise; CF, Cognitive Function; fMRI, functional magnetic resonance imaging; DSST, Digit Symbol Substitution Test.

TABLE 2 | Summary of controlled exercise program studies.

References	Sample description and size (mean age)	Description of the method: type of intervention, duration of intervention, duration of session, frequency	CBF measurement	CF measurement	Statistically significant imaging results	Statistically significant cognitive results
Cho and Roh (2019)	Older women 19 EXP (68.9); 18 CON (69)	Taekwondo 16 weeks; 60 min 5×/week	Transcranial Doppler ultrasonography	MMSE; SCWT	No $p < 0.05$ results	SCWT test ($p = 0.022$)
Stringuetta Belik et al. (2018)	Haemodialysis patients 15 EXP (50.3); 15 CON (57.8)	Aerobic training, cycle ergometer Four months; 30 min increasing toward 45 min; 3×/week	Transcranial Doppler ultrasonography	MMSE	Maximum cerebral arterial flow velocity per area ($p = 0.002$)	MMSE ($p = 0.023$)
Northey et al. (2019)	Female cancer survivors 17 (HIIT $n = 6$, MOD $n = 5$, CON $n = 6$) (62.9)	HIIT or moderate training 12 weeks; 20–30 min; 3×/week	Transcranial Doppler ultrasonography	CogState battery, verbal learning, episodic memory, executive function, test working memory	No $p < 0.05$ results; a large-sized effect for HIIT in comparison to CON for resting MCAvmean	Episodic memory (moderate effects for both HIIT and MOD); executive function and working memory (HIIT group had large effects) in comparison to CON, between groups no significant differences
Moore et al. (2015)	Patients after stroke 20 EXP (68); 20 CON (70)	Community exercise vs. stretching 19 weeks; 45–60 min; 3×/week	MRI	ACE-R	Elevated CBF in medial temporal lobe region	ACE-R ($p < 0.01$)
Shimizu et al. (2018)	Older adults 30 EXP; 9 CON 74.90 MMT, 73.33 STT	Movement music therapy and single training task 12 weeks; 60 min in total; 1×/week	fNIRS	FAB test	Significantly higher activation between groups in Brodmann Area 10	Significant improvement in FAB after MMT, no after STT; however, no significant difference between the groups
Castellano et al. (2017)	Patients with mild AD 10 EXP (73)	Walking on a treadmill 12 weeks; Ph1 6 weeks 15–40 min (adding 5 min weekly); Ph2 40 min; 3×/week	PET-CT	3MS; HVLT; Verbal Digit Span; SCWT; DSST	Significantly higher global glucose metabolism	Shorter completion time on the TMT Awas related to higher global CMRacac ($p = 0.01$); A tendency toward improvement on condition 2 (color naming) of the SCWT
Stanek et al. (2011)	Cardiac rehabilitation patients 51 EXP (67.75) [36 stress test subset (68.72), 42 CBF measurement (68.17)]	Phase II CR program up to 12 weeks; 60 min; 3×/week	Transcranial Doppler ultrasonography	3MS; Attention-Executive-Psychomotor Trail Making Test A and B; Grooved Pegboard-dominant hand; FAB; Letter-Number Sequencing subtest of Wechsler Adult Intelligence Scale-III, Language- Boston Naming Test -Short form; Animal Naming	Significant change in ACA flow velocity ($p = 0.03$) in a subset of 42 individuals	Significant improvements: 3MS; Attention-Executive-Psychomotor (Letter-Number sequencing, Grooved Pegboard); HVLT (learning trial recall trial); Brief visuospatial memory test (learning trial, recall trial)

(Continued)

TABLE 2 | Continued

References	Sample description and size (mean age)	Description of the method: type of intervention, duration of intervention, duration of session, frequency	CBF measurement	CF measurement	Statistically significant imaging results	Statistically significant cognitive results
Guadagni et al. (2020)	Healthy low-active middle-aged and older adults 206 EXP (69.5 ± 6.4 years old)	Controlled exercise program aerobic exercise 6 months; increased 20–40 min; 3×/week	Transcranial Doppler ultrasonography	Card Sorting Test, SCWT, SDMT, Buschke Selective Reminding Test, Medical College of Georgia Complex Figure, Verbal Fluency Test from the Delis-Kaplan Executive Function system, Auditory Consonant Trigram Test	Resting baseline VP ($p = 0.014$); resting baseline CVCi ($p = 0.005$) determinations increased. A decrease in resting baseline CVRi was also found ($t202 = 3.378$, $p = 0.001$)	Positive changes before and after intervention in the executive functions/processing speed ($p = 0.029$), executive functions/concept formation ($p = 0.02$), verbal memory ($p = 0.001$), and fluency ($p = 0.004$) domains were observed. The figural memory domain showed a negative change ($p < 0.001$)
Lehmann et al. (2020)	34 healthy, right-handed adults of either sex 15 EXP (23); 16 CON (23.5)	Controlled exercise program cardiovascular exercise 2 weeks; 19 min; 3–4/week	fMRI	Motor learning time	Significant between group difference in frontal brain areas	Group EXELEARN learned the DBT at a significantly higher rate compared with RESTLEARN, $p = 0.025$

EXP, experimental group; CON, control group; MMSE, Mini-Mental State Examination; SCWT, Stroop Color and Word Test; MCAvmean, mean blood velocity in middle cerebral artery; ACE-R, Addenbrooke's Cognitive Examination Revised; fNIRS, functional near-infrared spectroscopy; FAB, Frontal Assessment Battery; AD, Alzheimer's disease; DSST, digit symbol substitution test; CMRacac, cerebral metabolic rate of acetoacetone; ACA, anterior cerebral artery; MMT, music movement therapy; STT, standard training therapy; HIIT, high-intensity interval training; MOD, moderate intensity exercise group; CR, Cardiac Rehabilitation; PET-CT, positron emission tomography; DBT, dynamic balancing; TMT, Trial Making Test; HVLT, Hopkins Verbal Learning Test; fMRI, functional magnetic resonance imaging; 3MS, Modified Mini-Mental State.

TABLE 3 | Summary of the acute exercise studies.

References	Sample description and size (mean age)	Description of the method, duration of exercise	CBF measurement	CF measurement	Statistically significant imaging results	Statistically significant cognitive results
Lefferts et al. (2016)	University community 15 men (22) 15 women (20 ± 3)	Cycle ergometer (hypoxic and normoxic exercise compared), 20 min	Transcranial Doppler ultrasonography	Eriksen Flanker test (executive function); N-back number task (working memory)	No significant differences	Differences in caution between normoxia and hypoxia
Decroix et al. (2016)	Healthy, well-trained men, some received coconut flavanoa oil 12 (30 ± 3)	Cycle ergometer, 30 min	fNIRS	SCWT	Significantly increased d(HBO_2, HHB, HBtot)	Increased speed of information processing (RT)
Olivo et al. (2021)	Older adults 49 24 EXP (69.6 ± 2.8) 25 CON (70.7 ± 3.1)	Cycle ergometer, 30 min	ASL	N-back task, MMSE	Elevated CBF between groups	No significant results between groups

fNIRS, functional near-infrared spectroscopy; SCWT, Stroop Color and Word Test; ASL, arterial spin labeling; MMSE, Mini-Mental State Examination; HbO_2, oxygenated hemoglobin; HHb, deoxygenated hemoglobin; HBtot, total hemoglobin; CF, Cognitive function; RT, reaction time.

the groups ($p = 0.95$). A significant difference was also observed ($p < 0.05$) in three of the cognitive assessment results (DSST, SCWT, and TMT B). Neuropsychological results indicate better performance in psychomotor speed after ILI, while memory and executive functioning did not show improvement. Higher CBF levels were associated with poorer composite cognitive scores in the DSE participants, but not in the ILI group. The possible explanation is that this reflects an adaptive response to greater metabolic requirements related to poorer cognitive efficiency through vascular dilation or angiogenesis (Loane and Kumar, 2016; Daulatzai, 2017). In the ILI group, no overall association between CBF and cognitive functioning was found. The authors of the study proposed an explanation linked to a blunted neurovascular response to decreases in cognition and neurodegeneration, including weight loss-induced alterations in apelin and leptin levels (Castan-Laurell et al., 2008; Abbenhardt et al., 2013), which are hormones that may promote angiogenesis and vasodilatation (Busch et al., 2011; Castan-Laurell et al., 2011; Khazaei and Tahergorabi, 2015; Sawicka et al., 2016) or decreases in cardiac output, which may lead to lower CBF independent of blood pressure (Lingzhong et al., 2015).

Psychomotor Speed and Functional Brain MRI 2 Years After Completing a Physical Activity Treatment

In the pilot study conducted by Rosano et al. (2010), 30 elderly participants took part in a follow-up 2 years after a 1-year treatment that consisted of BOLD-MRI examination, MMSE and DSST. Twenty of the participants completed a physical activity lifestyle intervention and remained active afterwards, and 10 patients who were in the control group ("Successful Aging" group) maintained <20 min a week of regular exercise. The imaging results showed a statistical difference in overall activation levels. Simultaneously, the results of DSST indicated a more widely distributed network that included executive function regions in the experimental group within the dorsolateral prefrontal, posterior parietal, and anterior cingulate cortices, compared with the active regions in the control group.

Controlled Exercise Program Studies

Aerobic Training in Different Age Groups of Healthy Subjects

In a study conducted by Cho and Roh (2019) researched the effects of Taekwondo exercise interventions on CBF and the cognitive functions of elderly women.

Participants were randomly assigned to Taekwondo or control groups, the intervention lasted 16 weeks and 60-min sessions were attended by the participants five times per week. CBF was measured using Doppler ultrasonography and the cognitive testing was tailored to the age of participants.

In the group of elderly women, the purpose of physical exercise is to delay the loss of cognitive function associated with aging (Cho and Roh, 2019). The study sample consisted of the taekwondo group ($n = 19$) with a mean age of 68.89 years and control group ($n = 18$), mean age 69 years. The findings regarding the cerebral blood velocity measurements were not statistically significant; however, cognitive functions were significantly ameliorated in the taekwondo group. Specifically, the SCWT score exhibited a significant difference ($p = 0.022$) between the groups, which indicates improvement in executive functions. Serum levels of neurotrophic grow factors (BDNF, VEGF, and IGF-1) were also significantly higher in the taekwondo group.

The study performed by Guadagni et al. (2020), analyzed a single group of 206 middle-aged and older participants (aged 69.5 ± 6.4 years), comparing results collected before and after a 6-month aerobic exercise intervention. Both assessments consisted of a transcranial Doppler ultrasonographic examination and a cognitive test battery, including the Card Sorting Test, SCWT, DSST, Buschke Selective Reminding Test, Medical College of Georgia Complex Figure, Verbal Fluency Test from the Delis-Kaplan Executive Function system, or the Auditory Consonant Trigram Test. Pre- and post-intervention differences in the physiological examination were found in baseline mean peak blood flow velocity and baseline cerebrovascular conductance index (an increase and a decrease of cerebrovascular resistance index). Cognitive testing revealed multiple positive changes before and after intervention in the executive functions/processing speed ($p = 0.029$), executive functions/concept formation ($p = 0.02$), verbal memory ($p = 0.001$), and fluency ($p = 0.004$) domains. The figural memory domain showed a negative change ($p < 0.001$).

A cohort of 18–35 years old participants was examined by Lehmann et al. (2020), with an experimental group of 15 subjects that completed a 2-week cardiovascular exercise program. There was a significant difference in BOLD-MRI results with higher activity level in the frontal brain areas, compared to a 16-participant control group. Additionally, motor learning time proved to be significantly shorter in the experimental group with $p = 0.025$.

Aerobic Training and Mild AD

Alzheimer's Disease is usually associated with a substantial decline in the rate of CBF, up to 40 percent compared to healthy individuals (De la Rosa et al., 2020). This decrease is most prominent in regions such as the precuneus, the hippocampus, the posterior cingulate gyrus and the temporal, occipital and parietal lobes (Johnson et al., 2005; Du et al., 2006; Asllani et al., 2008; Austin et al., 2011; Binnewijzend et al., 2013). Regular physical activity is known to increase the lowered level of CBF in areas such as the hippocampus and anterior cingulate gyrus in older adults (Ainslie et al., 2008; Burdette et al., 2010; Heo et al., 2010).

In the study conducted by Castellano et al. (2017) a group of 10 participants, average 73 years old, underwent a 3-month aerobic training program, consisting of 3 sessions a week of walking on the treadmill. The intervention was divided into two 6-week phases, in the first phase, the length of the sessions was increasing by 5 min weekly, finishing at 40 min, which was maintained until the end of the intervention.

The significantly elevated global glucose metabolism, which is an indicator of the elevated global perfusion rate (Baron et al., 1982), was observed on PET imaging after the intervention. Cognitive results were not significantly elevated; however, observed was a tendency toward improvement in executive functions [better results incondition 2 (color naming) of the SCWT ($p = 0.06$)].

Due to the relatively small group of participants in the study, the results should be treated as preliminary.

Physical Exercise in Mild Cognitive Impairment

A study conducted by Shimizu et al. (2018) was designed to compare the effect of a regular physical activity workout program and a program using the same movements, but with percussion music accompaniment (movement music training). All the participants were diagnosed with MCI. The group of patients taking part in the standard training therapy program (STT group) consisted of nine participants with mean age of 73.33 years and the music movement therapy (MMT group) consisted of 30 participants, mean age 74.9 years. CBF was assessed by fNIRS before and after the 12-week intervention and cognitive functions were measured on the same days, using frontal assessment battery (FAB). During the 3 months of the training program, the participants met once a week for a 60-min session. Post-intervention results showed a significantly higher activation between MMT and STT in Brodmann Area 10 of the prefrontal cortex and significant improvement in FAB results following MMT, compared to post-intervention outcomes of the STT; however, a p-value $= 0.088$ implicates some possible improvement of the results. No significant difference in cognitive results was observed between the groups.

The much smaller STT group is a big limitation of this study, as it is over three times smaller than the MMT group, mainly questioning the observed difference in significance of cognitive function measurement, and furthermore, no control group that would not undergo any exercise program.

Cardiac Rehabilitation and Cognitive Function

Patients suffering from cardiovascular disease (CVD) often experience an accelerated loss of cognitive abilities (Moser et al., 1999; Singh-Manoux et al., 2003) for multiple reasons, including low cardiac output (Jefferson et al., 2007), endothelial function (Moser et al., 2004), poor cardiovascular fitness (Gunstad et al., 2005) and CBF (Dai et al., 2008). Stanek et al. (2011) conducted a study to determine the effects of cardiac rehabilitation (CR) on the brain on a group of 51 patients with a mean age 67.75 years.

The patients were enrolled in a CR program (phase II CR program at Summa Health System's Akron Hospital, Ohio) customized to each individual with a duration of up to 12 weeks, three meetings per week, with 40 min of aerobic exercise for each session. Neuropsychological testing was focused on deriving a complex picture of each patient's cognitive functioning. Significant improvement was found upon analysis of the modified MMSE results ($p = 0.04$), Attention-Executive-Psychomotor function (observed through a significant improvement in Letter-Number Sequencing test, $p = 0.02$) and Grooved Pegboard-dominant hand test ($p = 0.02$). Moreover, a significant improvement ($p < 0.001$) was found in all the performed memory tests (Hopkins Verbal Learning Test—Revised: learning and delayed recall, Brief Visual Memory Test—Revised: learning, and delayed recall) from baseline to 12-week follow-up. CBF was evaluated in a subset of 42 individuals using transcranial Doppler ultrasonography and a significant improvement in anterior cerebral artery flow velocity was noted.

Community Exercise Therapy Following Stroke

Stroke and reduced levels of CBF are among many cerebrovascular dysfunctions induced by common metabolic abnormalities, including impaired glucose control, dyslipidemia, hypertension, obesity and low cardiorespiratory fitness (Caplan and Hennerici, 1998; Creager et al., 2003; Versari et al., 2009; Kernan et al., 2014). One of the main reasons for an accelerated process of age-related decline in CBF, brain atrophy and cognitive functions following stroke is the patient's low level of physical activity in particular (Rand et al., 2009). The community exercise therapy described in the study design of Moore et al. (2015) aimed to investigate post-stroke functional benefits in patients. A total of 40 participants were randomly divided into two groups, an exercise group ($n = 20$, mean age $= 68 \pm 8$ years) and a control group ($n = 20$, mean age $= 70 \pm 11$ years); 37 participants experienced an ischemic stroke, and three, a haemorrhagic stroke. The exercise group completed a 19-week (three times a week, 45–60 min each session) exercise program that consisted of strength and balance exercises of increasing intensity, measured by heart rate monitors. The initial goal was 40–50% maximum heart rate at first, progressing toward 70–80%, with a 10% increase every 4 weeks, and the control group completed a matched-duration home stretching program. ASL-MRI imaging was performed both pre-intervention and post-intervention and no change in the global gray matter CBF post-intervention was observed. Regional blood flow of the medial temporal lobe in the exercise group was significantly increased ($p = 0.05$), but a between-group difference was not observed. Overall cognition, measured by Addenbrooke's Cognitive Examination Revised, improved with exercise ($p < 0.01$), which confirmed the hypothesis of this study.

Intradialytic Aerobic Training

Chronic kidney disease (CKD) is a risk factor for cognitive impairment (Kurella Tamura et al., 2008, 2011; Yaffe et al., 2010; Etgen et al., 2012) and up to 60% haemodialysed patients experience this condition (Murray et al., 2006; Kurella Tamura et al., 2011). One of the possible mechanisms responsible for the accelerated decrease of cognitive functioning is CVD among CKD patients. Stringuetta Belik et al. (2018) investigated the effects of intradialytic aerobic training on CBF (measured by transcranial Doppler ultrasound) and cognitive functions (with MMSE) in haemodialysis patients. The study participants ($n = 30$) were randomly assigned into two groups of 15. The intervention group ($n = 15$, mean age $= 50.3 \pm 17.24$ years) participated in a 16-week exercise program, three times a week of sessions of aerobic activity on a cycle ergometer, gradually increased in duration (starting with 30 min and finishing at 45 min), and the control group of the equal size (mean age $= 57.8 \pm 15.01$ years) maintained a regular lifestyle. Analysis of the post-intervention data found a significant difference between the groups in the transcranial Doppler examination results, the maximum cerebral arterial flow velocity (MCA-V) per area

($p = 0.002$), mean cerebral arterial flow velocity per area ($p = 0.038$), as well as the pulsatility index ($p = 0.015$) and a significant difference in the MMSE results ($p = 0.023$).

High-Intensity Interval Exercise and Moderate-Intensity Exercise in Breast Cancer Survivors

Seventy-five per cent of cancer survivors report cognitive impairment during and after treatment, particularly in the domains of working memory, executive functions and memory performance (Janelsins et al., 2014; Pendergrass et al., 2018).

The possible mechanisms by which cancer treatment may impact cognition are similar to age-related effects on the brain, although the decline tends to be more rapid in cancer survivors (Janelsins et al., 2014; Wefel et al., 2015; Ehlers et al., 2016; Zimmer et al., 2016). In a pilot study, performed by Northey et al. (2019), 17 women over the age of 50 years (mean age, 62.9 years) in remission of breast cancer were randomly allocated into three study groups. There were two exercise groups completing a 12-week exercise program (three times a week, 20–30 min of exercise), high-intensity interval training (HIIT) group ($n = 6$) and moderate exercise group ($n = 5$), as well as a control group ($n = 6$). CBF, measured by transcranial Doppler, showed no statistical difference in mean blood flow velocity of the middle cerebral artery (MCA_{vmean}) between the HIIT and moderate exercise groups. There was a large-sized effect ($d = 0.86$) for the HIIT in comparison to the CON for resting MCA_{vmean}. The outcomes of the cognitive function assessment, measured using tasks from the CogState battery, showed no statistically significant group × time interaction effects for verbal learning, episodic memory, executive function or working memory. However, both the HIIT and moderate-intensity exercise groups had moderate-sized effects for episodic memory in comparison to the control group. Although examined groups were relatively small (5-6 subjects).

Acute Exercise Studies

Two studies, conducted by Decroix et al. (2016) and Lefferts et al. (2016) examined the effect of acute exercise, 20 min and 30 min sessions, on a cycle ergometer in a group of young adults (respectively, mean age 22.2 and 30 years).

The first study compared the effects of exercise during normoxia and hypoxia in a group of 30 participants. The authors found no significant differences in transcranial Doppler ultrasonography measurements and a statistical difference in caution, measured by a battery of cognitive tests, consisting of the Eriksen Flanker test and N-back number task.

In the second study, which included 12 participants, the effect of exercise was individually examined and paired with cocoa flavanol oil supplementation. In the fNIRS imaging, d(HBO_2, HHB, HBtot) were increased after exercise. Stroop Color and Word test results showed significantly increased speed of information processing post-exercise.

A group of 49 older adults (mean age, 69.6 ± 2.8 years in the experimental group of 24 participants and 70.7 ± 3.1 years in the control group) similarly completed a 30 min cycling session. Subjects were afterwards examined with ASL-MRI, revealing a significant elevation in CBF levels in the exercise groups and with N-back task and MMSE. No significant difference was found in the cognitive results between the groups.

DISCUSSION

In this review, the studies of the relationships between physical exercise, CBF and cognitive functions were summarized.

From a theoretical point of view, there are three potential scenarios associated with aging-related cognitive deterioration: (1) decline in neuron number and function, (2) diminished cerebral perfusion, or (3) a combination of both factors. From a clinical perspective, simultaneous neuronal and perfusion decline is most likely a typical scenario.

For instance, in neurodegenerative disorders, the decrease in CBF could be implicated by the lowered energy demand of neuronal cells. Physical activity can stimulate these cells through multiple mechanisms of noradrenergic activation, elevation of lactic acid levels in blood, and increasing the release of BDNF (Lu et al., 2015), among other mechanisms. In these conditions, a CBF increase might not be directly correlated with effect on cognitive functions due to relative blood oversupply (compared to metabolic demand).

Such mechanism might have played a role in described studies in AD (Castellano et al., 2017; Shimizu et al., 2018) where increase in glucose metabolism (Castellano et al., 2017) and activation measured with BOLD signal (Shimizu et al., 2018) were not associated with any changes in cognitive functioning. AD is typically associated with glucose hypometabolism (Guan et al., 2021; Librizzi et al., 2021). Thus, reversal of glucose metabolism decline should be seen as a positive outcome. Significance of the reported findings (amelioration in metabolism/regional perfusion with no cognitive improvement) is nevertheless limited by small numbers of investigated patients.

In contrast, cognitive impairment, correlated with permanent hypoperfusion, has been described in vascular diseases. Thus, cardiovascular improvement, induced by regular physical exercise (for example, cardiac rehabilitation), should have a positive effect on cognitive functions because it would target the limiting factor of diminished CBF (**Figure 2**).

In studies in patients with CVD (Stanek et al., 2011; Moore et al., 2015) simultaneous increase in brain perfusion and cognitive functions were observed. Moreover, also in CKD (Stringuetta Belik et al., 2018) which is typically associated with CVD, both perfusion and cognition improved. The main limitation of these studies is lack of direct assessment of causality between perfusion and cognition.

Most of the analyzed research agree with the fact that physical exercise has positive effect on general cognitive functioning as well as several specific cognitive domains such as executive functions and psychomotor speed. Those observations can be found especially in elderly subjects and patients with CVD, diabetes or chronic kidney diseased who are treated with haemodialysis. In patients with chronic kidney disease and stroke survivors after physical activity even improvement in global cognitive functioning can be seen. When taking in consideration

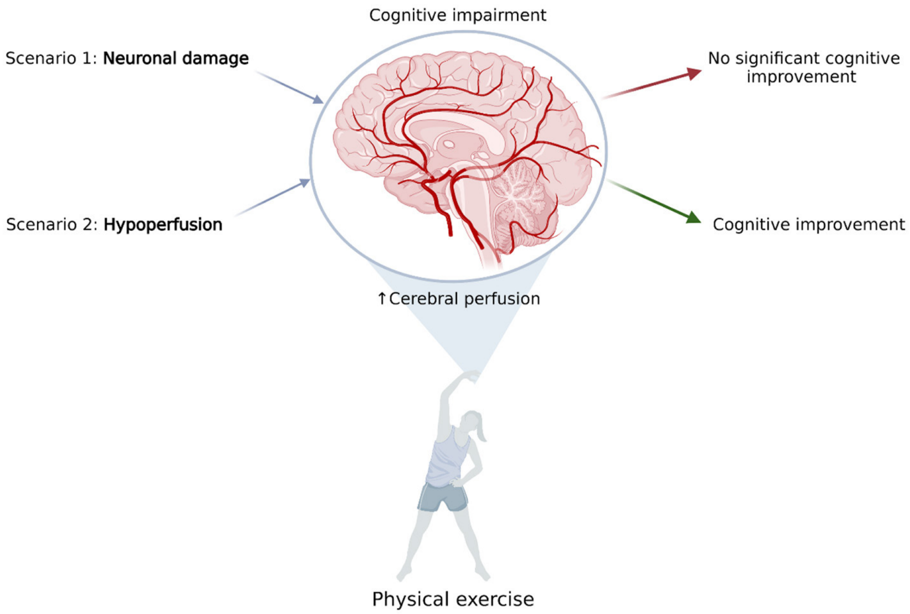

FIGURE 2 | The effect of elevated cerebral blood flow, resulting from physical exercise on common scenarios of cognitive impairment. Scenario 1: Cognitive impairment is caused by neuronal damage; for example, in neurodegenerative diseases. Elevating cerebral perfusion is not efficient due to relative blood oversupply. Scenario 2: Cognitive impairment is caused by hypoperfusion; for example, in vascular disease. Elevating cerebral blood flow may improve patients' cognitive abilities. Proposed mechanisms have yet to be proved experimentally (Created with BioRender.com).

that both renal dysfunction (Marini et al., 2021) and diabetes (Sigurdsson et al., 2021) are robustly associated with acute and chronic forms of cerebrovascular disease those results indicate that exercise may be helpful intervention especially in patients with high risk of cerebrovascular accidents.

While in patients with CVD or chronic somatic disorders cognitive decline might be visible and also cognitive improvement might be found even in general tests like MMSE or MoCA in healthy elderly subjects more sensitive test should be used. Majority of conducted studies included only singe test or various test measuring one function. Possibly wider range of tests might bring new insight in understanding impact of physical exercise and CBF on cognition. Especially memory functions might be important aspect needing more research. From all included studies only four examined learning and memory but only two found significant improvement after physical exercises (Guadagni et al., 2020; Lehmann et al., 2020).

CBF in healthy individuals does not show much connection with cognition. This is not surprising as in healthy subjects, there is a relative oversupply in terms of blood flow through the brain (Hall et al., 2016). Improvements in information processing speed and caution were reported after acute exposure to exercise.

Physical exercise affects the brain on anatomic, cellular and molecular levels which can enhance learning, memory and brain plasticity (De la Rosa et al., 2020). The potential protective mechanisms of exercise on brain aging are lowering levels of oxidative stress, regulating hormonal response, stimulating neurogenesis, elevating levels of neurotrophic factors and increasing CBF (Van Praag et al., 1999; Cotman and Berchtold, 2002; Colcombe and Kramer, 2003; Farmer et al., 2004; Heyn et al., 2004; Weuve et al., 2004; Eggermont et al., 2006; Deslandes et al., 2009). The association between exercise, cognitive functions and some of these factors have already been reviewed.

BDNF production and secretion are increased as a result of physical activity, and more importantly, BDNF has a causative role in the cognitive improvement induced by exercise. Furthermore, low serum levels of BDNF in humans have been linked to neurodegenerative diseases, such as AD, and high levels of BDNF are associated with increased hippocampal volume (Walsh and Tschakovsky, 2018; Tari et al., 2019).

Lactate is an important energy substrate in astrocytes, and at the same time, it plays a protective or modulatory role at the level of primary cortical areas (such as M1, V1, or S1) (Coco et al., 2020). Regular physical exercise diminishes blood-brain barrier permeability as it reinforces anti-oxidative capacity, reduces oxidative stress and has anti-inflammatory effects resulting in enhanced cognitive functions (Małkiewicz et al., 2019).

CBF changes are observed during acute physical exercise and following a long-term exercise program. Global CBF during exercise is primarily regulated by momentary arterial carbon dioxide partial pressure and the interactions of blood pressure and neurogenic activity (Smith and Ainslie, 2017). The effects of regular physical exercise are constantly investigated for its effects on brain function, which might be linked with improved cerebrovascular plasticity (Nishijima et al., 2016), maximal oxygen uptake (VO_2max), cardiac output and arterial pressure (Querido and Sheel, 2007).

CONCLUSIONS AND FUTURE DIRECTIONS

Elevating CBF may induce improvement in conditions in which hypoperfusion is potentially a limiting factor; for instance, in patients suffering from cardiovascular abnormalities. Defining clinical conditions in which CBF decline is a limiting factor of cognitive impairment might be particularly clinically important because it could assist in the design of effective preventive and therapeutic programmes for patients.

Most of the studies found positive effect of physical activity on cognitive functioning, especially in executive functions and psychomotor speed, in elderly subjects and patients with chronic disorders with higher risk of cerebrovascular disease. Those results support hypothesis that exercise may bring eligible therapeutic effect in patients with high risk of cerebrovascular accidents.

The available data demonstrate that the relationship between exercise-induced improvements in perfusion and cognition has yet to be studied. In none of the reviewed studies was such association the primary endpoint of the study.

Carefully designed clinical studies focusing on cognitive and perfusion variables are needed to provide a response to the question whether exercise-induced cerebral perfusion augmentation is of clinical importance. Wider range of neuropsychological tests, especially assessing memory functions might bring important insight in understanding impact of physical exercise and cerebral blood flow on cognition. Such studies are urgently needed as physical exercise is widely recognized as relatively low-cost and safe supporting therapy in many cardiovascular and neurodegenerative disorders.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

AM and PW: conceptualization. MR: methodology, investigation, writing—original draft preparation, and project administration. AM, SK, and PW: validation and supervision. MR and AM: formal analysis. PW: resources. MR, SK, and PW: funding acquisition. All authors: writing—review and editing, read, and agreed to the published version of the manuscript.

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Influence of Transcranial Direct Current Stimulation Dosage and Associated Therapy on Motor Recovery Post-stroke: A Systematic Review and Meta-Analysis

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Purpose: (1) To determine the impact of transcranial direct current stimulation (tDCS) applied alone or combined with other therapies on the recovery of motor function after stroke and (2) To determine tDCS dosage effect.

Methods: Randomized controlled trials comparing the effects of tDCS with sham, using the Barthel Index (BI), the upper and lower extremity Fugl–Meyer Assessment (FMA), and the Modified Ashworth Scale (MAS), were retrieved from PubMed, Medline (EBSCO), and Cumulative Index to Nursing and Allied Health Literature (CINAHL) from their inception to June 2021. Calculations for each assessment were done for the overall effect and associated therapy accounting for the influence of stroke severity or stimulation parameters.

Results: A total of 31 studies involving metrics of the BI, the upper extremity FMA, the lower extremity FMA, and the MAS were included. tDCS combined with other therapies was beneficial when assessed by the BI (mean difference: 6.8; $P < 0.01$) and these studies typically had participants in the acute stage. tDCS effects on the upper and lower extremity FMA are unclear and differences between the sham and tDCS groups as well as differences in the associated therapy type combined with tDCS potentially influenced the FMA results. tDCS was not effective compared to sham for the MAS. Stimulation types (e.g., anodal vs. cathodal) did not influence these results and dosage parameters were not associated with the obtained effect sizes. Conventional therapy associated with tDCS typically produced greater effect size than assisted therapy. The influence of stroke severity is unclear.

Conclusion: Potential benefits of tDCS can vary depending on assessment tool used, duration of stroke, and associated therapy. Mechanistic studies are needed to understand the potential role of stimulation type and dosage effect after stroke. Future studies should carefully conduct group randomization, control for duration of stroke, and report different motor recovery assessments types.

Systematic Review Registration: [https://www.crd.york.ac.uk/PROSPERO/], identifier [CRD42021290670].

Keywords: brain stimulation, tDCS, stroke, Barthel Index, Fugl–Meyer, Ashworth Scale, rehabiliatation

INTRODUCTION

In the United States alone, it has been estimated that every 40 s, someone suffers from a stroke, averaging more than 795,000 incidents of stroke every year with around 185,000 of those stroke occurrences happening in people who have already suffered from a stroke (CDC, 2021). Stroke is also regarded as one of the leading causes for disability, leading to reduced motor function, which limits participation in normal activities of daily life, such as locomotion, dressing, or eating (Kim et al., 2014; Hatem et al., 2016). This reduction in daily activities of life and physical activity due to disability further increases the affected person's risk for further cardiovascular disease, which may lead to a subsequent stroke (Adeyemo et al., 2012). Stroke frequently leads to significant alterations in cortical excitability of the primary motor cortex in the affected and unaffected hemispheres, which lead to the idea that manipulating the cortical excitability may have an influence on stroke recovery (Hummel and Cohen, 2006).

Transcranial direct current stimulation (tDCS) is a non-invasive brain stimulation technique that involves applying a small current to the scalp aiming to modulate cortical excitability (Nitsche and Paulus, 2000; Bikson et al., 2016; Orrù et al., 2019). A common way of applying tDCS is based on the interhemispheric competition model aiming to reduce interhemispheric inhibition and increase excitability of lesioned hemisphere. Typical configurations of tDCS are: (1) the anode electrode placed over the brain area of interest aiming to increase excitation and the cathode electrode placed as a reference (i.e., anodal stimulation); (2) cathode electrode placed over the contralesional hemisphere, aiming to decrease excitability, and the anode electrode placed as reference such as the ipsilesional supraorbital region (i.e., cathodal stimulation); and (3) bihemispheric stimulation aiming to both decrease contralesional and increase ipsilesional excitability. However, applying tDCS in accordance to the interhemispheric competition model is currently under debate considering reports challenging the influence of interhemispheric imbalance on motor recovery (Di Pino et al., 2014; Xu et al., 2019).

Earlier meta-analysis evaluating upper limb motor function suggested that tDCS could be beneficial for individuals with chronic stroke (Butler et al., 2013; Chhatbar et al., 2015). However, a more recent comprehensive systematic review is inconclusive on the effects of tDCS on several aspects of physical function (Elsner et al., 2020), whereas others suggest that tDCS could be beneficial for the upper limb motor function (Van Hoornweder et al., 2021). Several factors are suggested to influence the tDCS results such as tDCS dosage, severity of disease, and type of associated therapy (Chhatbar et al., 2015; Elsner et al., 2020; Van Hoornweder et al., 2021). Thus, further analysis is still necessary on the effects of associated therapy used with tDCS, dosage effect, and severity of disease in multiple domains of motor function recovery. Minimal clinically important differences (MCIDs) were also not compiled in the previous reviews and they are another relevant information. Thus, the purpose of this systematic review is two-fold: (1) to determine the influence of tDCS alone or combined with other therapies on the recovery of motor function after stroke and (2) to determine the influence of therapy type, stimulation configuration (e.g., anodal vs. cathodal), and tDCS dosage (i.e., current, duration, electrode size, session number, and frequency) on the potential benefits of tDCS. We hypothesized that tDCS combined with other therapies would be beneficial for stroke recovery and the results will be dependent on the assessment used, dosage, severity, and the type of combined therapy.

MATERIALS AND METHODS

We followed the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist (Page et al., 2021) for study retrieval and subsequent analysis.

Search Strategy

The online databases that were searched are PubMed, Medline (EBSCO), and Cumulative Index to Nursing and Allied Health Literature (CINAHL). In each of these databases, we used a combination of terms "stroke," "tDCS or transcranial direct current stimulation," and "Fugl–Meyer or Ashworth or Barthel" to locate relevant articles. The most recent search of PubMed, Medline (EBSCO), and CINAHL using the combined terms produced 45, 89, and 34 results, respectively.

Inclusion and Exclusion Criteria

Randomized controlled trials assessing the effects of tDCS compared to a sham intervention were included. For the sham, typically tDCS is turned off within the first min to simulate the itching sensation from the beginning of stimulation. The trials contained results for one of or a combination of the Barthel Index (BI), the upper extremity Fugl–Meyer Assessment (FMA), the lower extremity FMA, and the Modified Ashworth

Scale (MAS) were included in this study. Studies used either anodal, cathodal, or bihemispheric tDCS to rehabilitate patients after suffering from either a hemorrhagic or ischemic stroke. As this review focuses on the effects of tDCS on stroke, any study, which includes the use of brain stimulation aside from tDCS such as, transcranial random noise stimulation, was excluded. Additionally, the use of combined stimulation techniques, such as the use of tDCS in combination with repetitive tDCS, was excluded.

Data Extraction

One of the authors (A-MC) extracted the following variables from each study: (1) mean score and SD before and after treatment for each assessment used to measure functional recovery alone (i.e., the BI, the FMA, and the MAS). The first data point after treatment was used in case multiple follow-ups were reported; (2) number of intervention sessions in which tDCS was applied; (3) application time of tDCS during each session; (4) total time of tDCS application during all the testing sessions; (5) current; (6) electrode size; (7) current density of tDCS; (8) charge of tDCS; (9) charge density of tDCS; (10) total charge of tDCS; (11) total charge density of tDCS; (12) placement of the tDCS electrodes (e.g., ipsilesional hemisphere or contralesional supraorbital region); (13) stimulation type (e.g., anodal, cathodal, or bihemispheric); (14) type of stroke, whether ischemic or hemorrhagic; (15) time after occurrence of stroke before intervention; and (16) type of therapy used. Data from figures were extracted using WebPlotDigitizer (version 4) (Kim et al., 2010; Bolognini et al., 2011, 2020; Khedr et al., 2013; Fusco et al., 2014; Beaulieu et al., 2019; Bornheim et al., 2020; Prathum et al., 2021). Studies that presented data as mean ± SE were manually converted to mean ± SD. Authors were contacted via email for studies whose data could not be extracted from visual inspection (Rossi et al., 2013; Ilic et al., 2016; Andrade et al., 2017; Cheng et al., 2021) and a response was not obtained.

Dosage Calculations

Information regarding the characteristics of the studies, such as number of tDCS sessions and stroke duration, can be found in **Supplementary Table 1** and information regarding the calculation of tDCS total charge density, such as electrode size and current, can be found in **Supplementary Table 2**. We used previous reported equations (Chhatbar et al., 2015) to calculate the dosage effect.

- Current density (mA/cm^2) = Current (mA) ÷ Electrode size (cm^2)
- Charge = Current (mA) × tDCS duration (min) ÷ 60
- Charge density (mAh/cm^2) = Charge (mAh) ÷ Electrode size (cm^2)
- Total charge (mAh) = Charge (mAh) × Number of sessions (cm^2)
- Total charge density (mAh/cm^2) = Charge density (mAh/cm^2) × tDCS sessions

Two additional equations were used to calculate total tDCS application time and number of sessions per week:

- Total tDCS time (min) = Number of sessions × Session time (min)
- Sessions per week = Number of sessions ÷ Intervention period (weeks).

Risk of Bias Assessment

The Cochrane Risk of Bias 2 tool (August 2019 version) was used. This tool assesses selection, reporting, performance, detection, and attrition biases in a 5-domain list containing multiple items with risk of bias being declared as high, low, or unclear. Two authors (JS and ADC) separately assessed each article's risk of bias using this tool and discussed the results. Any conflicting results were further discussed in extensive detail with a third investigator to come to a consensus.

Statistical Analysis

Forest plots were generated using Review Manager (RevMan version 5.4.1). Meta-analyses were performed for each of the four assessments for motor function recovery comparing the post-intervention data between the groups. Additionally, because minimal differences in the baseline motor function between the tDCS and sham groups were previously suggested to influence the results of tDCS intervention (Chhatbar et al., 2015), we also performed meta-analysis with the change score (mean difference between baseline and post-intervention) and pooled SD for each group. The influence of stroke severity and therapy type was investigated with tests for subgroup differences and significance was set at $P = 0.10$. For each comparison, mean differences between the groups were calculated with 95% CIs. For each analysis, a fixed effects model was used if the results were homogenous ($P > 0.10$) and a random effects model was used if heterogeneity was present. Sensitivity analysis was performed by determining the influence of each study from the model. Funnel plot's visual inspection indicated publication bias was unlikely.

Statistical Package for the Social Sciences (SPSS) (version 27) was used to assess the association between Hedge's *g* effect size (Hedges, 1981) and dosage (i.e., current density, charge, charge density, total charge, total charge density, and total tDCS time). Hedge's *g* effect size was calculated for each study using scores from pre- to post-intervention (i.e., post-intervention values – preintervention/pooled SD) of the tDCS groups for each assessment. Spearman's rho was used for the association analysis because of the lack of normal distribution in several variables according to the Shapiro–Wilk test. For all the analyses, the significance was set at $P < 0.05$.

Minimal clinically important difference was determined by the difference in pre- and post-intervention scores reaching a minimal value. To indicate a MCID in the tDCS or sham group, an increase must be shown in the score of the BI by at least 1.85 points (Hsieh et al., 2007), the upper extremity FMA by at least 5.25 points (Page et al., 2012), and the lower extremity FMA by at least 6 points (Pandian et al., 2016). To indicate a MCID for the MAS, however, a reduction of at least 0.48 points must be shown (Chen et al., 2019).

RESULTS

After excluding duplicates and performing a manual search on the reference list of the retrieved manuscripts, a total of 31 individual manuscripts were included in this review (**Supplementary Figure 1**). Five manuscripts (Kim et al., 2010; Hesse et al., 2011; Khedr et al., 2013; Rocha et al., 2016; Yi et al., 2016) recruited independent groups of participants to assess the effects of stimulation type (e.g., anodal vs. cathodal) in comparison to sham and in this case, careful consideration was taken to not include the sham group twice in the total sample size. The number of participant assessed with the BI, the upper extremity FMA, the lower extremity FMA, and the MAS tested was 515, 913, 179, and 172, respectively. Despite all the studies being randomized controlled trials, out of the 31 studies that were included in this review, one study reported significant differences between the tDCS and sham groups at baseline (Pinto et al., 2021) and some studies made no mention of baseline differences either in their discussion or with a statistical analysis (Allman et al., 2016; Achacheluee et al., 2018; Oveisgharan et al., 2018). The rest of the included studies reported that the sham and tDCS groups were similar at baseline.

Studies were excluded for several reasons such as: (1) Pilot studies that were later published (Hesse et al., 2007; Mazzoleni et al., 2017); (2) tDCS in combination with other forms of electrical stimulation, such as repetitive tDCS or neuromuscular electrical stimulation; (3) Studies with electrode placements to rehabilitate cognition instead of motor function; (4) Not reporting data on stroke individuals; (5) Studies that failed to indicate post-intervention descriptive or numerical results; and (6) No use of the FMA, the BI, or the MAS.

Study Characteristics

The majority of studies used different participants for the sham and tDCS intervention groups (i.e., between-group design) and only one study used a within-group design with washout period of 72 h (Achacheluee et al., 2018; **Supplementary Table 1**). Some manuscripts reported more than one assessment. Ten of them investigated the BI (Kim et al., 2010; Hesse et al., 2011; Khedr et al., 2013; Fusco et al., 2014; Yi et al., 2016; Koo et al., 2018; Bolognini et al., 2020; Bornheim et al., 2020; Yao et al., 2020; Pinto et al., 2021), 25 included the upper extremity FMA (Lindenberg et al., 2010; Bolognini et al., 2011, 2020; Hesse et al., 2011; Nair et al., 2011; Khedr et al., 2013; Rossi et al., 2013;

Study or Subgroup	tDCS Mean	tDCS SD	tDCS Total	Sham Mean	Sham SD	Sham Total	Weight	Mean Difference IV, Fixed, 95% CI
1.1.2 Moderate Dependency 61-90								
Bornheim et al. 2019	85.6	19.89	25	73.96	19.89	25	6.3%	11.64 [0.61, 22.67]
Kim et al. 2010 (Anodal)	79.07	12.59	6	73.79	12.95	7	3.9%	5.28 [-8.63, 19.19]
Kim et al. 2010 (Cathodal)	92.25	12.42	5	73.79	12.95	7	3.6%	18.46 [3.95, 32.97]
Subtotal (95% CI)			36			39	13.9%	11.61 [4.19, 19.04]
Heterogeneity: Chi² = 1.65, df = 2 (P = 0.44); I² = 0%								
Test for overall effect: Z = 3.07 (P = 0.002)								
1.1.3 Severe Dependency 21-60								
Fusco et al. 2014	68.56	31.82	5	59.09	32.2	6	0.5%	9.47 [-28.50, 47.44]
Hesse et al. 2011 (Anodal)	53.6	14.5	28	56.3	15.5	28	12.4%	-2.70 [-10.56, 5.16]
Hesse et al. 2011 (Cathodal)	59.2	12.4	29	56.3	15.5	28	14.3%	2.90 [-4.40, 10.20]
Khedr et al. 2013 (Anodal)	51.84	9.3	14	41.14	9.51	13	15.1%	10.70 [3.60, 17.80]
Khedr et al. 2013 (Cathodal)	52.24	9.96	13	41.14	9.51	13	13.6%	11.10 [3.61, 18.59]
Koo et al. 2018	65.25	13.02	12	55.17	17.96	12	4.8%	10.08 [-2.47, 22.63]
Pinto et al. 2021	74.8	22.7	31	62.1	28.6	29	4.4%	12.70 [-0.42, 25.82]
Yao et al. 2020	72	17.1	20	64.5	12.4	20	8.9%	7.50 [-1.76, 16.76]
Yi et al. 2016 (Cathodal)	46	20.5	10	36.8	13.3	10	3.3%	9.20 [-5.95, 24.35]
Subtotal (95% CI)			162			159	77.5%	6.83 [3.69, 9.97]
Heterogeneity: Chi² = 10.31, df = 8 (P = 0.24); I² = 22%								
Test for overall effect: Z = 4.26 (P < 0.0001)								
1.1.4 Total Dependency 0-20								
Bolognini et al. 2020	34.66	17.05	16	40.07	17.05	16	5.5%	-5.41 [-17.22, 6.40]
Yi et al. 2016 (Anodal)	42.1	21.3	10	36.8	13.3	10	3.2%	5.30 [-10.26, 20.86]
Subtotal (95% CI)			26			26	8.6%	-1.49 [-10.91, 7.92]
Heterogeneity: Chi² = 1.15, df = 1 (P = 0.28); I² = 13%								
Test for overall effect: Z = 0.31 (P = 0.76)								
Total (95% CI)			224			224	100.0%	6.77 [4.01, 9.54]
Heterogeneity: Chi² = 17.71, df = 13 (P = 0.17); I² = 27%								
Test for overall effect: Z = 4.80 (P < 0.00001)								
Test for subgroup differences: Chi² = 4.60, df = 2 (P = 0.10), I² = 56.5%								

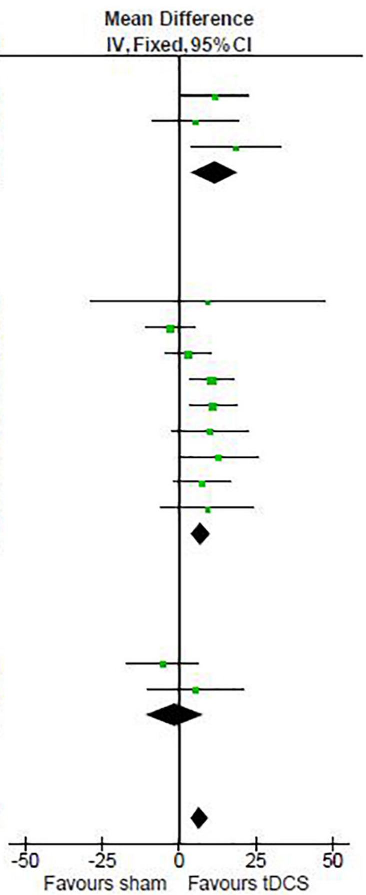

FIGURE 1 | Effects of transcranial direct current stimulation (tDCS) on stroke recovery as assessed by the post-intervention data of the tDCS and sham groups for the Barthel Index.

Fusco et al., 2014; Viana et al., 2014; Ang et al., 2015; Triccas et al., 2015; Allman et al., 2016; Kim et al., 2016; Rocha et al., 2016; Straudi et al., 2016; Yi et al., 2016; Mazzoleni et al., 2017; Achacheluee et al., 2018; Oveisgharan et al., 2018; Beaulieu et al., 2019; Edwards et al., 2019; Jin et al., 2019; Alisar et al., 2020; Bornheim et al., 2020; Liao et al., 2020; Yao et al., 2020; Pinto et al., 2021; Prathum et al., 2021), five included the lower extremity FMA (Chang et al., 2015; Seo et al., 2017; Bornheim et al., 2020; Pinto et al., 2021; Prathum et al., 2021), and nine included the MAS (Hesse et al., 2011; Viana et al., 2014; Andrade et al., 2017; Mazzoleni et al., 2017; Beaulieu et al., 2019; **Supplementary Table 1**). Characteristics of dosage used (i.e., number of sessions, time, current, etc.) are shown in **Supplementary Table 2**. In summary, the number of test sessions, which the intervention was given to subjects, varied from as little as a single session to as many as 40. Application time per session of tDCS ranged from 10 to 30 min, with the majority applying tDCS for 20 min per session. The majority of studies (∼48%) investigated tDCS effects on rehabilitation in patients with predominantly ischemic stroke and approximately 48% of studies investigated both the ischemic and hemorrhagic stroke (**Supplementary Table 1**). Three studies gave insufficient data or a range, so total charge density was not calculated (**Supplementary Table 2**). Six studies reported tDCS without the addition of other therapies, 11 studies used conventional therapy, 11 studies used assisted therapy, 1 study used a combination of both the conventional and robotic therapy, and three studies used other miscellaneous therapy types (**Supplementary Table 1**).

Risk of Bias

According to the Cochrane Risk of Bias 2 tool (**Supplementary Figures 2, 3**), common bias was related to inadequate description of allocation concealment, blinding of researchers, assessors, or therapists.

Overall Effects of Transcranial Direct Current Stimulation on Motor Recovery for Each Assessment and Influence of Stroke Severity or Stimulation Type

Barthel Index

Descriptive

Out of the 10 manuscripts reporting the BI, only three manuscripts concluded that there was a significant difference between the tDCS group and the sham group. All the 10 studies reported reaching MCID (**Supplementary Table 1**) in both the sham and tDCS groups (**Supplementary Table 1**).

Meta-Analysis

Post-intervention data showed that tDCS was beneficial when assessed by the BI [mean difference: 6.77 (Confidence Interval (CI): 4.01, 9.54); $P < 0.01$] (**Figure 1**). Similarly, meta-analysis using the change scores showed a positive effect of tDCS [mean difference: 6.13 (CI: 2.56, 9.69); $P < 0.01$]. Sensitive analysis because of large SD in one study (Fusco et al., 2014) revealed that it had no influence on the above results.

Influence of Stroke Severity

The baseline BI score of each study was used to classify stroke severity and divided in the following: total dependency (0–20), severe dependency (21–60), and moderate dependency (61–90) (Collin et al., 1988). Subgroup analysis shows that the severity of stroke had a trend to influence the results presented for the post-intervention data meta-analysis ($P = 0.10$), so that studies in the moderate and severe dependency categories had greater effect size than the studies in the total dependency category. The influence of stroke severity should be cautiously interpreted considering the majority of studies are in the severe dependency category (**Figure 1**) and change score meta-analysis had no influence of stroke severity ($P = 0.47$).

Influence of Stimulation Type

Studies were divided in the following subgroups: cathodal, anodal, and bihemispheric to investigate the influence of tDCS montage on the above meta-analysis. Type of stimulation had no influence on the meta-analysis results showed above (test for subgroup differences: post-intervention data: $P = 0.52$ and change score: $P = 0.25$). The cathodal group had 166 participants (sham: 84 vs. tDCS: 82), the anodal group had 190 participants (sham: 95 vs. tDCS: 95), and the bihemispheric group had 92 participants (sham: 45 vs. tDCS: 47).

Upper Extremity Fugl–Meyer Assessment

Descriptive

76 and 44% of the studies observed the tDCS and sham groups, respectively, reached MCID (**Supplementary Table 1**). The majority of the studies indicate both the sham and tDCS groups reached MCID and out of the 25 studies, only 8 studies reported that MCID was reached in the tDCS group, but not in the sham group.

Meta-Analysis

Post-intervention data showed that tDCS was not superior to sham (**Figure 2**). However, the meta-analysis of change scores showed a positive effect of tDCS [mean difference: 1.68 (CI: 0.25, 3.11); $P = 0.02$] (**Figure 3**). Sensitive analysis because of large SD in one study (Fusco et al., 2014) showed that it had no influence on the above results.

Influence of Stroke Severity

Subgroup analysis by severity of stroke, calculated with the upper extremity FMA score at the beginning of the intervention, as previously done (Van Hoornweder et al., 2021), did not influence the meta-analysis results (post-intervention data: $P = 0.36$ and change score: $P = 0.16$) (**Figures 2**, **3**). However, the majority of studies are from the severe and moderate categories (9 and 12 studies, respectively) compared with only 4 studies in the mild impairment category.

Influence of Stimulation Type

Test of subgroups indicate that the meta-analysis showed above was not influenced by the type of stimulation (post-intervention data: $P = 0.32$ and change score: $P = 0.74$). For this comparison, there were 408 participants in the anodal stimulation (sham: 203 vs. tDCS: 205), 148 participants in

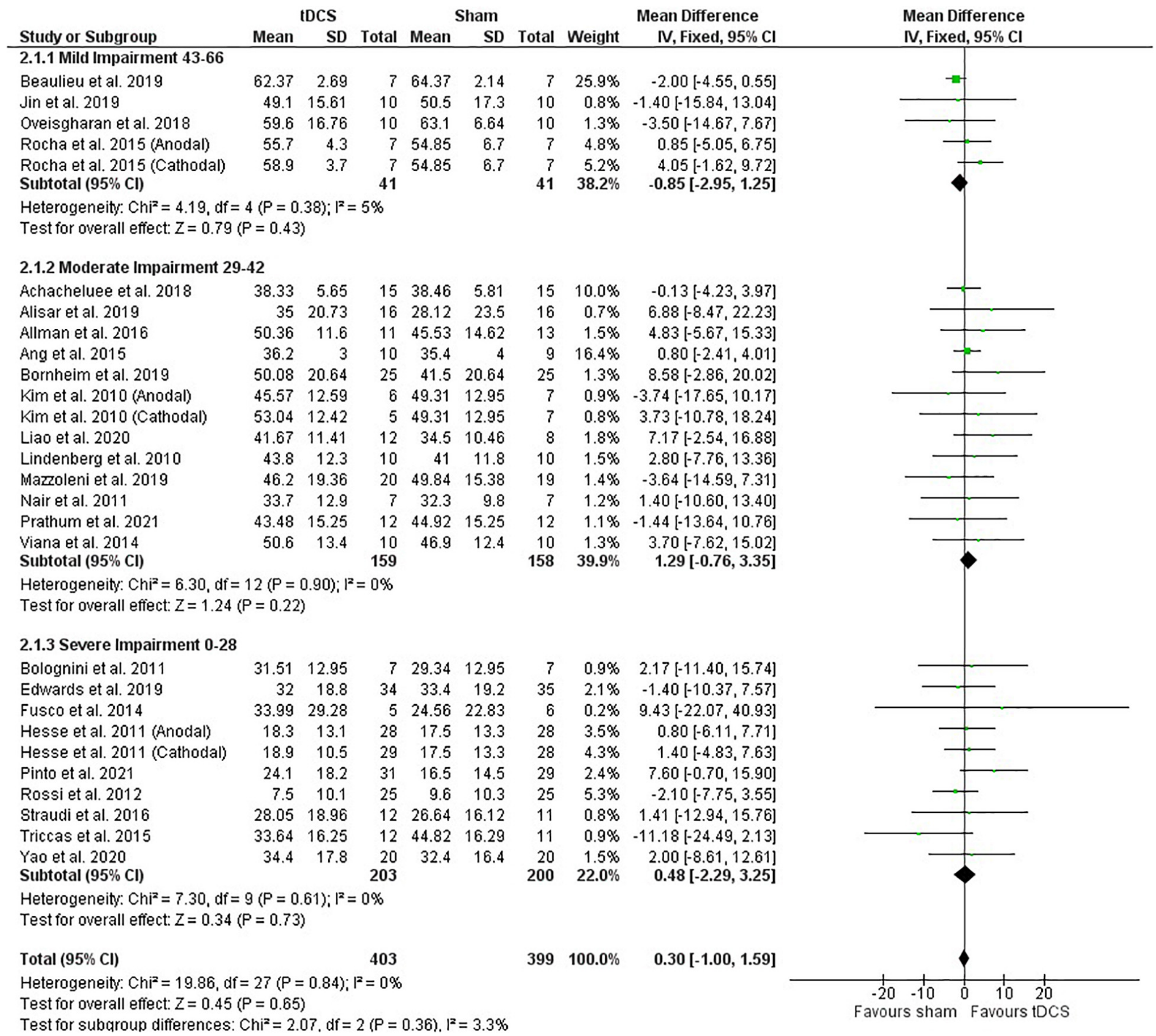

FIGURE 2 | Effects of tDCS on stroke recovery as assessed by the post-intervention data of the tDCS and sham groups for the upper extremity Fugl–Meyer Assessment.

the cathodal stimulation (sham: 75 vs. tDCS: 73), and 246 participants in the bihemispheric stimulation (sham: 121 vs. tDCS: 125).

Lower Extremity Fugl–Meyer Assessment

Descriptive

Out of the five studies that reported data from this assessment, three studies concluded that the use of tDCS was able to significantly improve recovery compared to sham. However, only one study reached MCID by an increase in score of at least six points in the tDCS group. No study reported MCID in the sham group (**Supplementary Table 1**).

Meta-Analysis

Post-intervention data showed that tDCS had a positive effect on motor recovery compared with sham [mean difference: 2.19 (CI: 1.07, 3.30); $P < 0.01$] (**Figure 4**). One study had a heavy weight on this analysis due to small SD reported (Chang et al., 2015) and removing this study from calculations maintained the positive effect of tDCS compared with sham intervention [mean difference: 2.51 (CI: 0.07, 4.94); $P = 0.04$]. However, meta-analysis of change scores showed no effect of tDCS [mean difference: −0.26 (CI: −1.82, 1.31); $P = 0.75$].

Influence of Stroke Severity

The lower extremity FMA score at the beginning of the intervention had no influence on the meta-analysis results (post-intervention data: $P = 0.43$ and change score: $P = 0.54$). However, there was only one study in the severe category (score < 21) and four studies in the moderate category (score > 21) (Kwong and Ng, 2019; **Figure 4**). The study with heavier weight in the meta-analysis is in the moderate impairment category.

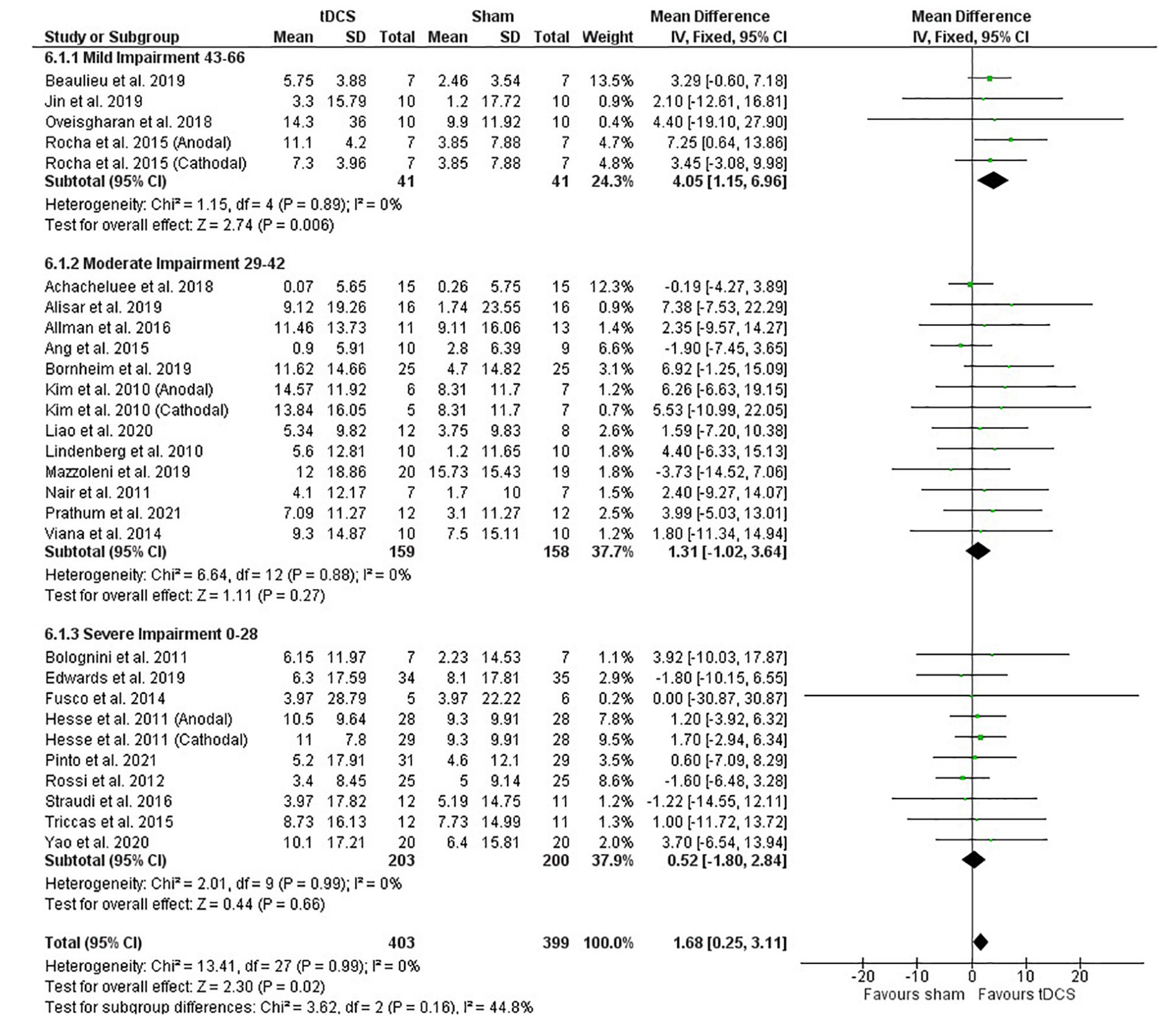

FIGURE 3 | Effects of tDCS on stroke recovery as assessed by the change scores (mean difference between baseline and post-intervention) of the tDCS and sham groups for the upper extremity Fugl–Meyer Assessment.

Influence of Stimulation Type

Subgroup test indicates that the meta-analysis presented above was not influenced by stimulation type (post-intervention data: $P = 0.95$ and change score: $P = 0.56$). For this analysis, there were 95 participants in the anodal subgroup (sham: 47 vs. tDCS: 48) and 84 participants in the bihemispheric subgroup (sham: 41 vs. tDCS: 43). No study using the lower extremity FMA used cathodal stimulation.

Modified Ashworth Scale

Descriptive

Out of the three studies that reported this assessment, none of the study had found MCID in either the tDCS or sham groups (**Supplementary Table 1**).

Meta-Analysis

Post-intervention data showed no effect of tDCS on the MAS (**Figure 5**). Likewise, the meta-analysis of change scores showed no effect in favor of tDCS [mean difference: −0.25 (CI: −0.76, 0.27); $P = 0.35$].

Influence of Stroke Severity

Subgroup analysis by severity was not performed for the MAS, as they reported similar baseline average values.

Influence of Stimulation Type

Test for subgroups indicate that there was no influence of type of stimulation on the meta-analysis described above (post-intervention data: $P = 0.77$ and change score: $P = 0.47$). Only one study used cathodal stimulation and no study used bihemispheric

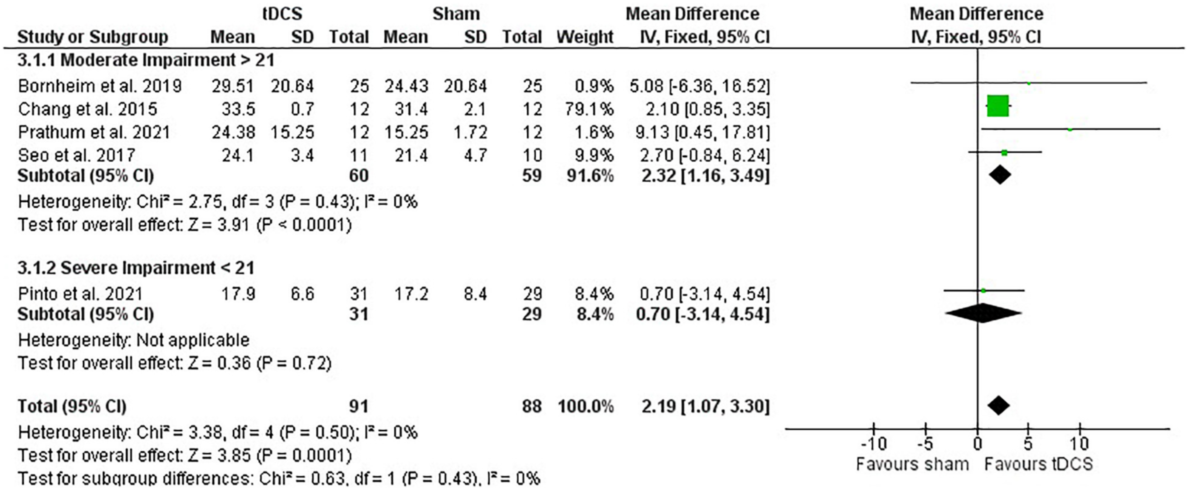

FIGURE 4 | Effects of tDCS on stroke recovery as assessed by the post-intervention data of the tDCS and sham groups for the lower extremity Fugl–Meyer Assessment.

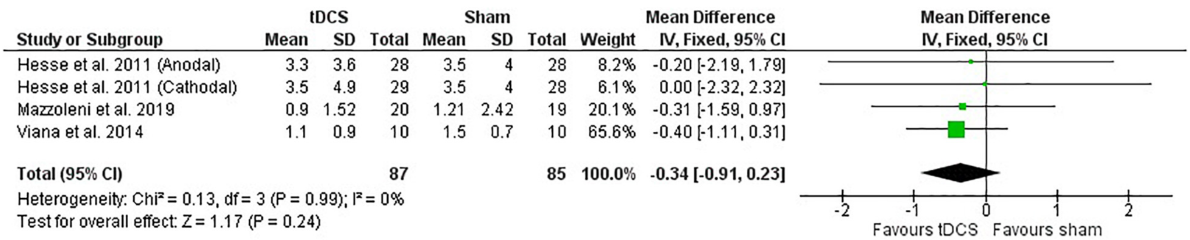

FIGURE 5 | Effects of tDCS on stroke recovery as assessed by the post-intervention results of the tDCS and sham groups for the Modified Ashworth Scale.

stimulation. The subgroup for the anodal stimulation involved 115 individuals (sham: 57 vs. tDCS: 58) and the subgroup for the cathodal stimulation involved 57 individuals (sham: 28 vs. tDCS: 29).

Transcranial Direct Current Stimulation as a Stand-Alone Therapy

Subgroup meta-analysis was conducted on studies reporting the effects of tDCS without other intervention. Studies available assessed the effects of tDCS on the BI and the upper extremity FMA, but not the lower extremity FMA or the MAS. tDCS was not different than sham when used as a stand-alone therapy for the post-intervention data or change scores for either the BI or the upper extremity FMA (**Supplementary Table 3**).

Influence of Stroke Severity

For the BI, two studies had individuals in the severe dependency category (Fusco et al., 2014; Koo et al., 2018), but only one study found that tDCS was effective compared with sham (Koo et al., 2018). Also, for the BI, one study had individuals in the total dependency category (Bolognini et al., 2020) and tDCS was not beneficial compared with sham. For the upper extremity FMA, two studies had individuals in the severe category (Rossi et al., 2013; Fusco et al., 2014) and one study had individuals in the moderate category (Achacheluee et al., 2018) and all of them showed that tDCS was not beneficial compared with sham. However, one study recruiting individuals in the mild category showed that tDCS was beneficial compared with sham (Oveisgharan et al., 2018).

Influence of Stimulation Type

For the BI, out of the three studies included in this review, one study used cathodal, one study used anodal, and one study used bihemispheric (**Supplementary Table 1**). Only one study using anodal stimulation showed a statistical difference between the sham and tDCS groups (Koo et al., 2018). Out of the four studies assessing the upper extremity FMA, two used anodal, one study used cathodal, and one study used bihemispheric stimulations. From these studies, the only one showing statistical significant differences between the tDCS and sham groups used bihemispheric stimulation (Oveisgharan et al., 2018).

Influence of the Type of Therapy Associated With Transcranial Direct Current Stimulation

Three subgroups of therapy types were previously suggested (Elsner et al., 2020) and used in this review: (1) conventional (e.g., physical therapy or occupational therapy); (2) assisted (e.g., mirror, virtual reality, robot-assisted, or brain–computer interface-assisted motor imagery); and (3) miscellaneous (e.g., constraint-induced movement therapy). In these comparisons one study was excluded because it used a combination of two of the subgroups (Pinto et al., 2021).

Barthel Index

Meta-analysis of the post-intervention data shows that studies using conventional therapy associated with tDCS had improvement in the BI score, but not the studies using assisted therapy (subgroup difference: $P < 0.01$) (**Figure 6**). Meta-analysis with change score data agrees with the post-intervention data ($P < 0.01$) (**Supplementary Figure 4**).

Upper Extremity Fugl–Meyer Assessment

Meta-analysis of the post-intervention data shows that studies using conventional therapy associated with tDCS had similar results compared with studies using assisted or miscellaneous therapies (4.2 vs. 0.7 vs. 2.5; test for subgroup differences: $P = 0.46$) (**Supplementary Figure 5**). However, meta-analysis with change score data indicates that studies using conventional therapy were superior to assisted or miscellaneous therapies (3.9 vs. 0.4 vs. 5.19, respectively; test for subgroup differences: $P = 0.07$) (**Supplementary Figure 6**). The miscellaneous groups have fewer subjects compared with the other therapy types, but sensitive analysis shows that the above results are maintained (change score: $P = 0.06$ and post-intervention data: $P = 0.27$).

Lower Extremity Fugl–Meyer Assessment

Meta-analysis of both the post-intervention data and change scores shows that studies using conventional therapy associated with tDCS had similar results compared with assisted therapy combined with tDCS (test for subgroup differences: post-intervention data: $P = 0.75$; change score: $P = 0.18$). These results, however, may be a consequence of the lower overall number of studies and the majority using conventional therapy compared with assisted therapy (3 vs. 1) (**Supplementary Figure 7**). Moreover, the only study using assisted therapy found that tDCS combined with a robotic-assisted therapy was not beneficial as compared with sham (Seo et al., 2017). No study was included in the miscellaneous therapy subgroup. One study was excluded from this calculation because it used a combination of assisted and conventional therapies (Pinto et al., 2021).

Modified Ashworth Scale

Meta-analysis could not be conducted on the effects of therapy type using the MAS, as all the studies that provided pre- and post-intervention data belonged to the same subgroup (i.e., all used assisted therapy).

Dose Response

We investigated if the Hedge's g effect size of tDCS intervention was influenced by: (1) number of sessions, (2) sessions per week, (3) session time, (4) total tDCS application time, (5) current, (6) electrode size, (7) current density, (8) charge, (9) charge density, (10) total charge, and (11) total charge density.

Barthel Index

Overall, there was no association between any of the dosage metrics with Hedge's g effect size (**Figure 7**) (All $P > 0.05$, **Supplementary Table 4**). These results were not influenced by the stimulation type.

Upper Extremity Fugl–Meyer Assessment

When all the available studies were included in the calculations, there was no influence of any metrics of dosage on effect size (**Figure 8**) (All $P > 0.05$, **Supplementary Table 4**). Of note, session time had a trend of negative association with effect size ($r = -0.38$; $P = 0.05$). The session time ranged from 9 to 40 min (**Supplementary Table 2**) and the negative trend was not maintained by removing a study with large effect size and short session time (Rocha et al., 2016). These results were not influenced by the stimulation type (i.e., cathodal vs. anodal vs. bihemispheric).

Modified Ashworth Scale and Lower Extremity Fugl–Meyer Assessment

For both the assessments, there was no association between any of the dosage metrics with Hedge's g effect size (all $P > 0.05$) (**Supplementary Figures 8, 9**). However, cautious interpretation is required due to the small number of studies reporting these assessments.

DISCUSSION

Transcranial direct current stimulation alone was ineffective to improve motor recovery after stroke. However, tDCS applied in combination with other therapies was somewhat beneficial for motor recovery of stroke survivors and the improvements could be dependent on the assessment used and associated therapy. Specifically: (1) tDCS applied in combination with other therapies was beneficial when assessed by the BI but not by the MAS, and the effects on the upper or lower extremity FMA are unclear (2) conventional therapy combined with tDCS had a greater impact on motor function relative to assisted therapy combined with tDCS when assessed by the BI for either post-scores (∼13 vs. ∼2, respectively, **Figure 6**) or changes scores (∼11 vs. 2, respectively, **Supplementary Figure 4**). Additionally, for the upper extremity FMA, tDCS combined with conventional and miscellaneous therapies had greater benefits than assisted therapy (3.9 vs. 5.9 vs. 0.44, respectively) when change scores, which are more likely to detect small alterations in motor recovery, were used for meta-analysis. Type of stimulation (i.e., anodal vs. cathodal vs. bihemispheric) had no influence on the motor recovery, which agrees with previous reviews (Elsner et al., 2020; Van Hoornweder et al., 2021). Contrary to our hypothesis, tDCS dosage has minimal influence on the recovery of motor function after stroke. Another new aspect in this review is the evaluation of MCID. Conversely to statistical differences between the tDCS and sham groups, MCID analysis adds to the interpretation by showing that MCID is frequent in both the sham and tDCS groups, particularly when using the BI and the FMA, but not the MAS assessment. The improvement in

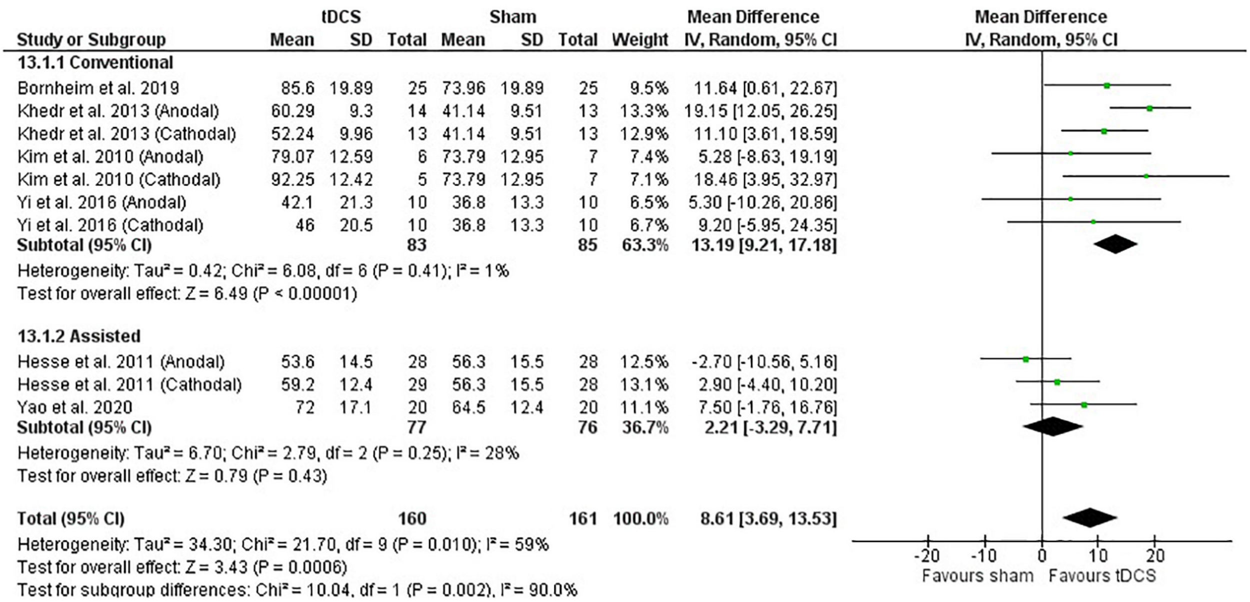

FIGURE 6 | Effects of therapy (conventional and assisted) combined with tDCS on stroke recovery as assessed by the post-intervention data of the tDCS and sham groups for the Barthel Index.

MCID in the sham group shows the effectiveness of the associated therapy. tDCS benefits, estimated with group differences in effect sizes, were observed, despite the associated therapy. Our results agree with others (Elsner et al., 2020; Van Hoornweder et al., 2021) showing limited, but positive evidence of effect of tDCS on upper limb motor function (i.e., the FMA) and gross motor recovery (i.e., the BI). For muscle tone and the lower extremity function, the evidence is scarce.

Potential Factors Influencing the Transcranial Direct Current Stimulation Results on Motor Recovery in This Review

Randomized controlled trials assume the groups are similar at baseline, and statistical differences post-treatment are a consequence of the intervention. However, in stroke individuals, minimal differences in function between the sham and tDCS groups at the start of treatment could influence the overall interpretation considering that randomized controlled trials are typically underpowered to detect between group differences at baseline (Chhatbar et al., 2015). This is shown in our meta-analyses for the upper and lower extremity FMA. Specifically, tDCS had a significant effect on post-stroke recovery for the upper extremity FMA (25 studies included) when using change scores (i.e., mean difference between baseline and post-intervention for each group), but not with the post-intervention data. For the lower extremity FMA (five studies), the post-intervention data meta-analysis showed positive results of tDCS compared with sham, but the change score data, which is more sensitive to small changes from the intervention, showed that tDCS had no benefit compared with sham.

It was previously reported that the severity of stroke can influence the tDCS results, so less severe individuals have greater recovery using linear regressions or subgroup analysis (Baltar et al., 2020). Our subgroup analysis showed that the stroke severity did not influence the meta-analysis results for the upper and lower FMA and the MAS; however, for the BI assessment, the studies with less severe individuals had a trend for better recovery compared with studies using more severe individuals. Heterogeneity in the participant's characteristics across different assessments can potentially explain the results of the current review. Specifically, out of the 10 total possible studies included in the BI meta-analyses, the majority of the studies had subacute participants (i.e., between 1 week and 3 months) compared with chronic (i.e., >3 months) (approximately 60 vs. 10%, respectively), whereas 30% did not clearly state the duration of stroke. Out of the 25 total possible studies include in the upper extremity FMA meta-analyses, approximately 32% had subacute participants, approximately 52% had chronic participants, and approximately 16% did not clearly indicate stroke duration.

Differences in the assessment scales themselves should also be considered. The BI is an assessment for gross movements used for activities of daily living scored broadly, whereas the upper extremity FMA and the lower extremity FMA are assessments for specific movements related to motor function with highly detailed scoring. Lastly, the MAS assesses muscle tone with a small scoring range. There are ample opportunities for future studies to investigate the effects of tDCS using multiple assessments, as the effects of tDCS may be dependent on the assessment used and combined therapy. Reporting individual effect size from the sham and tDCS intervention for each assessment, as well as stroke severity, will also provide opportunities for more advanced analysis in future reviews.

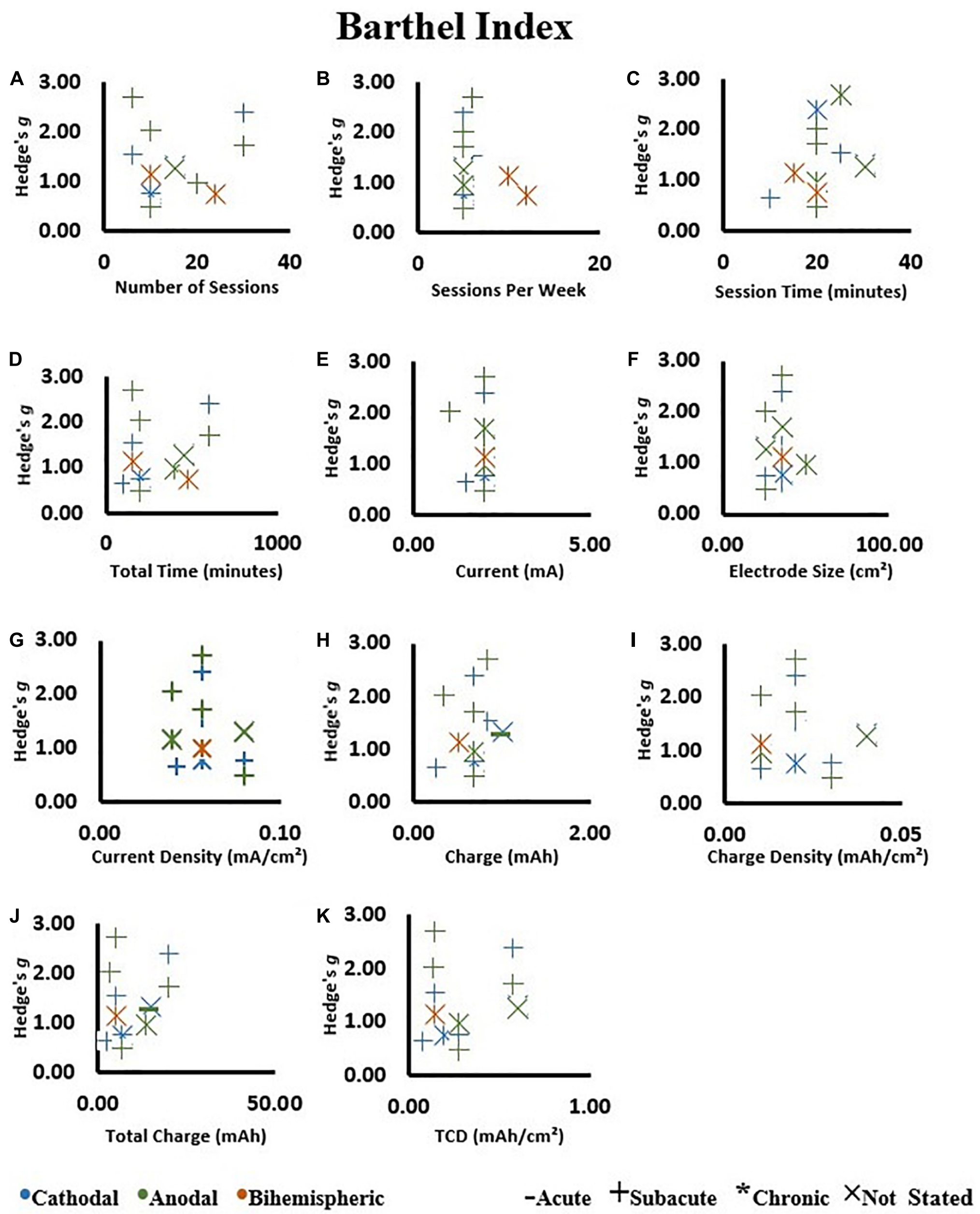

FIGURE 7 | Correlations on change scores in the tDCS groups as assessed by the Barthel Index. **(A)** Number of sessions, **(B)** sessions per week, **(C)** session time, **(D)** total tDCS application time, **(E)** current, **(F)** electrode size, **(G)** current density, **(H)** charge, **(I)** charge density, **(J)** total charge, and **(K)** total charge density (TCD). An increase in Hedge's *g* effect size indicates a better score.

Effect of Therapy Type Combined With Transcranial Direct Current Stimulation

Meta-analyses of post-intervention results between the tDCS and sham groups suggest that the type of therapy post-stroke patients receive in combination with tDCS may determine the overall effectiveness of recovery. Specifically, the BI post-intervention and change scores results strengthen the evidence that assisted-type and conventional-type therapies have a positive effect on recovery for this assessment type. Additionally, the effect size of conventional therapy was larger than the assisted therapy for the BI, which mostly involves studies using more acute participants compared to the other assessments (**Supplementary Table 1**). For the upper extremity FMA, conventional therapy was beneficial compared with assisted therapy when change score data was analyzed. Miscellaneous-type therapy had a positive effect on upper extremity motor recovery using the upper extremity FMA only. However, evidence of using miscellaneous therapy in addition to tDCS is scarce and heterogeneous thus

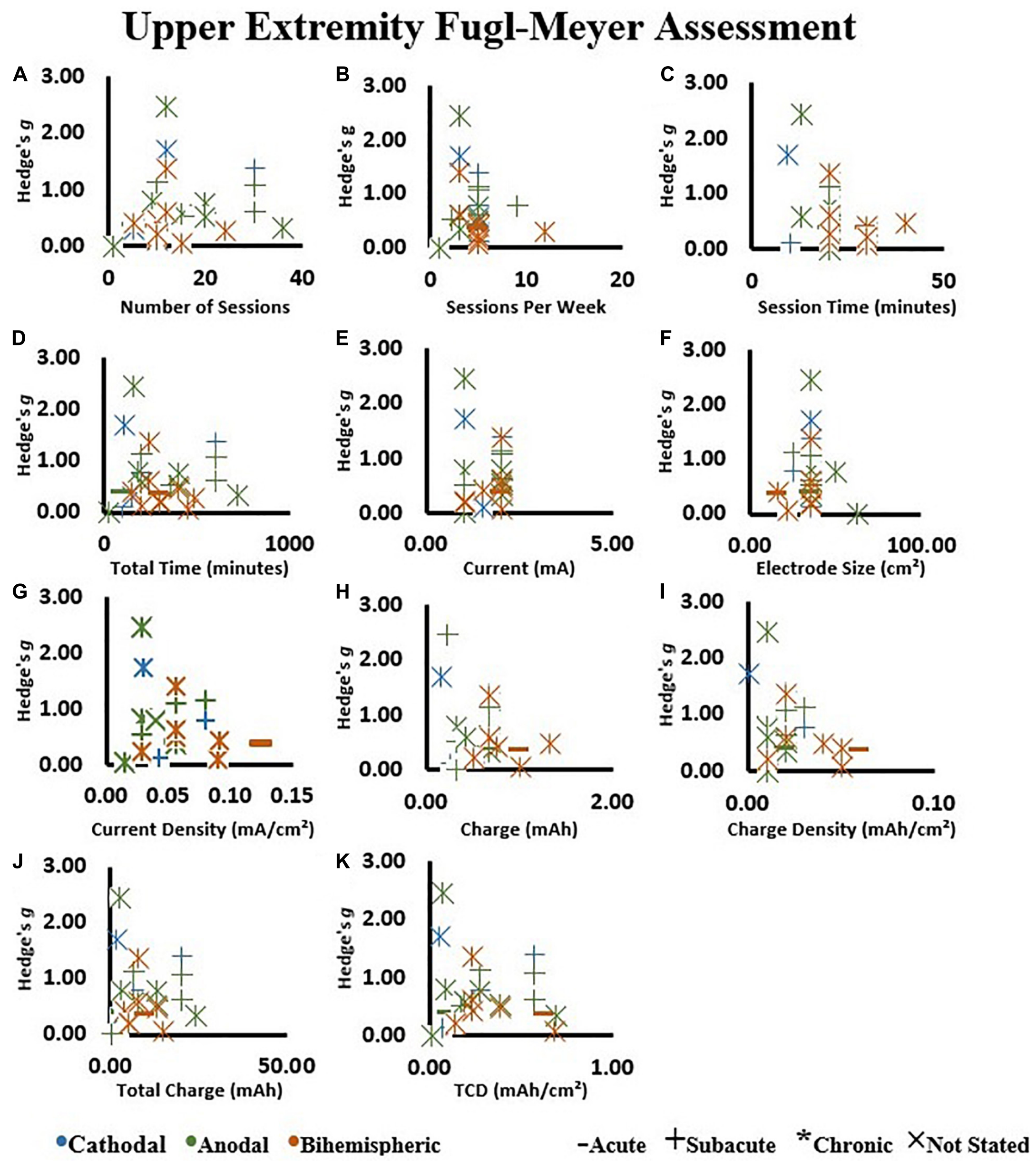

FIGURE 8 | Effect size in the tDCS groups assessed by the upper extremity Fugl–Meyer Assessment relative to: **(A)** Number of sessions, **(B)** sessions per week, **(C)** session time, **(D)** total tDCS application time, **(E)** current, **(F)** electrode size, **(G)** current density, **(H)** charge, **(I)** charge density, **(J)** total charge, and **(K)** total charge density (TCD). An increase in Hedge's *g* effect size indicates a better score.

results should be interpreted cautiously. Likewise, there are a reduced number of studies in the comparison of therapy type when using the MAS and the lower extremity FMA assessments.

Dose Effect of Transcranial Direct Current Stimulation

The dosage effect was investigated using several parameters from tDCS and obtained effect size. The obtained effect size was not influenced by any metrics of dosage and there was also no influence of stimulation type (anodal vs. cathodal vs. hemispheric) or stroke duration. A previous review investigated the effects of dosage on motor recovery after stroke; however, only using the upper extremity FMA (Chhatbar et al., 2015). They showed that electrode size (cm^2), charge density (mAh/cm^2), and current density (mA/cm^2) had significant dose-response relationships with upper extremity FMA and bihemispheric stimulation could be advantageous, which contrast with the current findings. Others also investigated the dosage effect by clustering studies in subgroups (Van Hoornweder et al., 2021) and found that the current, charge density, and stimulation duration influenced the obtained effect size. The previous review, however, included between 8 and 18 manuscripts, whereas the current review included 25 manuscripts (three of them conducting more than one study) for the upper extremity FMA and may explain the discrepancy between reviews. We also conduct analysis on the BI, which was not previously investigated. There are ample opportunities for mechanistic studies investigating dosage effect in stroke individuals.

Limitations and Future Directions

Precaution toward the results of the lower extremity FMA and the MAS should be given due to a low number of studies retrieved. The larger effect size of conventional therapy studies may be consequence of assisted studies using techniques that are in preliminary stages. Small difference in baseline function between the groups was found to influence the comparison between the tDCS and sham groups and should be considered when designing new randomized controlled trials. Future studies should provide clear details of participant's baseline function, stroke duration, and allocation concealment. Likewise, blinding the investigators applying the assessment scales from the participant group allocation is encouraged to minimize bias toward study's hypothesis. Given that tDCS effects may be dependent on the assessment used and stroke duration, future original studies should report multiple motor function aspects in the same participants such as muscle tone, specific and gross movements (as indicated by the MAS, the FMA, and the BI, respectively), as well as carefully balance the groups for stroke duration. Additionally, because placement of reference electrode is heterogeneous (**Supplementary Table 1**), mechanistic studies should investigate its effects in patients with stroke.

CONCLUSION

Evidence for the use of tDCS as a stand-alone therapy tDCS is weak. However, tDCS associated with other therapies had a positive effect when assessed by the BI but not by the MAS. The impact of tDCS is unclear when assessed by the upper or lower extremity FMA. Severity of stroke had minimal influence in these analyses and the effect of stroke duration is unclear. These findings combined suggest that tDCS could be beneficial for functionality and dependent on the assessment tool used. Dosage (e.g., sessions per week, duration, or charge) as well as stimulation type (anodal vs. cathodal) had no influence on the tDCS results, which may simplify the prescription of the technique. Large prospective controlled studies using different types of assessment should investigate the potential task-dependent benefit of tDCS in stroke individuals.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available upon reasonable request to the corresponding author.

AUTHOR CONTRIBUTIONS

A-MC, HP, HW, and JK designed the study. A-MC and JS reviewed the original studies and assessed the risk of bias. A-MC performed all the calculations and wrote the main draft. All authors approved the final version of the manuscript.

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STUDY PROTOCOL
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Effects of Remotely Supervised Physical Activity on Health Profile in Frail Older Adults: A Randomized Controlled Trial Protocol

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Background: Frailty is considered a major public health challenge of the 21st century, characterized by the decline of multiform body functions. Physical activity may be the most effective intervention to delay frailty. This study aims to verify the effect of remotely supervised physical activity on health profile in community-dwelling frail older adults.

Design: This is a multicenter, three-blind, two-arm, and cohort randomized controlled study.

Methods: The intelligent exercise rehabilitation management system (IERMS) is an integrated digital platform that involves evaluation, guidance, monitoring, and feedback. A total of 120 participants aged $\geq$ 65 years and diagnosed as frailty on the FRAIL scale will be recruited and randomly divided into two groups. Group 1 will receive a 12-week IERMS-based intervention, and Group 2 will receive the usual care. Data will be collected at baseline, 12 and 24 weeks. The primary outcome is the physical function, and secondary outcomes include gait parameters, psychology, and cognition measurements. Analyses will be performed using DSS statistics, version 25. $P < 0.05$ will be considered statistically significant.

Conclusion: We believe that intervention plays a positive role in delaying the frailty. If our program is effective, we will provide a viable means to promote healthy aging in primary healthcare.

Trial registration number: ChiCTR2100052286; Pre-results.

Keywords: remotely supervised, physical activity, intelligent system, frailty, health profile

INTRODUCTION

Frailty is a kind of clinical syndrome in older adults who are easily affected by stress. Physical frailty, originally defined by Fried et al. (2001), includes slow gait speed, weakness, self-reported exhaustion, low activity, and weight loss. Due to differences in regions, diagnostic criteria, and other factors, the prevalence of frailty is changed in different parts of the world; previous studies have shown that the prevalence ranged from 4 to 59% and increased with age (Choi et al., 2015; Hoogendijk et al., 2019). It is associated with the development of most chronic diseases, falls, fractures, disabilities, and other adverse outcomes (Theou et al., 2017; Hanlon et al., 2018). Fortunately, frailty is a dynamic reversible process, and measures can be taken to prevent it in advance (Lang et al., 2009).

The health benefits of physical activity have been widely recognized (Cheng et al., 2021). Proper physical activity can improve muscle, heart, and lung function and reduce the risk of high blood pressure, coronary heart disease, stroke, diabetes, cancer, depression, sleep disorders, falls, and fracture (de Labra et al., 2015; Dipietro et al., 2019; Mugueta-Aguinaga and Garcia-Zapirain, 2019). The WHO recommends that adults over 65 years of age engage in at least 150 min of moderate-intensity physical activity per week or at least 75 min of vigorous-intensity physical activity per week, or a combination of moderate and vigorous-intensity physical activity to achieve this amount of physical activity, with at least 10 min of continuous activity each time (van der Ploeg and Bull, 2020).

Recent research has found that physical activity may be the most effective intervention for frailty (Cheng et al., 2021). It is much more accomplished and effective when performed under supervision (Bonnefoy et al., 2012). Home-based supervised training has a better effect on strength and physical function and is more intense (Lacroix et al., 2017; Suikkanen et al., 2021). However, the allocation of health technicians is far from meeting the requirements of the training supervised by physiotherapists at home, so the current focus of primary healthcare is how to maximize the use of existing medical resources and benefit more people. Remote supervision based on wearable devices gradually attracts the attention of researchers (Garcia-Moreno et al., 2020; Zacharaki et al., 2020). This study aims to verify the effect of remotely supervised physical activity on health profile and observe the lingering effect in community-dwelling frail older adults.

METHODS

This study was designed and will be conducted and reported in keeping with the Consolidation Standards of Reporting (CONSORT) 2010 statement (Eldridge et al., 2016).

Platform Delivery

The intelligent exercise rehabilitation management system (IERMS) was designed and developed by the research group independently (Xu et al., 2020). It is an integrating evaluation, guidance, monitoring, and feedback of an integrated intelligent motion rehabilitation management system. It consists of three parts: sensing device layer, management data layer, and application layer. The sensing layer collects the health data, including smart insoles, bracelets, and other common terminals; the management layer conducts data processing; and the application layer visualizes the health results, including websites, applications, and applets. Smart insole is a kind of sensing device that contains eight inertial and thin-film pressure sensors (FSR 400) and grants China an invention patent (Publication Patent Number: 201810114305.3).

Study Design

A three-blind, two-arm, cohort randomized controlled trial will be conducted to evaluate the effects of IERMS-based physical activity on health performance in frail older adults (Registration number: ChiCTR2100052286)[1]. A total of 120 participants will be recruited according to the screening criteria from six community health service centers in Changchun, China, and the participants will be randomly divided into two groups. Participants in the first group will receive a 12-week IERMS-based intervention, and participants in the second group will receive a 12-week conventional care. Then, there will be a 12-week follow-up. Data will be collected at baseline, 12 and 24 weeks. The study design is shown in **Figure 1**. After the intervention, the same guidance will be given to the second group to ensure that more older adults benefit.

Participants

Ethics Approval

The research protocol was approved by the Human Research Ethics Committee of the School of Nursing, Jilin University (HREC 2020122001). All participants will provide a signed informed consent when entering the study.

Eligibility and Recruitment

Participants will be recruited from six centers at the same time. Once there are 20 samples in a certain community, they will undergo the next step. Inclusion criteria are $\geq$ 65 years old, meeting the FRAIL scale for frail status, and familiar with the use of smartphones and tablets or computers. Exclusion criteria are nerve dysfunction (stroke, Parkinson's disease, or lower limbs) with paraplegia, serious cardiovascular disease, cognitive impairment, continuous joint pain, severe muscle bone damage, life expectancy $<$ 6 months of serious illness, serious

[1] http://www.chictr.org.cn/searchproj.aspx

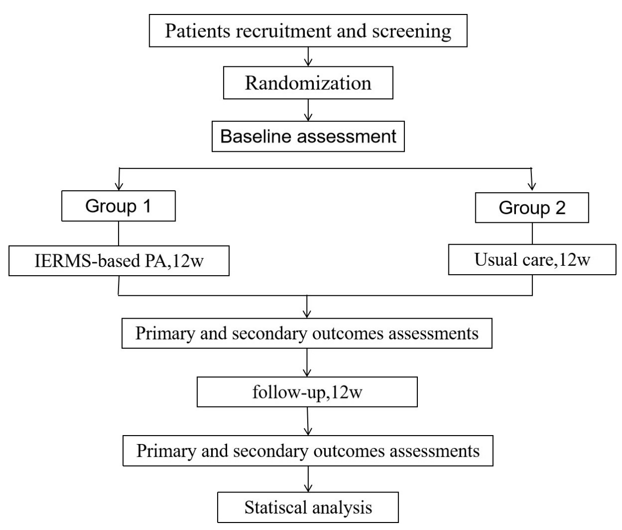

FIGURE 1 | Flow chart of the experimental procedure.

hearing or visual impairment, severe depression or anxiety, other major diseases affecting training safety, hospitalization, and involvement in other clinical studies during this study.

Calculation of Sample Size

Based on *a priori* power analysis (G*Power 3.1.9.3) using a power of 0.90 and error probability of 0.05, a sample size of 50 participants will be required for each group to detect an assumed 20% difference in walking speed between the two groups. In addition, with an assumption of 15% dropout rate, a sample size of 120 participants will be initially targeted.

Randomization and Blinding

From each center, 20 participants will be recruited and stratified by gender and age; then, they will be randomly assigned to the first or second group in a 1:1 ratio through a computer-generated randomized list. This task will be performed independently by individuals not involved in the research process. All researchers will be divided into two teams: one team will be responsible for the guidance of group 1, and the other team conduct routine education, they will be ignorant of each other's content. Throughout the intervention, neither the participants nor the researchers conducting the intervention or the data collection will be aware of the grouping. The study designer and the staff responsible for allocation concealment and data processing will be not permitted to participate in the whole intervention.

Intervention

Training Based on Intelligent Exercise Rehabilitation Management System

At baseline, all participants will undergo physical function, physical activity, psychology, and cognition assessments. These assessments will be repeated at 12 and 24 weeks. Participants in the first group will receive a pair of smart insoles and a patient-side APP installed on their phone and will learn all the functions of the system. According to the participants' physical activity level at baseline, professional rehabilitation therapists will select the activity plan from the default scheme (**Table 1**); upload it to the cloud, which is the management data layer; and send the plan for the next week according to the participants' weekly completion. If the activity goal of the week is not reached, the plan of the week will be continued. Once the current week's activities are completed, the plan for the next phase will be carried out.

TABLE 2 | List of physical activities available to participants.

01. Walking quickly	11. Badminton	21. Plank support
02. Running	12. Table tennis	22. Pushups
03. Tai Ji	13. Volleyball	23. Sit-ups
04. Skipping rope (≥100 time/min)	14. Football	24. Pull-ups
05. By bike (outdoor > 8 km/h)	15. Basketball	25. Lunge
06. By bike (gym > 8 km/h)	16. Tennis	26. Jumping jacks
07. Upstairs	17. Swimming	27. Squat
08. Downstairs	18. Martial arts	28. Pilates
09. Wash the car	19. Skating	29. Aerobic dance
10. Do housework	20. Skiing	30. Yoga

Participants will choose the type of physical activity (**Table 2**) in the APP according to their preferences and choose the activity day of the week and the training time of each activity according to the target activity days. The system will automatically generate the particular week's schedule according to participants' choices and remind them at the time set by participants. At the end of each activity, participants will upload the daily completion of the activity and fill in the specific activity time for unfinished projects. They will have access to view the week's activity plan at any time and generate the week's activity schedule every Monday. During the workout, participants will be asked to wear smart insoles that monitor dynamic changes in gait parameters and synchronize them to the cloud in real time. In addition, patients will communicate with professionals through a short messaging service built into the APP and receive feedback within 24 h. The APP interface is shown in **Figure 2**. Before the start of each training, the user will receive a reminder as follows:

Before activity: Warm-up ≥ 5 min.

After activity: stretch ≥ 5 min.

The time of each successive activity: ≥ 10 min.

The interval between two activities: ≤ 3 days.

Please don't be nervous if you feel strenuous or the heart rate significantly accelerated in the process of activity, this is a normal phenomenon. But if you feel unwell, please seek medical advice immediately.

Routine Care

All participants will receive a routine nursing care. The rehabilitation therapist will provide health education on frailty and physical activity: manifestation, risk, prevention, screening,

TABLE 1 | Weekly training schedule.

Current PA (min)	Target PA (min/w)	Mon.	Tue.	Wed.	Thur.	Fri.	Sat.	Sun.
0–30	≥30	Upload last week's completion Make plans for this week	3 days,1 time/day, 10 min/time					
30–60	≥60		4 days,1time/d 1 time:10 min, 2–3 time:15 min, 4 time:20 min					
60–90	≥90		4 days, 1 time/day 1–2 time: 20 min, 3–4 time: 25 min					
90–120	≥120		5 days, 1 time/day, 25 min/time					
120–150	≥150		5 days, 1 time/day, 30 min/time					

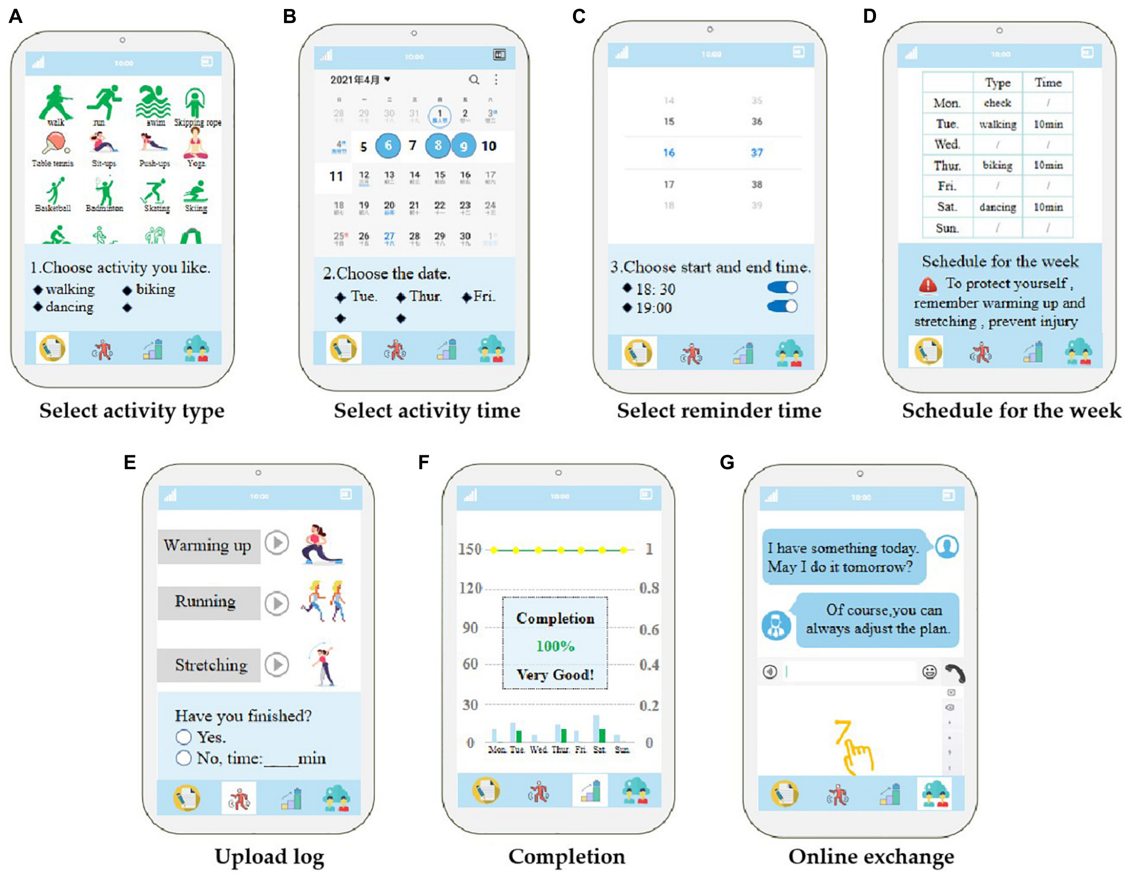

FIGURE 2 | Prototype of the app user interface.

and treatment of frailty; benefits of moderate physical activity; and introduction of common forms are listed in **Table 2**. A registered nurse will conduct a telephonic follow-up for all participants once in a month.

Outcome Measures

In this study, the primary outcome will be the objective changes in physical function. At the same time, other measuring tools will be used to evaluate the multidimensional efficacy of the intervention, and a less number of participants will be selected for semi-structured interviews to gain an in-depth understanding.

Primary Outcome

Physical Function

The physical function will be evaluated by the Timed Up & Go (TUG) test (Mathias et al., 1986), which assesses the basic mobility skill as well as strength, balance, and mobility. In this test, the subjects will stand up from a standard chair (the chair with a height of 46 cm and arms with a height of 65 cm), wear comfortable shoes, walk at a regular speed of 3 m, turn around, walk back to the chair, and sit down in the chair, and then will stop the timer. According to the test results, $\leq$ 10 s will be considered completely independent, 10–19 s will be considered to be independent, between 20 and 29 s will be considered a "gray area," and more than 30 s will be considered to be completely dependent. Its reliability and effectiveness have been verified in various populations (Chan et al., 2017; Yuksel et al., 2017).

Secondary Outcomes

Gait Parameters

Gait parameters include walking speed, symmetry, and variability. Participants will wear smart insoles and walk more than 25 m on barrier-free horizontal roads for at least 2 min at their self-selected comfortable pace. The walking process will include four parts, namely, acceleration, deceleration, uniform speed, and turning. The system will complete the gait analysis during this period. Walking speed (m/s) is defined as the walking distance per unit time, and when it is less than 0.6 (Zaccardi et al., 2019), there will be a higher risk of falls. Gait variability is defined as the variable coefficient of all the step-by-step cycles and is used to evaluate the variation of temporal parameters. The normal range is 2–3%, and higher values are regarded as unstable. Gait symmetry is defined as the ratio of the swinging time of biped in the air and is usually around 1.02% for healthy adults.

Frail Score

The frailty phenotype represents the most known operational definitions of frailty in older persons (Fried et al., 2001).

According to the Fried phenotype: 0 = health; 1–2 = pre-frailty; and ≥ 3 = frailty. Walking speed, grip strength, weight, physical activity, and self-reported fatigue will be measured by the methods as shown in **Table 3**. One point will be recorded when any items reach the cutoff value.

Moderate-to-Vigorous-Intensity Physical Activity Per Week (MET-Min/Week)

Moderate-to-vigorous-intensity physical activity (MVPA) will be evaluated by the International Physical Activity Questionnaire (IPAQ) (Bassett, 2003). The IPAQ Questionnaire comprises 7 questions about the frequency and duration of vigorous activity (8 MET), moderate activity (4 MET), walking (3.3 MET), and sitting. The total physical activity will be calculated by multiplying the time (minutes per week) by the intensity [metabolic equivalent of task (MET) unit]. Its effectiveness in evaluating the physical activity level has been verified in various populations in China (Hu et al., 2015; Ren et al., 2017). Data processing principle: the cutoff value of the daily time of a certain intensity physical activity is 180 min; if the total daily time of three intensities physical activity is > 960 min (16 h), data will be excluded from the analysis; if the daily time of a certain intensity physical activity is < 10 min, the time and corresponding weekly frequency will be recorded as 0.

Psychological Condition

Patients' psychological condition will be reflected by anxiety, depression, and sleep quality. Anxiety will be evaluated by the Generalized Anxiety Disorder 7-item (GAD-7) Scale within 7 questions and a total score of 0–21 (Spitzer et al., 2006). Depression will be assessed by the Patients Health Questionnaire 9-item (PHQ-9) within 9 questions and a total score of 0–27 (Kroenke et al., 2001). The Pittsburgh Sleep Quality Index (PSQI) will be used to evaluate the sleep quality in the last month, which consists of 19 self-report items and 5 other-report items; the 19th self-report item and 5 other-report items will not be scored. The total score ranged from 0 to 21; the higher the score, the worse the sleep (Liu et al., 2021).

Cognitive Function

The Mini-Mental State Examination (MMSE) is one of the standardized intelligence examination tools and is widely used in the screening of Alzheimer's disease (Folstein et al., 1975). Cognitive function will be evaluated by testing their orientation, memory, attention, calculation, recall, and language ability. The total score is related to education level with a range of 0–30.

Adherence and Security

If 9 weeks and more reach to the target activity levels during the entire intervention period, it will be considered as good adherence. The incidence of adverse events, including falls and all-cause hospital admissions, will be assessed by patient self-report.

Other Secondary Outcomes

The difference between the percentage of walking speed < 0.6m/s, gait variability > 3%, frailty score ≥ 3, and low physical activity will also be compared.

Statistical Analysis

Categorical variables will be described by frequency and percentage. Continuous variables will be described by means and standard deviations. Social demographic and clinical data between the groups will be presented using appropriate descriptive statistics and evaluated for homogeneity using independent *t*-test, Mann-Whitney, chi-square, and Fisher's exact tests, as appropriate. The differential changes of the primary and secondary outcomes at T1 and T2 concerning T0 between the two groups will be assessed using generalized estimating equations (GEE). The baseline variable will be adjusted, and group effects, time effects, and interaction effects will be observed. DSS statistics 25 will be used for data analysis, and $P < 0.05$ will be considered statistically significant.

Quality Control

Our research group has established a team of experienced clinical nurses and rehabilitation therapists at a rehabilitation center in Changchun, China. Experienced clinical nurses and researchers from the team will be responsible for recruiting participants. Participants meeting the inclusion criteria will be screened, they will be informed of the study details by the investigator, and if they agree to participate, they will be asked to sign a consent form. If there is a complex clinical problem, our researchers, nursing specialists, and rehabilitation therapists will work together to find a solution.

DISCUSSION

The benefits of physical activity on the frail older adults have been widely recognized (Liu et al., 2018; Trombetti et al., 2018), but which part caused the improvement of health profile is still uncertain. Wearable devices have been widely used in healthcare (Chromik et al., 2022); however, it still needs to be further verified whether the remote evaluation of frailty (Angulo et al., 2020) and obtaining objective feedback can be realized. In this study, the IERMS will be used to intervene the physical activities to evaluate the changes in body performance, which will provide a new method for the remote assessment and supervision of the frail older adults living in the community.

During the COVID-19 pandemic, central-based or home-based face-to-face supervision has been forced to stop, and we need an alternative delivery mode (García Pérez de Sevilla et al., 2021). Remote assessment and guidance become the most feasible way (Liao et al., 2021). Although compared with traditional training, there is no significant difference in remote supervision, but it reached the same benefits at least (Geraedts et al., 2021; Gagnon et al., 2022). We will conduct a randomized controlled trail based on a digital platform, provide the personalized activity plan according to their own condition, and improve the compliance of schedule by increasing the interaction to ensure the intervention efficacy.

Multidimensional objective measurement reduces the subjective bias. Gait has been described as the "sixth vital sign" in recent years (Fritz and Lusardi, 2009). It

TABLE 3 | Indicators collected and assessment tools at each time point.

Test	Content		Time point: Screen	Baseline	12 w	24 w
FRAIL	The simple "FRAIL" questionnaire screening tool		√			
	Fatigue	Are you fatigued?				
	Resistance	Cannot walk up one flight of stairs?				
	Aerobic	Cannot walk one block (500 m)?				
	Illnesses	Do you have more than 5 illnesses?				
	Loss of weight	Have you lost more than 5% of your weight in the last 6 months?				
	Scoring: 3 or greater = frail; 1 or 2 = prefrail					
Demographic	Standardized questionnaire assessing age, gender, education level, residential status, falls history, medical history and so on.			√	√	√
Gait	Gait parameters generated by the device			√	√	√
TUG	Timed up and go test			√	√	√
Fried	Scoring: 3 or greater = frail; 1 or 2 = prefrail; 0 = health			√	√	√
	Walking speed	Slow gait: < 1.0 m/s				
	Grip strength	Measure three times and take the optimum				
		Low grip strength as follows:				

Males: BMI	Males: Grip strength (kg)	Females: BMI	Females: Grip strength (kg)
≤24	≤29	≤23	≤17
24.1–28	≤30	23.1–26	≤17.3
≥28	≤32	26.1–29	≤18

Test	Content		Screen	Baseline	12 w	24 w
	Weight loss	Methods: measure three times and take the average, after urination in the morning				
		Weight loss: an unintentional weight loss ≥ 10 kg/10% over the previous year or an average monthly loss ≥ 1 kg/1%				
	Insufficient physical activity	≤150 min of light to moderate physical activity per week, or ≤ 75 min of vigorous physical activity per week, or the total level of physical activity did not achieve the same amount of expenditure				
	Fatigue	Asking question "Do you feel too weak to do what you want to do in the last month?" If the participants answered "yes," they will be considered fatigued				
MVPA	Short International Physical Activity Questionnaire			√	√	√
	High	Meet any one of the following 2 standards				
		Vigorous activity ≥ 3 days and total level ≥ 1,500 MET				
		The total physical activity ≥ 7 days and 3,000 MET-min/w				
	Sufficient	Meet any one of the following 3 standards				
		Vigorous activity ≥ 20 min per day and total ≥ 3 days				
		Moderate and/or walking ≥ 30 min per day and total ≥ 5 days				
		The total physical activity ≥ 5 days and 600 MET-min/w				
	Low	Meet any one of the following 2 standards				
		No activity was reported				
		Some activities reported, but not meet the criterion of the above sufficient and high				
PHQ-9	Patients Health Questionnaire 9-item			√	√	√
GAD-7	Generalized Anxiety Disorder 7-item			√	√	√
MMSE	Mini-Mental State Examination			√	√	√
PSQI	Pittsburgh Sleep Quality Index			√	√	√

is an integrative performance of body function with the complication of controlling walking and is associated with frailty (Montero-Odasso et al., 2011; Bortone et al., 2021). However, few wearable devices evaluate gait (Greene et al., 2014), due to the difficulty of obtaining gait parameters, even in today's exponential development of digital health. Because of the lack of sensitivity and convenience, the existing methods of frail assessment are not suitable for wide-scale popularization. Through the use of smart insoles, we will be able to collect gait parameters continuously and dynamically. Gait analysis may become a new strategy to predict frailty.

However, this study still has certain limitations. First, the sample size is small and the population is limited to five communities in Changchun, so the results may not be fully promoted. Second, the training log is uploaded by the participants themselves, and there is still a certain problem with its authenticity. Finally, the body activity amount is calculated by the self-reported exercise form and metabolic equivalent, so there is a certain deviation in the calculation of exercise amount.

CONCLUSION AND IMPLICATIONS

In general, we designed a personalized remotely supervised physical activity program and expected to add effect by increasing the participation. Based on the evidence, we are convinced that this intervention program will be able to delay or reverse the progress of frailty. If the intervention produces a significant positive effect, the findings will potentially provide valuable evidence and serve as convenient and feasible strategies for primary healthcare to promote healthy aging.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Human Research Ethics Committee of the School of Nursing, Jilin University. The patients/participants will provide their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

XZ and FL: study concept and design. XZ, JL, TZY, XL, and TYY: acquisition of data. XZ, YP, and LZ: analysis and interpretation of data. XZ, FL, and LX: drafting of the manuscript. XS, HX, and YL: critical revision of the manuscript for important intellectual content. All authors contributed to the article and approved the submitted version.

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Tract-Based Spatial Statistics Analysis of Diffusion Tensor Imaging in Older Adults After the PICMOR Intervention Program: A Pilot Study

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Diffusion tensor imaging (DTI) enables the investigation of white matter properties *in vivo* by applying a tensor model to the diffusion of water molecules in the brain. Using DTI metrics including fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD), an attempt has been made to detect age-related alterations in the white matter microstructure in aging research. However, the use of comprehensive DTI measures to examine the effects of cognitive intervention/training on white matter fiber health in older adults remains limited. Recently, we developed a cognitive intervention program called Photo-Integrated Conversation Moderated by Robots (PICMOR), which utilizes one of the most intellectual activities of daily life, conversations. To examine the effects of PICMOR on cognitive function in older adults, we conducted a randomized controlled trial and found that verbal fluency task scores were improved by this intervention. Based on these behavioral findings, we collected in this pilot study diffusion-weighted images from the participants to identify candidate structures for white matter microstructural changes induced by this intervention. The results from tract-based spatial statistics analyses showed that the intervention group, who participated in PICMOR-based conversations, had significantly higher FA values or lower MD, AD, or RD values across various fiber tracts, including the left anterior corona radiata, external capsule, and anterior limb of the internal capsule, compared to the control group, who participated in unstructured free conversations. Furthermore, a larger improvement in verbal fluency task scores throughout the intervention was associated with smaller AD values in clusters, including the left side of these frontal regions. The present findings suggest that left frontal white matter structures are candidates for the neural underpinnings responsible for the enhancement of verbal fluency. Although our findings are limited by the lack of comparable data at baseline, we successfully confirmed the hypothesized

Abbreviations: AD, axial diffusivity; DTI, diffusion tensor imaging; FA, fractional anisotropy; FDT, FMRIB's Diffusion Toolbox; FMRIB, Functional MRI of the Brain; FSL, FMRIB's Software Library; ICBM, International Consortium of Brain Mapping; JHU, Johns Hopkins University; MD, mean diffusivity; MMSE-J, Japanese version of the Mini-Mental State Examination; MNI, Montreal Neurological Institute; MRI, magnetic resonance imaging; PICMOR, Photo-Integrated Conversation Moderated by Robots; RCT, randomized controlled trial; RD, radial diffusivity; SD, standard deviation; TBSS, tract-based spatial statistics; TIV, total intracranial volume.

pattern of group differences in DTI indices after the intervention, which fits well with the results of other cognitive intervention studies. To confirm whether this pattern reflects intervention-induced white matter alterations, longitudinal data acquisition is needed in future research.

Keywords: cognitive intervention, conversation, diffusion tensor imaging, PICMOR, tract-based spatial statistics

INTRODUCTION

Diffusion tensor imaging (DTI) is a neuroimaging technique that enables researchers to investigate white matter properties *in vivo* by applying a tensor model to the diffusion of water molecules in the brain (Rowe et al., 2016). In aging research, an attempt has been made to detect age-related structural changes in white matter fibers using DTI indices, including fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD; Madden et al., 2009, 2012; Bennett and Madden, 2014). However, a relatively small number of studies have used comprehensive DTI metrics to assess the effects of cognitive intervention/training on white matter fiber health in older adults (Wassenaar et al., 2019). Using DTI measures comprehensively, this pilot study aimed to characterize white matter fiber tracts in older adults who participated in a conversation-based intervention program named Photo-Integrated Conversation Moderated by Robots (PICMOR; Otake-Matsuura et al., 2021).

Normal aging is associated with changes in white matter microstructure (Madden et al., 2009, 2012; Bennett and Madden, 2014). For example, a large-scale DTI study using the United Kingdom Biobank resource reported that older age was associated with decreased FA and increased MD, AD, and RD across numerous white matter tracts, including association fibers, such as the inferior fronto-occipital, inferior longitudinal, superior longitudinal, and uncinate fasciculi, and thalamic radiation fibers, such as the anterior, superior, and posterior thalamic radiation, as well as the forceps minor (Cox et al., 2016). To prevent or slow age-related changes in cognitive function and white matter, various cognitive intervention/training paradigms have been developed (Wassenaar et al., 2019). Previous studies have attempted to elucidate intervention/training-induced white matter changes using DTI (Lovden et al., 2012; Chapman et al., 2015; Nozawa et al., 2015; Antonenko et al., 2016; Fissler et al., 2017; Dziemian et al., 2021). However, the use of comprehensive DTI metrics to assess intervention/training effects on white matter fiber health in older adults remains limited (Lovden et al., 2010; Engvig et al., 2012; Strenziok et al., 2014; Lampit et al., 2015; Cao et al., 2016; de Lange et al., 2016, 2017; Youn et al., 2019). One such study reported that older adults who were assigned to the training group and received memory strategy training for 10 weeks showed a less age-related decline in white matter microstructure, including the corpus callosum, corticospinal tract, cingulum bundle, superior longitudinal fasciculus, and anterior thalamic radiation, than those assigned to the control group (de Lange et al., 2017). From baseline to follow-up, the control group showed a greater decrease in FA and a greater increase in MD, AD, and RD relative to the training group in these fiber tracts. Another study reported that the intervention group who practiced multi-domain cognitive training tasks, including working memory, episodic memory, and perceptual speed tasks, in about 100 daily sessions over approximately 6 months increased FA values and decreased MD and RD values in the genu of the corpus callosum between the pre- and post-intervention period, while no significant change in these metrics was identified in the control group (Lovden et al., 2010). Taken together, although the fibers considered to reflect intervention/training effects differ among studies, possibly due to differences in intervention/training methodologies, a consistent pattern can be seen in the DTI indices of the post-intervention period: larger FA values or smaller values in other metrics in the intervention group compared to the control group.

In terms of availability and sustainability, it is important to design a cognitive intervention paradigm that utilizes daily life activities. Social activity is one of the most intellectual activities of daily life and the level of activity engagement is related to cognitive function and white matter microstructure in older adults (Kelly et al., 2017; Anaturk et al., 2018); hence, it can be incorporated into such intervention paradigms. Of the various forms of social activity, conversation is a promising approach to improving or maintaining cognitive health in older adults because it requires elaborate cognitive processes, such as organizing one's thoughts and understanding others' ideas (Dodge et al., 2015). The PICMOR program, which we recently developed, is a cognitive intervention method based on group conversations (Otake-Matsuura et al., 2021). In this method, conversations among group members are prompted and chaired by a robot. The robotic management enables equal allocation of speaking time to everyone, and each participant is encouraged by the robot to talk about a topic within the allocated time. The system also enables giving everyone equal discussion time, and the participants are required to ask and answer questions. In the discussion period, the robot monitors the utterances of each participant in real-time and automatically encourages and stops their utterances to guarantee equal amounts of speaking time. The nature of this communication task involves exercising executive functions, such as flexibility, planning, working memory, and response inhibition, by encouraging the participants to talk within a limited time, to have a flexible discussion by asking and answering questions, to temporarily store and manipulate information necessary to ask questions, and to refrain from interrupting other group members. Thus, we expected that cognitive ability involving executive functions, such as the ability to produce words within a certain length of time, would be better trained by group conversations employing the PICMOR method than by conventional group conversations.

Recently, we conducted a randomized controlled trial (RCT) to assess the effects of interventions involving this method on cognitive function in older adults (Otake-Matsuura et al., 2021). Consistent with our idea, the results of the phonological verbal fluency task, in which the ability to produce as many words as possible starting with a designated letter within a limited time is tested (Fujiwara et al., 2010; Lezak et al., 2012), showed a significantly greater improvement in the intervention group, who participated in the PICMOR program, than in the control group, who participated in unstructured free conversations among group members without robotic assistance. Based on the behavioral results, we assumed that differences in white matter properties underlie group differences in cognitive enhancement. Specifically, we hypothesized that if such difference was measurable, it would emerge as higher FA values or lower MD, AD, or RD values in the intervention group compared to the control group. Such a pattern in DTI metrics was based on previous findings from cognitive intervention studies that used comprehensive DTI indices to assess the intervention/training effects on white matter fiber health in older adults (Lovden et al., 2010; Engvig et al., 2012; Cao et al., 2016; de Lange et al., 2017). Given the evidence from neuropsychological studies demonstrating the contribution of the left frontal region to verbal fluency (Stuss et al., 1998; Baldo et al., 2006, 2010; Robinson et al., 2012; Biesbroek et al., 2016, 2021; Chouiter et al., 2016; Li et al., 2017; Thye et al., 2021), white matter structures in this region may show the assumed DTI pattern. This idea is also supported by our preliminary findings from a resting-state functional magnetic resonance imaging (MRI) study (Sugimoto et al., 2020) showing that the left cortical frontal area, which is a core region for verbal fluency (Costafreda et al., 2006; Wagner et al., 2014), had differential functional connectivity between the two groups. The purpose of this pilot study was to identify candidate structures for white matter alterations induced by conversation-based interventions, which were also associated with enhanced verbal fluency, by examining the hypothesized pattern in DTI measures after the intervention period.

METHODS

Participants

All participants of our previous RCT (Otake-Matsuura et al., 2021) were recruited, and 61 out of 65 participants (31 and 30 in the intervention and control groups, respectively) participated in this additional MRI experiment. As previously reported (Sugimoto et al., 2020; Sugimoto and Otake-Matsuura, 2022), no significant group differences were found in terms of age [the intervention group, mean ± standard deviation (*SD*) = 72.84 ± 3.45 years; the control group, mean ± *SD* = 72.03 ± 2.72 years], sex (the intervention group, 15 females and 16 males; the control group, 17 females and 13 males), and educational level (the intervention group, 20 people with education for 13 years and more; the control group, 17 people with education for 13 years and more). The MRI data from four RCT participants were not available for the following reasons: claustrophobia, being equipped with a pacemaker, or declining to participate in the MRI scans. All participants provided written informed consent for the protocol, which was approved by the Institutional Review Board of RIKEN. The participants were right-handed and native Japanese-speaking individuals. The demographic and behavioral data from pre/post cognitive tests, including the verbal fluency task, are detailed elsewhere (Sugimoto et al., 2020; Sugimoto and Otake-Matsuura, 2022).

Intervention Procedures

Details of the intervention procedures have been described in our previous study (UMIN000036667; Otake-Matsuura et al., 2021). Briefly, 72 community-dwelling older adults were recruited from the Silver Human Resources Center for our previous RCT. Based on screenings and baseline assessments, we excluded participants meeting the following criteria: dementia, neurological impairment, any disease or medication known to affect the central nervous system, and scoring less than 24 in the Japanese version of the Mini-Mental State Examination (MMSE-J; Sugishita et al., 2018). Consequently, 65 people were enrolled and randomly assigned to the intervention or control groups. The intervention period lasted for 12 weeks, during which both the intervention and control groups participated in group conversations once a week. The intervention period was followed by a post-assessment of cognitive function. Finally, the MRI experiment was conducted.

For group conversations during the intervention period, both the intervention and control groups were divided into eight subgroups, each with four members (except for one control subgroup with five members), and instructed to talk with other members of the subgroup. In the group conversation provided for the control group, participants joined unstructured free conversations where they talked freely among subgroup members, as they would converse in daily life. By contrast, the group conversation provided for the intervention group was controlled by a robotic assistive system, in which a robot acted as a chairperson and assisted the conversation by encouraging each participant to describe their daily life experiences and discuss them with other group members. Each participant was prompted by the robot to talk about an event along a predetermined theme for 1 min using a photo displayed on the screen they had taken beforehand. The 1-min talking period was repeated to explain another event related to the same theme using another photo. During this period, the other members of the subgroup were required to listen carefully and ask questions later. Following this, a 2-min discussion period was provided, during which the participant had to answer questions raised by other group members. The 2-min discussion period was repeated to discuss the second event. During the discussion period, the robot monitored the utterances of each member in real-time and controlled the conversations by encouraging or stopping utterances to balance the amount of talking time for each person. Using this robotic assistive system, strict time management and automatic turn-taking based on the actual speech time of each participant were achieved. All members were provided with 1-min talking periods and 2-min discussion periods.

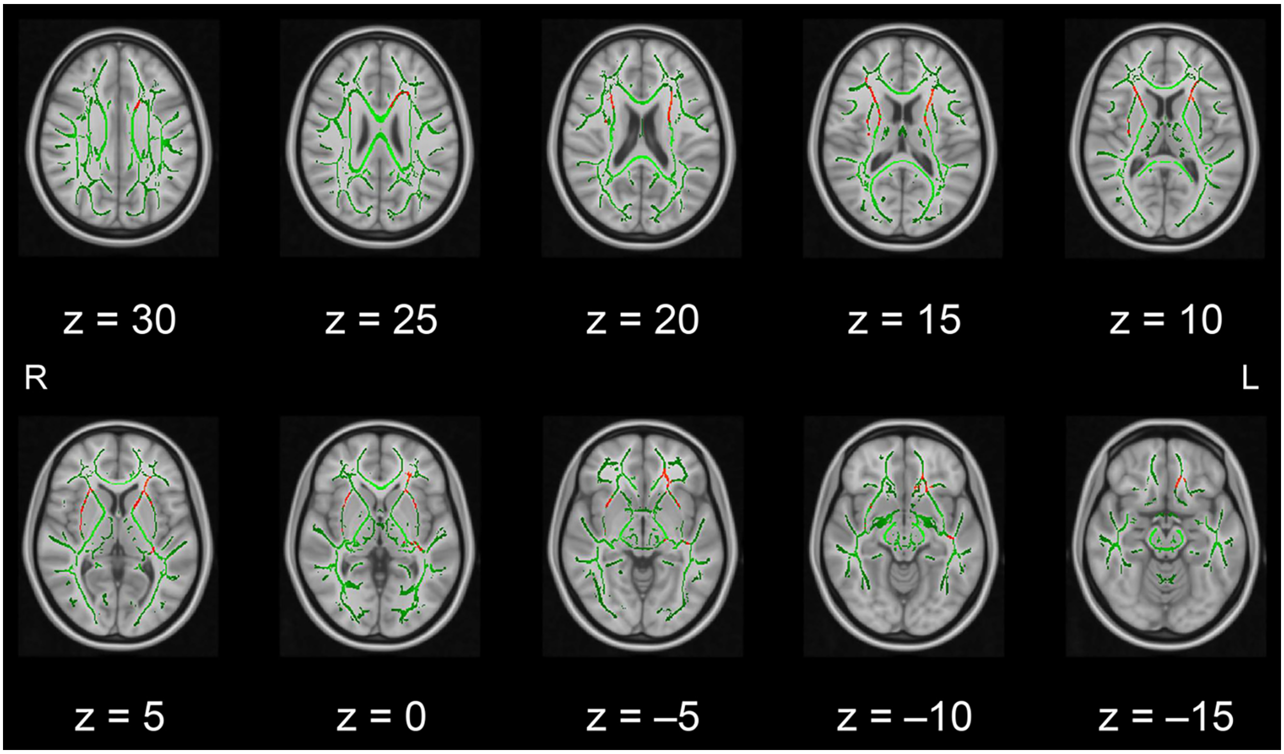

FIGURE 1 | White matter fiber tracts showing significantly higher FA values in the intervention group than in the control group (displayed in red). The results are overlaid on the mean FA skeleton (shown in green) and the standard MNI152 T1 1-mm^3 brain template. The value of *z* in the horizontal plane represents the MNI *z*-coordinate. Abbreviation: FA, fractional anisotropy; L, left; MNI, Montreal Neurological Institute; R, right.

Data Acquisition and Analysis

All MRI data were collected after the intervention period using a Philips Achieva 3.0 Tesla scanner at the Advanced Imaging Center Yaesu Clinic, Tokyo. During the scanning, the participants' head movements were minimized by a belt and foam pads, and the participants were required to stop their body motion. Diffusion-weighted images were acquired using a single-shot, spin-echo, echo-planar imaging pulse sequence with the following parameters: repetition time = 6,968 ms, echo time = 69 ms, field of view = 35.0 × 35.0 cm, matrix size = 128 × 128, slice thickness/gap = 2.7/0 mm, 59 horizontal slices, 40 diffusion gradient directions with *b*-value = 1,000 s/mm^2, and an additional volume with *b*-value = 0 s/mm^2. The data were visually inspected for imaging artifacts. In addition, T1-weighted structural and resting-state functional images were obtained. The results of these anatomical and functional scans have been reported previously (Sugimoto et al., 2020; Sugimoto and Otake-Matsuura, 2022).

Diffusion-weighted images were analyzed using Functional MRI of the Brain (FMRIB)'s Software Library (FSL) software version 6.0.3[1] (Smith et al., 2004; Jenkinson et al., 2012) implemented in Lin4Neuro 18.04[2] (Nemoto et al., 2011). The images were preprocessed using tools and scripts provided by MRtrix3[3] (Tournier et al., 2019) in accordance with the following procedure. First, the *dwidenoise* command was executed to reduce thermal noise (Veraart et al., 2016a,b). Second, the *mrdegibbs* command was used to reduce Gibbs-ringing artifacts (Kellner et al., 2016). Third, motion and eddy-current distortions were corrected using the *dwipreproc* command, in which the *-rpe_none* option was chosen because inverted phase-encoding image data, i.e., anterior-to-posterior, were not available (Andersson and Sotiropoulos, 2016). In addition, the *--slm=linear* option was employed in this step. Fourth, B1 field inhomogeneity correction was performed using the *dwibiascorrect* command with the *-ants* option (Tustison et al., 2010). Finally, the *dwi2mask* command was executed to generate a whole-brain mask from the preprocessed dataset. Using the preprocessed data and whole-brain mask, a diffusion tensor model was fitted at each voxel using FSL's *dtifit* program, a part of the FMRIB's Diffusion Toolbox (FDT). The default outputs of this procedure included whole-brain maps of AD, MD, and FA computed from the first, second, and third eigenvalues (λ_1, λ_2, and λ_3, respectively) corresponding to the three directions of water diffusivity, as follows: The RD maps were created using the *fslmaths* command.

[1]https://fsl.fmrib.ox.ac.uk/fsl/fslwiki
[2]http://www.lin4neuro.net/lin4neuro/
[3]https://www.mrtrix.org/

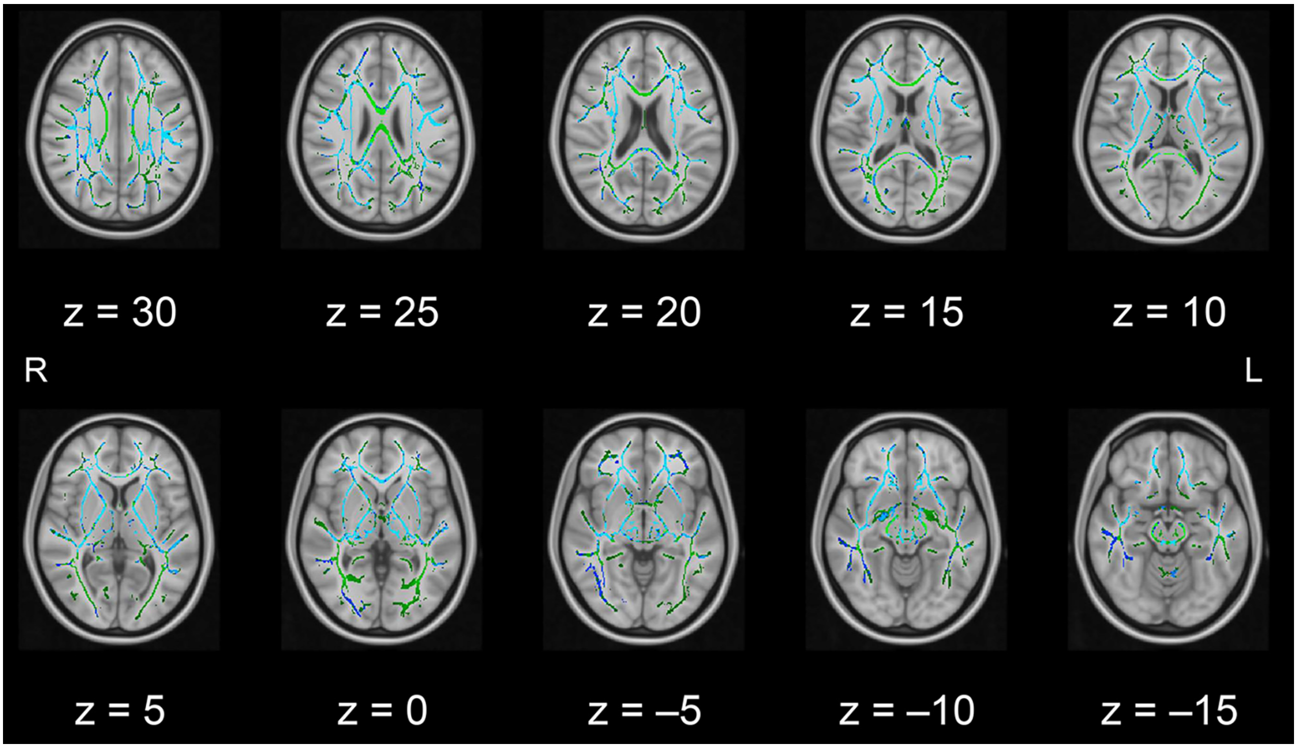

FIGURE 2 | White matter fiber tracts showing significantly lower MD values in the intervention group than in the control group (displayed in blue). The results are overlaid on the mean FA skeleton (shown in green) and the standard MNI152 T1 1-mm^3 brain template. The value of *z* in the horizontal plane represents the MNI *z*-coordinate. Abbreviation: FA, fractional anisotropy; L, left; MD, mean diffusivity; MNI, Montreal Neurological Institute; R, right.

$$AD = \lambda_1$$
$$RD = \frac{\lambda_2 + \lambda_3}{2}$$
$$MD = \frac{\lambda_1 + \lambda_2 + \lambda_3}{3}$$

$$FA = \sqrt{\frac{(\lambda_1 - \lambda_2)^2 + (\lambda_2 - \lambda_3)^2 + (\lambda_3 - \lambda_1)^2}{2(\lambda_1^2 + \lambda_2^2 + \lambda_3^2)}}$$

Voxel-based statistical analysis of the DTI metrics was performed using FSL's tract-based spatial statistics (TBSS) as follows (Smith et al., 2006). First, the FA images were preprocessed using the *tbss_1_preproc* command to eliminate probable outliers from the diffusion tensor fitting. Second, the *tbss_2_reg -T* command was executed to perform nonlinear registration, aligning the FA images of all participants into the FMRIB58_FA_1mm standard-space image. Third, using the *tbss_3_postreg -S* command, each participant's FA image was affine-transformed into the Montreal Neurological Institute (MNI152) standard space. In this step, all individual FA images were averaged to create a mean FA image, and this image was applied to generate a mean FA skeleton that represents the center of the fiber tracts common to all participants. For the mean FA skeleton, a threshold was set at 0.2 with the *tbss_4_prestats* command. Executing this command resulted in projecting all individual FA images onto the mean FA skeleton and generating a four-dimensional image file containing the skeletonized FA data for all participants. Finally, using a binary mask of the FA skeletonized image as a mask image, a voxel-wise statistical comparison between the intervention and control groups was performed on the four-dimensional skeleton image file using FSL's *randomise* program (Winkler et al., 2014) with the number of random permutations set to 5,000 (Nichols and Holmes, 2002). Data for the other DTI metrics, including MD, AD, and RD, were analyzed using the *tbss_non_FA* script to generate a four-dimensional skeleton image file for each of the other DTI metrics. These files were then used for statistical comparisons using the *randomise* program (Winkler et al., 2014). All metrics were analyzed using the general linear model built using the FEAT toolbox with a higher-level design. The statistical model included age, sex, educational level, and total intracranial volume (TIV; Takao et al., 2011, 2014) as covariates of no interest. TIV was estimated in our previous voxel-based morphometry study (Sugimoto and Otake-Matsuura, 2022). As a complementary analysis, we also conducted a regression analysis for each DTI index using the *randomise* program (Winkler et al., 2014) with the increase in verbal fluency task scores from pre-intervention to post-intervention (i.e., post-minus pre-intervention) as the regressor. This model also included age, sex, educational level,

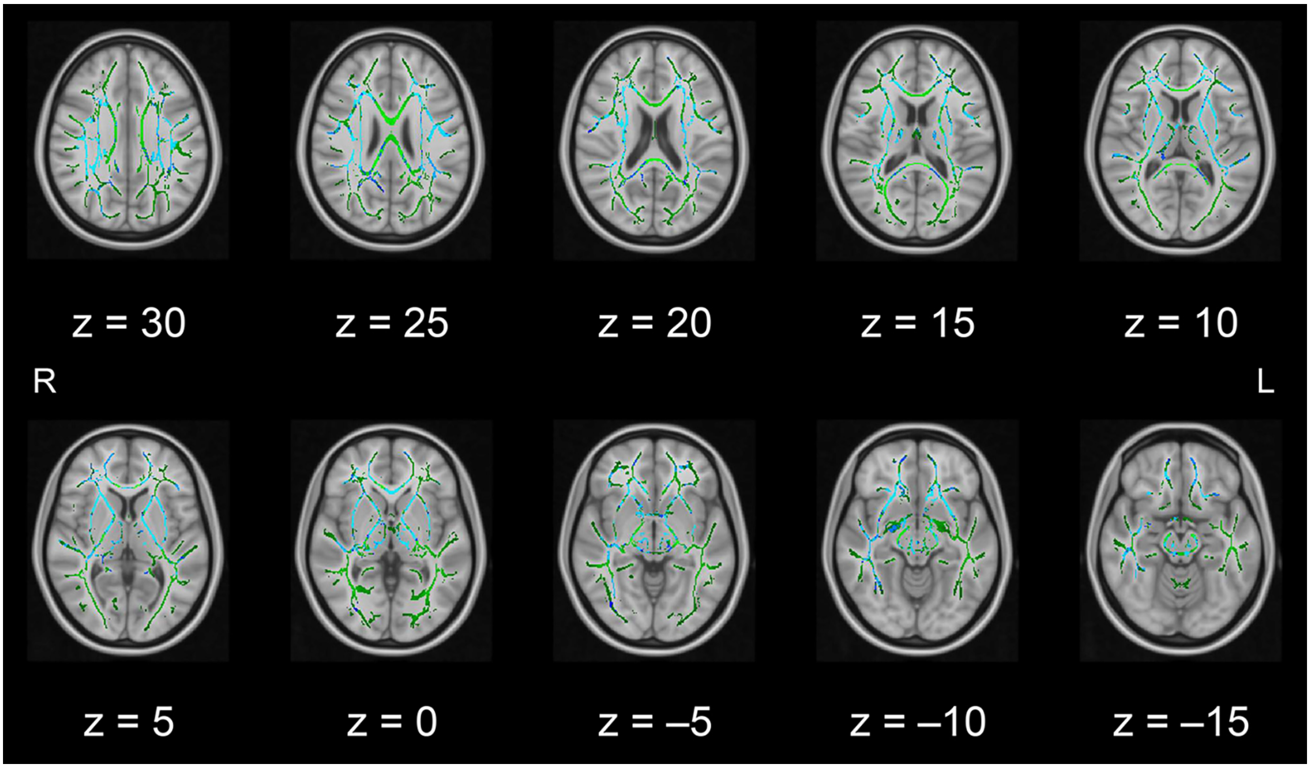

FIGURE 3 | White matter fiber tracts showing significantly lower AD values in the intervention group than in the control group (displayed in blue). The results are overlaid on the mean FA skeleton (shown in green) and the standard MNI152 T1 1-mm^3 brain template. The value of *z* in the horizontal plane represents the MNI *z*-coordinate. Abbreviation: AD, axial diffusivity; FA, fractional anisotropy; L, left; MNI, Montreal Neurological Institute; R, right.

and TIV as nuisance covariates. In all analyses, the statistical threshold was set at $p < 0.05$, corrected for multiple comparisons by controlling the family-wise error rate and employing the threshold-free cluster enhancement method (Smith and Nichols, 2009). The anatomical sites of significant clusters were primarily defined using the Johns Hopkins University (JHU) International Consortium of Brain Mapping (ICBM)-DTI-81 white matter labels atlas (Mori et al., 2008) implemented in the FSL.

RESULTS

In this pilot study, the diffusion metrics were compared between the intervention and control groups. Consistent with the hypothesized pattern, the intervention group showed in numerous white matter regions, including the left frontal area, significantly higher FA values or lower MD, AD, or RD values than the control group (see **Figures 1**–**4**, respectively). As shown in **Figure 1**, the bilateral anterior and superior corona radiata, external capsule, anterior and posterior limbs of the internal capsule, left genu and body of the corpus callosum, corticospinal tract, sagittal stratum (which includes the inferior longitudinal and inferior fronto-occipital fasciculi), retrolenticular part of the internal capsule, and fornix (cres)/stria terminalis had significantly higher FA values in the intervention group. As shown in **Figures 2**–**4**, these clusters overlapped with regions where significantly lower MD, AD, and RD values were observed in the intervention group. Furthermore, lower values of MD, AD, or RD were more widely found in regions such as the anterior, superior, and posterior corona radiata; external capsule; anterior and posterior limbs of the internal capsule; retrolenticular part of the internal capsule; genu, body, and splenium of the corpus callosum; corticospinal tract; sagittal stratum including the inferior longitudinal and inferior fronto-occipital fasciculi; superior and inferior longitudinal fasciculi; uncinate fasciculus; fornix; cingulum (cingulate gyrus); posterior thalamic radiation including the optic radiation; and midbrain regions. The findings from FA, MD, AD, and RD maps are detailed in **Table 1**. Importantly, the inverse pattern, i.e., lower values in FA or higher values in the other three metrics in the intervention group relative to the control group, was not found in any fibers.

As a complementary analysis, regression analysis was performed for each DTI index in relation to the score increases in the verbal fluency task throughout the intervention period. The results showed that a larger increase in task scores was associated with smaller AD values in clusters including the left anterior corona radiata, external capsule, or anterior limb of the internal capsule (see **Figure 5**). These clusters were located in regions where significant group differences in FA, MD, AD, and RD

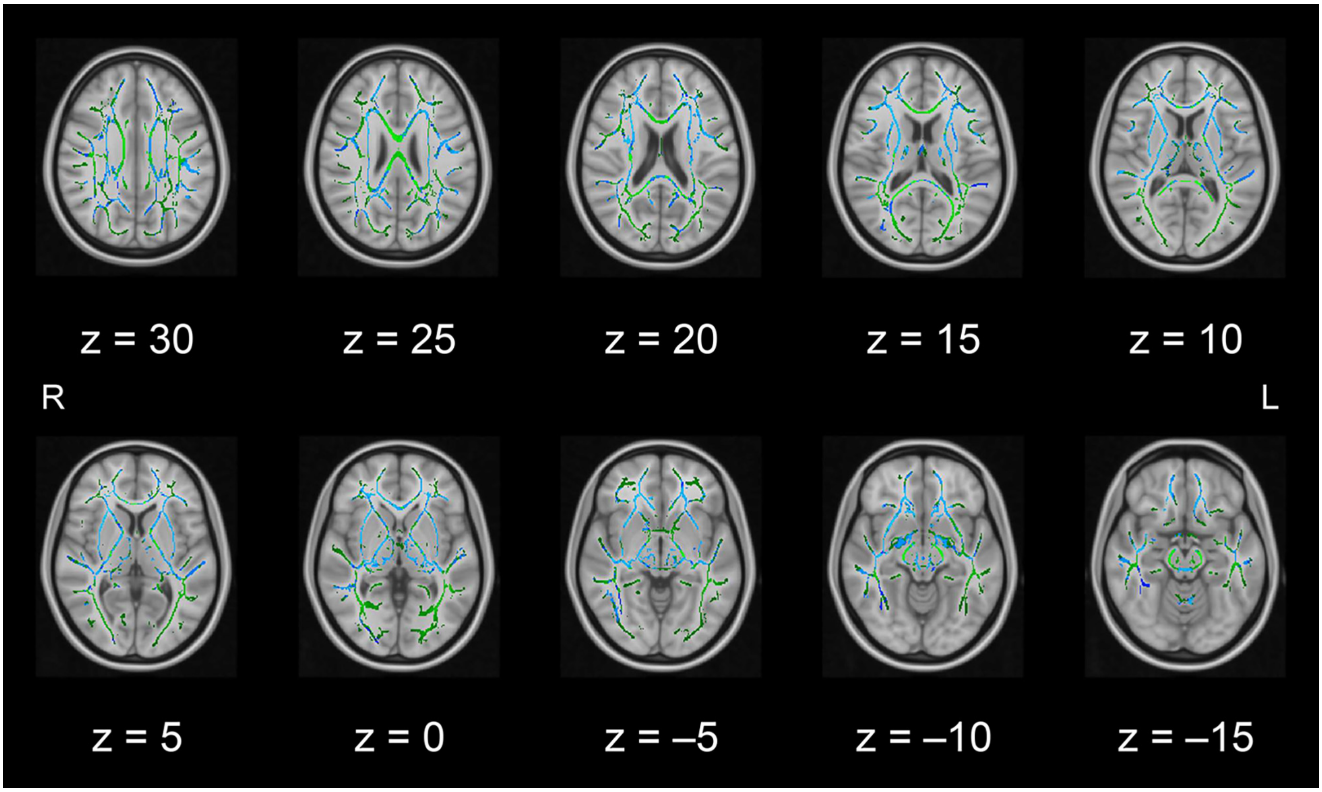

FIGURE 4 | White matter fiber tracts showing significantly lower RD values in the intervention group than in the control group (displayed in blue). The results are overlaid on the mean FA skeleton (shown in green) and the standard MNI152 T1 1-mm^3 brain template. The value of *z* in the horizontal plane represents the MNI *z*-coordinate. Abbreviation: FA, fractional anisotropy; L, left; MNI, Montreal Neurological Institute; R, right; RD, radial diffusivity.

values were observed. The results of the regression analysis are summarized in **Table 2**. We found no significant correlations between increased task scores and other metrics, including FA, MD, and RD, in any fiber tract.

DISCUSSION

This pilot DTI study aimed to identify candidate structures for white matter alterations possibly induced by the PICMOR intervention program. To achieve this purpose, TBSS analysis was performed, and comprehensive DTI metrics including FA, MD, AD, and RD were compared between the intervention and control groups. We found significantly larger FA values or smaller values in the other three indices in the intervention group compared to the control group in numerous white matter fiber tracts, including the left anterior corona radiata, external capsule, and anterior limb of the internal capsule. By contrast, no region showed the inverse DTI index pattern. Furthermore, larger improvements in verbal fluency task scores from baseline to follow-up were associated with smaller AD values in several white matter regions, such as the left anterior corona radiata, external capsule, and anterior limb of the internal capsule. These findings suggest that conversation-based cognitive interventions have the potential to maintain or improve white matter fiber health in older adults and that left frontal white matter structures are candidate regions that contribute to the enhancement of verbal fluency by this intervention.

The DTI pattern identified in this study, i.e., higher FA values or lower MD, AD, or RD values in the intervention group than in the control group, is consistent with previous findings from cognitive intervention studies using comprehensive DTI metrics (Lovden et al., 2010; Engvig et al., 2012; Cao et al., 2016; de Lange et al., 2017). Given that normal aging is typically associated with decreases in FA or increases in MD, AD, or RD across numerous white matter tracts (Madden et al., 2009, 2012; Bennett and Madden, 2014), including the fiber tracts identified in the present study, the DTI pattern at follow-up can be interpreted as evidence that age-related alterations in the white matter microstructure were attenuated by conversation-based cognitive interventions. Although the neurobiological interpretability of these DTI patterns is limited (Beaulieu, 2014), comprehensive use of DTI metrics would still be useful for characterizing intervention/training-induced changes in the white matter microstructure. This pilot study demonstrated the applicability of comprehensive DTI analyses in intervention studies and extended previous findings by demonstrating that intervention methodologies based on daily

TABLE 1 | White matter structures showing significant differences in DTI metrics between the intervention and control groups.

Labels of white matter structures included in clusters	MNI coordinates of the peak voxel			Number of voxels
	x	*y*	*z*	
FA (Intervention > Control)				
Left ACR, SCR, EC, ALIC, PLIC, GCC, and BCC	−25	17	16	1,836
Right ACR, SCR, EC, and ALIC	26	13	18	1,081
Left EC	−31	11	−4	115
Right EC	35	−8	−11	20
Right ALIC and PLIC	21	−3	14	93
Left CT	−19	−22	−4	40
Left SS (includes ILF and IFOF) and RPIC	−40	−19	−10	193
Left fornix (cres)/ST	−31	−24	−7	7
MD (Control > Intervention)				
Bilateral ACR, SCR, PCR, EC, ALIC, PLIC, RPIC, GCC, BCC, SCC, CT, SS (includes ILF and IFOF), SLF, UF, fornix (cres)/ST, fornix (column and body of fornix), cingulum (CG), PTR (includes OR), and midbrain	45	0	−31	57,187
AD (Control > Intervention)				
Bilateral ACR, SCR, PCR, EC, ALIC, PLIC, RPIC, GCC, BCC, SCC, CT, SLF, fornix (column and body of fornix), PTR (includes OR), and midbrain, and right SS (includes ILF and IFOF), UF, fornix (cres)/ST, and cingulum (CG)	36	−36	22	34,288
RD (Control > Intervention)				
Bilateral ACR, SCR, PCR, EC, ALIC, PLIC, RPIC, GCC, BCC, SCC, CT, SS (includes ILF and IFOF), SLF, UF, fornix (cres)/ST, fornix (column and body of fornix), cingulum (CG), PTR (includes OR), and midbrain	30	6	−12	49,218
Right ILF	31	−86	−4	119
Right ILF	25	−88	−5	13

Abbreviations: ACR, anterior corona radiata; AD, axial diffusivity; ALIC, anterior limb of the internal capsule; BCC, body of the corpus callosum; CG, cingulate gyrus; CT, corticospinal tract; DTI, diffusion tensor imaging; EC, external capsule; FA, fractional anisotropy; GCC, genu of the corpus callosum; IFOF, inferior fronto-occipital fasciculus; ILF, inferior longitudinal fasciculus; MD, mean diffusivity; MNI, Montreal Neurological Institute; OR, optic radiation; PCR, posterior corona radiata; PLIC, posterior limb of the internal capsule; PTR, posterior thalamic radiation; RD, radial diffusivity; RPIC, retrolenticular part of the internal capsule; SCC, splenium of the corpus callosum; SCR, superior corona radiata; SLF, superior longitudinal fasciculus; SS, sagittal stratum; ST, stria terminalis; UF, uncinate fasciculus.

social activities like conversations have the potential to improve or maintain white matter fiber health in older adults. Considering the difference in structured conversations for the intervention group enabled by a chair robot and unstructured free conversations for the control group, the structured nature of conversations may play an important role in the possible intervention effect on white matter microstructure. As noted earlier, structured conversations offer opportunities to train executive functions, such as flexibility, planning, working memory, and response inhibition. Indeed, verbal fluency ability was improved by structured conversations (Otake-Matsuura et al., 2021). Together with the behavioral findings, the PICMOR method could have a beneficial effect on older adults' health at both the behavioral and neural levels.

In the present study, a larger increase in verbal fluency task scores throughout the intervention period was associated with a smaller AD value in the left anterior corona radiata, external capsule, and anterior limb of the internal capsule (see **Figure 5**). These regions showed higher FA and lower MD, AD, and RD in the intervention group than in the control group (see **Figures 1–4**, respectively). The present findings are consistent with neuropsychological evidence demonstrating the contribution of the left frontal region to verbal fluency (Stuss et al., 1998; Baldo et al., 2006, 2010; Robinson et al., 2012; Biesbroek et al., 2016, 2021; Chouiter et al., 2016; Li et al., 2017; Thye et al., 2021). For instance, voxel-based lesion-symptom mapping studies have revealed that damage to white matter tracts located in the left hemisphere, such as the anterior corona radiata, external capsule, or anterior limb of the internal capsule, is associated with deficits in verbal fluency (Chouiter et al., 2016; Thye et al., 2021). Likewise, DTI studies have shown that white matter properties in the left frontal region are associated with verbal fluency (Theilmann et al., 2013; Rodriguez-Aranda et al., 2016). For example, one DTI study examined patients with Parkinson's disease and reported that verbal fluency scores were correlated with FA values in several regions, including the left anterior corona radiata (Theilmann et al., 2013). Taken together, the present findings suggest that left frontal white matter structures, including the anterior corona radiata, external capsule, and anterior limb of the internal capsule, are candidates for the neural underpinnings responsible for the beneficial effects of PICMOR on verbal fluency in older adults. Interestingly, our preliminary study using resting-state functional MRI revealed that left frontal cortical regions located near the regions identified in the present DTI study showed differential functional connectivity in the two groups (Sugimoto et al., 2020). Compared to the control group, the right prefrontal cortex and temporal pole in the intervention group had increased resting-state functional connectivity with the left prefrontal cortex, which is the most important cortical region for verbal fluency (Costafreda et al., 2006; Wagner et al., 2014). The strength of functional connectivity between the left prefrontal cortex and the right temporal pole was positively correlated with increased verbal fluency task scores,

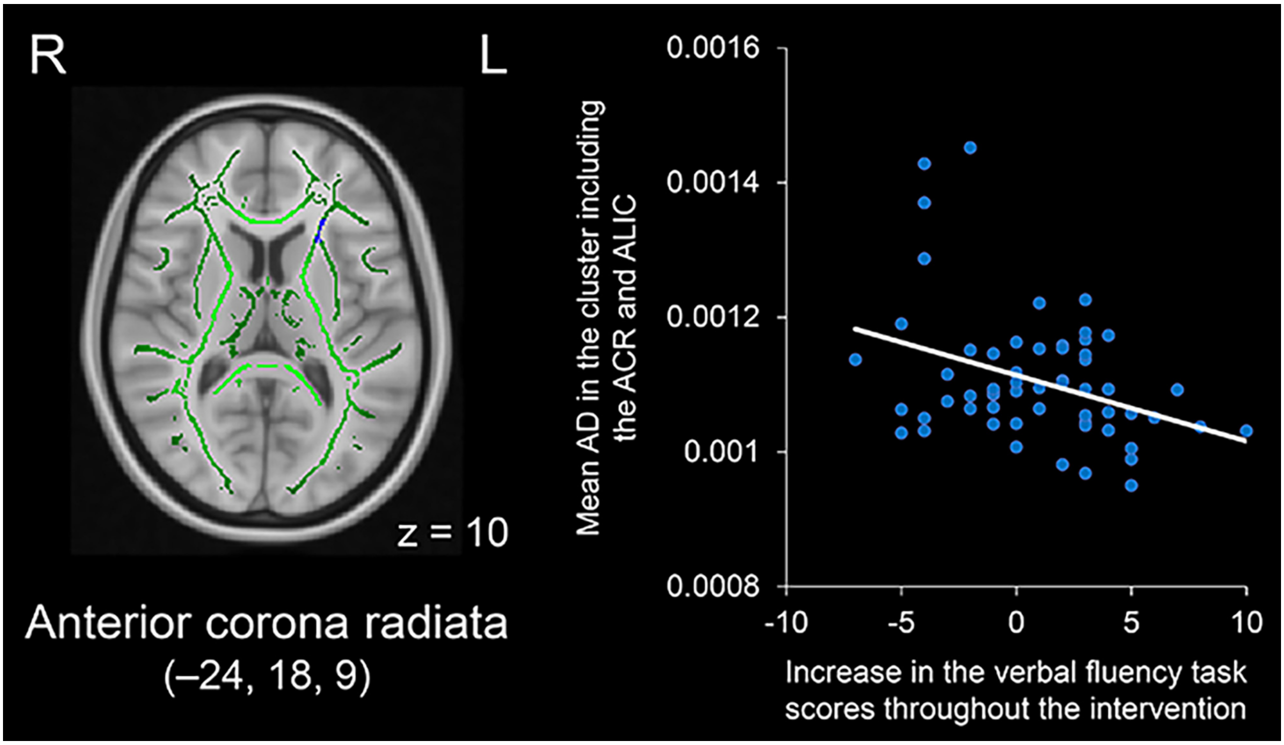

FIGURE 5 | Negative correlation between increases in verbal fluency task scores throughout the intervention period and AD values in the cluster including the left ACR and ALIC (displayed in blue). The cluster is overlaid on the mean FA skeleton (shown in green) and the standard MNI152 T1 1-mm^3 brain template. The value of z in the horizontal plane represents the MNI z-coordinate. MNI coordinates of the peak voxel are x = –24, y = 18, z = 9. Abbreviations: ACR, anterior corona radiata; AD, axial diffusivity; ALIC, anterior limb of the internal capsule; FA, fractional anisotropy; L, left; MNI, Montreal Neurological Institute; R, right.

whereas the strength between the left and right prefrontal cortices showed no significant correlation with the task scores (Sugimoto et al., 2020). Further analysis using voxel-based morphometry demonstrated that the right prefrontal region had increased volumes in the intervention group compared to the control group, although the volume of this region was not correlated with task scores (Sugimoto and Otake-Matsuura, 2022). In the present DTI study, higher FA and lower MD, AD, and RD in the intervention group were observed in both left and right frontal regions, although a significant correlation with task scores was identified only on the left side. Thus, these findings could be interpreted as evidence that conversation-based cognitive interventions have the potential to induce structural and functional changes not only on the left side of the frontal area as a core region for verbal fluency but also on the right side of this area as a supplementary region that indirectly supports verbal fluency. This idea should be further examined in future studies by employing equivalent criteria for statistical significance among different modalities.

Our findings are limited by the lack of comparable MRI data at baseline. Any difference observed in the post-intervention period cannot be fully considered an intervention effect because such difference may have already existed before the intervention. Although we adopted the random allocation of participants

TABLE 2 | White matter structures whose AD values showed negative correlations with increases in verbal fluency task scores throughout the intervention period.

Labels of white matter structures included in clusters	MNI coordinates of the peak voxel			Number of voxels
	x	*y*	*z*	
Left ACR and ALIC	−24	18	9	144
Left EC	−24	13	−11	32
Left EC	−23	20	−7	8

Abbreviations: ACR, anterior corona radiata; AD, axial diffusivity; ALIC, anterior limb of the internal capsule; EC, external capsule; MNI, Montreal Neurological Institute.

to the study groups (Otake-Matsuura et al., 2021) and found no significant group differences at baseline in the task scores of almost all cognitive tests, including the verbal fluency task (Sugimoto and Otake-Matsuura, 2022), we cannot rule out the possibility of baseline differences. To examine whether the possible white matter alterations identified in this pilot study were indeed induced by PICMOR-based conversations, it is necessary to collect longitudinal DTI data including both pre- and post-intervention periods and to compare longitudinal changes between intervention and control groups. Despite this limitation, we successfully identified the hypothesized DTI pattern, i.e., intervention-induced increases in FA or decreases in

MD, AD, or RD, which should be confirmed by future research using a longitudinal study design.

CONCLUSION

Although we cannot conclusively identify the neural underpinnings of the beneficial effects of PICMOR on cognitive function due to the lack of DTI data at baseline, this pilot study successfully identified candidate structures by comparing comprehensive DTI metrics at follow-up between the intervention and control groups. The observed DTI pattern is consistent with those identified in other cognitive intervention studies. Taken together with ample evidence from aging research that normal aging is associated with changes in DTI indices, the present findings suggest that conversation-based cognitive interventions have the potential to maintain or improve white matter fiber health in adults affected by age-related alterations. Furthermore, the findings from the regression analysis suggest that left frontal white matter structures are candidates that contribute to the intervention-induced enhancement of verbal fluency. Definitive conclusions may be obtained by comparing in future research longitudinal changes in DTI measures from baseline to follow-up in candidate regions.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because joint research agreement is required for data sharing. Requests to access the datasets should be directed to Hikaru Sugimoto, hikaru.sugimoto@riken.jp.

ETHICS STATEMENT

This study was reviewed and approved by the Institutional Review Board of RIKEN. The participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

MO-M designed the study. HS collected and analyzed the data and wrote the manuscript under the supervision of MO-M. All authors contributed to the article and approved the submitted version.

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Combined Functional Assessment for Predicting Clinical Outcomes in Stroke Patients After Post-acute Care: A Retrospective Multi-Center Cohort in Central Taiwan

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Background and Objective: In 2014, Taiwan's National Health Insurance administration launched a post-acute care (PAC) program for patients to improve their functions after acute stroke. The present study was aimed to determine PAC assessment parameters, either alone or in combination, for predicting clinical outcomes.

Methods: We retrospectively enrolled stroke adult patients through one PAC network in central Taiwan between January 2014 and December 2020. We collected data on post-stroke patients' functional ability at baseline and after PAC stay. The comprehensive assessment included the following: Modified Rankin Scale (MRS), Functional Oral Intake Scale (FOIS), Mini-Nutritional Assessment (MNA), Berg Balance Scale (BBS), Fugl-Meyer Assessment (FMA), Mini-Mental State Examination (MMSE), aphasia test, and quality of life. The above items were assessed first at baseline and again at discharge from PAC. Logistic regression was used to determine factors that were associated with PAC length of stay (LOS), 14-day hospital readmission, and 1-year mortality.

Results: A total of 267 adults (mean age 67.2 $\pm$ 14.7 years) with completed data were analyzed. MRS, activities of daily living (ADLs), instrumental activities of daily living (IADLs), BBS, and MMSE all had improved between disease onset and PAC discharge. Higher baseline and greater improvement of physical and cognitive functions between initial and final PAC assessments were significantly associated with less readmission, and lower mortality. Furthermore, the improved ADLs, FOIS, MNA, FMA-motor, and MMSE scores were related to LOS during PAC. Using logistic regression, we found that functional improvements $\geq$5 items [adjusted odds ratio (aOR) = 0.16; 95% confidence interval (CI) = 0.05–0.45] and improved MMSE (aOR = 0.19; 95%

CI = 0.05–0.68) were significantly associated with reduced post-PAC mortality or readmission. Whereas, functional improvements ≥7 items, improved FOIS, and MNA significantly prolonged LOS during PAC.

Conclusion: Physical performance parameters of patients with acute stroke improved after PAC. PAC assessment with multiple parameters better predicted clinical outcomes. These parameters could provide information on rehabilitation therapy for acute stroke patients receiving PAC.

Keywords: Berg Balance Scale, Fugl-Meyer Assessment, Functional Oral Intake Scale, post-acute care, mortality, readmission

INTRODUCTION

The main purpose of post-acute care (PAC) is to achieve functional and occupational recovery and to maintain psychospiritual homeostasis after acute illness, especially on patients with rehabilitation potential but in advanced age and with multimorbidity (Pyrkov et al., 2021). Current guideline, from both the American Heart Association and American Stroke Association (Winstein et al., 2016), and the National Health Service in the United Kingdom, recommend that patients who are candidates for post-acute rehabilitation to receive individualized, interprofessional care, and multicomponent exercise intervention including high-intensity resistance training, to reverse functional decline after major diseases. To improve rehabilitation outcomes on neuromuscular performance (muscle strength and power), mobility, and spasticity, several interventions, including whole-body vibration exercise, mirror therapy, proprioceptive neuromuscular facilitation, and neuro-developmental technique also referred as the Bobath concept, have been used in patients after acute stroke (Liao et al., 2015; Guiu-Tula et al., 2017; Oliveira et al., 2018; Sañudo et al., 2018; Thieme et al., 2018; Díaz-Arribas et al., 2020). Based on the variable effectiveness of different techniques, knowledge for response prediction seems important in people with stroke to guide better individualized rehabilitation protocols.

In the report of U.S. Nursing Home Compare (Burke et al., 2021), the target of payment reforms or payment in the performance program for skilled nursing facility (SNF) was based on patient outcome in terms of successful community discharge rate (Burke et al., 2021). However, PAC should also target patient-oriented outcomes (e.g., 1-year mortality, 14-day or 30-day hospital readmission, and functional improvement) along with the growing concern regarding those elderly with poor resilience being “rehabbed to death” (Burke et al., 2021). The medical literature reported, on functional improvements of acute stroke patients, prognostic factors like the onset time of rehabilitation, duration and intensity of treatment, and the place of care (Vazquez-Guimaraens et al., 2021). To improve clinical outcomes after PAC, knowledge of their determinant factors is important. It was reported that a combination of the severity of deficits, cognitive ability, comorbidity, and response to objectives, can provide a more individualized treatment period, improving clinical outcomes, such as emergency room visit, hospital readmission, and mortality (Stinear et al., 2017; Vazquez-Guimaraens et al., 2021).

In Taiwan, the PAC network for patients with acute cerebrovascular accidents (CVA) started in January 2014 (Lee et al., 2014), and the National Health Insurance (NHI) covers costs up to a maximal 12 weeks of PAC-CVA when patients receive rehabilitation of physical, occupational, and speech therapy. Unlike multiple choices (SNFs, long-term care hospitals, inpatient rehabilitation, and home health services) for PAC settings in United States and United Kingdom (White, 2019), in Taiwan, most PAC settings are community hospital-based with reimbursement from the NHI for clinicians, physical, occupational specialists, and speech-language pathologists who have been well-trained with cross-regional working ability (Lee et al., 2014). Several studies reported the effectiveness of PAC in helping patients return home after a stroke, improving and accelerating functional recovery (Peng et al., 2017; Wang et al., 2017; Hsieh et al., 2018). In Taiwan's PAC program several parameters are assessed, like Modified Rankin Scale (MRS), Functional Oral Intake Scale (FOIS), Berg Balance Scale (BBS), Fugl-Meyer Assessment (FMA), Mini-Nutritional Assessment (MNA), Mini-Mental State Examination (MMSE), Concise Chinese Aphasia Test (CCAT), and 3-level 5-dimensional Euro-Quality of Life (EQ-5D-3L). Initial functional status, disease severity, and balance status were reported to be associated with mortality in patients with acute stroke (Ho et al., 2014; Foroozanfar et al., 2020). Furthermore, cognitive impairment after stroke is related to poor clinical outcomes, such as a higher rate of disability, the institutionalization of long-term care facilities, recurrence of stroke, and mortality (Li J. et al., 2020). During hospitalization for stroke, premorbid undernutrition, and oropharyngeal dysphagia are known to have adverse effects on the prognosis of stroke patients by having greater complications, mortality, length of stay (LOS), and poor neurological outcomes (Kang et al., 2020; Souza et al., 2020). Prognosis of stroke reflects complex interactions of multiple risk factors, and that can be better judged through the construction of tools. Here, we hypothesized that by combining multiple clinical measures in the PAC program, those patients with a greater chance of recovery after rehabilitation can be identified. Consequently, individualized care planning can be made to improve patients' clinical outcomes. To test the hypothesis, a multi-center cohort was conducted. We aimed to use comprehensive assessments in patients with acute CVA at the acute hospital and under PAC settings and to evaluate factors associated with clinical outcomes, including LOS at PAC, 14-day hospital readmission, and 1-year mortality.

MATERIALS AND METHODS

Study Design

We used a retrospective longitudinal design to explore clinical relevant factors of PAC outcomes in acute stroke patients, including LOS at PAC, 14-day hospital readmission, and 1-year mortality. In reporting this study, the standard methodology was reported according to "Strengthening the Reporting of Observational Studies in Epidemiology" (STROBE) guidelines (Cuschieri, 2019). The study was approved by the Institutional Review Board of TCVGH (No. CE21441B).

Setting

In this study, the PAC network (virtual private network, VPN) was created in January 2014 in our general hospital with 37 community hospital mastering PAC–stroke rehabilitation. Candidate patients in acute ward would first be evaluated by a case manager, and then transferred to PAC hospital for rehabilitation if they met the program criteria, where a hospital-based multidisciplinary team, composed of a physiatrist, physical therapist, occupational therapist, speech therapist, social worker, and case manager, managed the rehabilitation program with 1–3 h of intensive rehabilitation per workday over the following 6–12 weeks. A formal functional assessment was evaluated in those acute stroke participants before discharge in the acute ward of general hospital, and subsequently several times in the PAC hospital at admission, first re-evaluation 14 days later, second re-evaluation 7 days later, third re-evaluation 7 days later, and case closure (**Figure 1**).

Study Participants

During the study period, patients with a primary diagnosis of acute stroke in our hospital, met the following criteria: (1) stroke onset time within 1 month, (2) stable hemodynamic parameters and no neurological deterioration within 72 h, and MRS between 2 and 4 (between 3 and 4 since July 2017 due to the policy change), and being transferred to PAC hospital with complete admission and discharge records, were enrolled. Those patients with (1) incomplete physical or cognitive assessment and (2) being transferred back to the medical center, or a nursing home before discharge were excluded. Overall, there were 702 patients with stroke who received the PAC program between January 2014 and December 2020. However, among those who were successfully transferred to a PAC institution, we excluded 423 patients due to no closure report, and 93 with incomplete data on their functional ability during PAC stay. Besides, four patients who ended their PAC due to hospitalization for acute illness, and one patient who was admitted to a nursing home due to non-stroke disease progression, were excluded. Finally, 267 post-stroke patients who completed their PAC stay and for whom complete data on functional ability were available were enrolled in our study (**Figure 2**).

Assessments of Stroke Severity and Functional Abilities

Baseline characteristics of patients including index data in the general hospital and PAC community hospital were collected. Besides, medical staff routinely conducted a minimum of 10 measurements on a patient with CVA in the multiple PAC settings (**Figure 2**). The MRS was used to measure stroke severity and handicap (Burn, 1992). The Barthel Index was used to evaluate ADLs, and the Lawton scale was used to evaluate IADLs (Lawton and Brody, 1969; Collin et al., 1988). The MNA and MMSE were used to identify CVA patients at risk for malnutrition and memory impairment (Guigoz, 2006). The FOIS (Crary et al., 2005) was recorded with a score of 1 [(worse) nothing by mouth] to 7 [(best) complete oral diet with no restrictions]. The interrater reliability was determined with six speech-language pathologists. The total scale and subscales of the BBS were further used to evaluate the functional independence of patients with CVA (Cheng et al., 2014). Both upper extremity motor subscore (0–66) and modified sensation (range of joint motion; 0–44) of the FMA (five domains: motor function, sensory function, balance, joint range of motion, joint pain) were used as predictors of poor functional recovery after sensorimotor stroke (Sullivan et al., 2011). For all sensory and motor assessments, we found high consistency between the therapist raters and expert raters among PAC settings. Language performance was assessed against all language modalities with the CCAT designed for standardized, linguistically, culturally neutral, and native Mandarin Chinese speakers (Tsai et al., 2014). We evaluated four subcategories of CCAT related to language production. They were conversation, family picture description, object naming and expression, and repetition. For assessment of the quality of life, we used the EQ-5D-3L tool (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) (Lin et al., 2020).

Outcome Measurements and Factor Analyses

A primary clinical outcome was 1-year mortality or 14-day unplanned hospital readmission. Information on all-cause mortality was obtained from the PAC network, with validation in Taiwan's National Death Registry, according to the ICD-9 (ICD9 001.x-999.x) or ICD10 (A00.x-Z99.x). LOSs in the PAC hospital were stratified into four quartiles, and LOS exceeding 42 days [the third quartile (Q3)] was defined as a secondary outcome.

To allow better prediction of clinical outcomes, various combinations of improved functional parameters were analyzed. Functional improvement at the end of PAC training was defined by improved scores of MRS, ADLs, IADLs, FOIS, MNA, BBS, FMA-motor, FMA-modified sensation, MMSE, and CCAT (Lai et al., 2017).

Statistical Analyses

For continuous variables, we first used the Kolmogorov–Smirnov test to determine the normality of sample

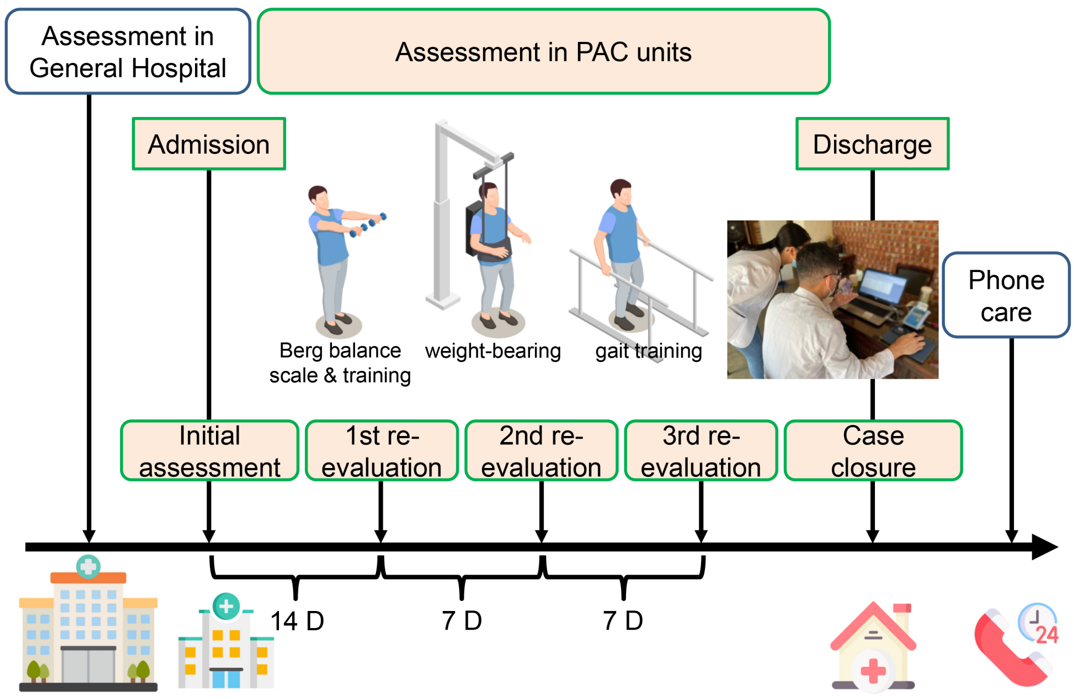


FIGURE 1 | A simple schematic diagram illustrating the assessment and measurement protocol executed in the general hospital, followed by post-acute care units. PAC, post-acute care. Some images are edited by Freepik free website and software, https://www.freepik.com/home.

distribution. Continuous variables were then analyzed with the Mann–Whitney *U* test, generating the median and interquartile range (IQR). Categorical variables, expressed as percentages, were tested with Chi-square or Fisher's exact test. We used Wilcoxon signed-rank test, a non-parametric test, to test the location of a set of samples or to compare locations of two populations using a set of matched samples. Both primary and secondary outcomes were correlated and delineated based on previously defined functional status in general hospitals and community PAC hospitals, regarding demography and laboratory test results. Logistic regression analyses were finally applied. Specifically, we used multivariate analyses to estimate odds ratios (ORs) of outcomes after adjusting for age, gender, body mass index (BMI), and cardiovascular disease (CVD). Besides, to test the discrimination ability of the item numbers of improved functionality on clinical outcome, a cut-off value was determined by the area under the ROC curve (AUC) under the non-parametric assumption. *p*-Values for non-linearity were calculated using the null hypothesis test. Statistical significance was set at $p < 0.05$. All analyses were performed with the SPSS for Windows version 22.0 (SPSS Institute Inc., Chicago, IL, United States).

RESULTS

The median age of 267 CVA patients was 67.0 years (IQR = 58.0–79.0), 32.2% with smoking behaviors, 17.6% with alcohol consumption. Their median BMI was 24.4 kg/m^2 (IQR = 22.1–27.3), 36.3% had diabetes mellitus, 84.3% with hypertension, median LDL-c was 100.0 mg/dL (IQR = 85.0–125.0), fasting glucose was 123 mg/dL (IQR = 105.0–159.0), and glycated hemoglobin (Hba1c) was 6.0% (IQR = 5.6–6.6) (**Table 1**). Among patients with CVA, median MRS was 4.0 (IQR = 4.0–4.0), ADLs was 35.0 (IQR = 20.0–55.0), and IADLs was 1.0 (IQR = 0.0–2.0). They showed moderately severe disability and were unable to walk and unable to attend to bodily needs without assistance. FOIS with a median of 6.0 (IQR = 3.0–6.0) meant that CVA patients suffered from nasogastric tube dependent on the consistent oral intake of food or liquid to total oral diet with multiple consistencies without special preparation, but with specific food limitations. EQ-5D-3L, a multi-dimensional term, showed an average sub-score of 2.0–3.0, reflecting that these patients were not satisfied with their physical, social, and emotional well-being.

When initial values were compared with those after this program in the PAC settings, we found significant improvements in all functionalities, including MRS, ADLs, IADLs, FOIS, MNA, BBS, FMA, MMSE, CCAT, and EQ-5D-3L (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) (**Table 2**). At enrollment in the PAC settings, 16 patients (6.0%) were classified as MRS 2, 59 patients (22.1%) as MRS 3, and 190 (71.2%) patients as MRS 4 (**Supplementary Table 1**). Upon case closure, 143 patients (53.6%) showed improved MRS levels by scores ≥1. The difference in ADL scores before and after hospitalization showed improvements in 227 patients (85.0%). The score of FOIS improved in 108 patients (40.4%) and similarly BBS scores improved in 231 patients (86.5%). **Table 2** shows changes of EQ-5D-3L.

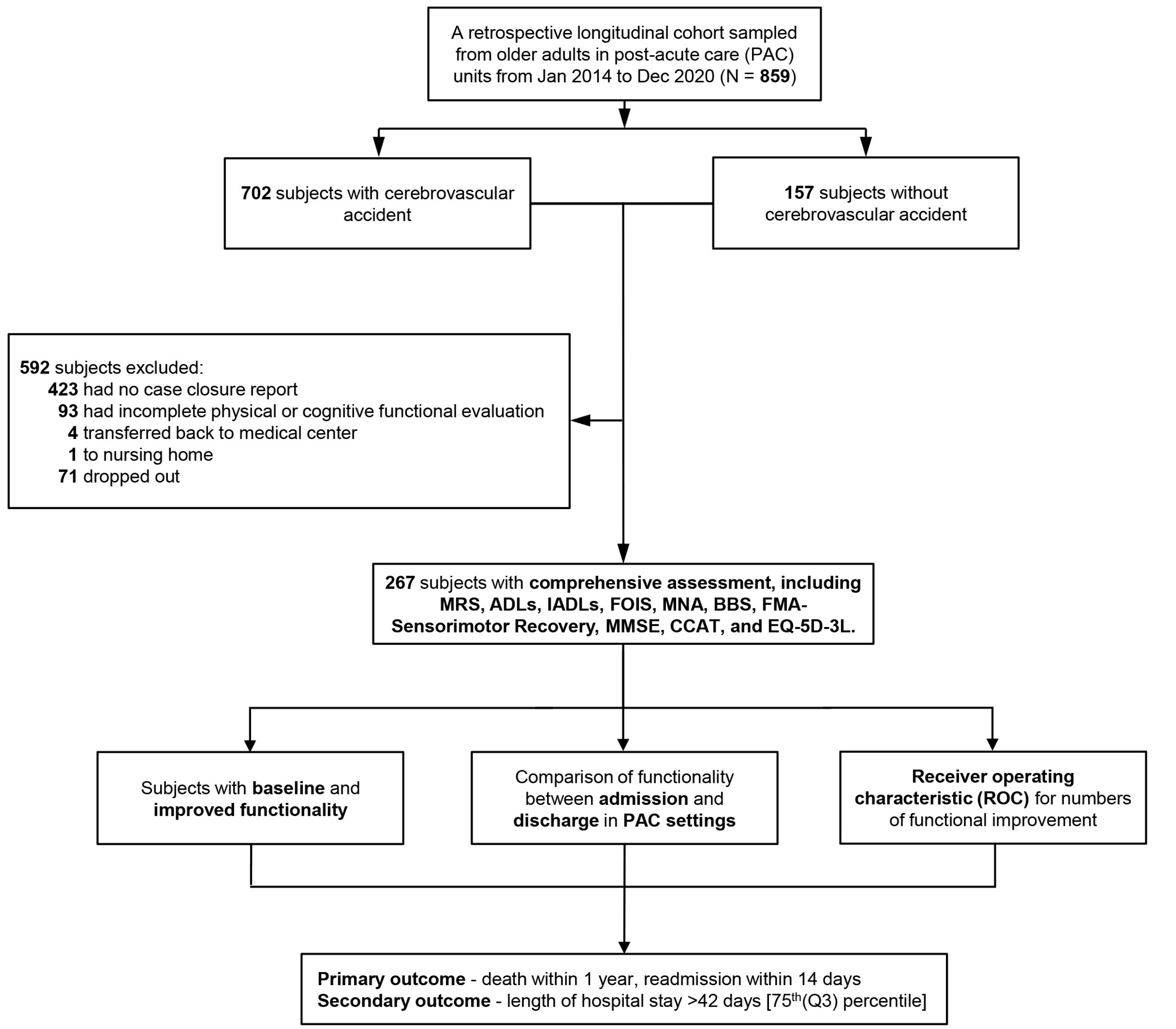


FIGURE 2 | Flowchart of patient selection. MRS, Modified Rankin Scale; ADLs, activities of daily living; IADLs, instrumental activities of daily living; FOIS, Functional Oral Intake Scale; MNA, Mini-Nutritional Assessment; BBS, Berg Balance Scale; FMA, Fugl-Meyer Assessment; MMSE, Mini-Mental State Examination; CCAT, Concise Chinese Aphasia Test; EQ-5D-3L, 3-level 5-dimensional European Quality of Life questionnaire; PAC, post-acute care.

The functional changes of patients at baseline and discharge from the PAC hospital were shown in **Table 2**. The mean MRS score was 3.7 (SD 0.6) at admission, and that improved to 2.9 (SD 1.0) at discharge. The ADL scores improved from 43.2 (SD 26.3) at admission to 66.2 (SD 27.5) at discharge; IADLs also improved from 1.5 (SD 1.6) to 2.5 (SD 2.1). Similarly, the nutritional status measured by FOIS improved from 5.4 (SD 2.0) to 6.1 (SD 1.7), and by MNA improved from 18.0 (SD 5.1) to 19.8 (SD 5.3). In the balance domain, BBS improved from 21.9 (SD 18.2) before PAC training to 34.7 (SD 17.9) at discharge. In the mental status, the MMSE score improved from 18.6 (SD 9.0) initially to 22.2 (SD 8.5) at discharge. In the language aspect, the CCAT score also improved from 8.9 (SD 3.6) to 9.4 (SD 3.4). In the EQ-5D-3L dimension of the generic health status of the significant improvements were observed for all subcategories at discharge, including mobility [from 2.2 (SD 0.6) to 1.8 (SD 0.6), $p < 0.001$], self-care [from 2.3 (SD 0.6) to 1.8 (SD 0.6), $p < 0.001$], usual activity [from 2.3 (SD 0.6) to 2.0 (SD 0.7), $p < 0.001$], pain/discomfort [from 1.5 (SD 0.6) to 1.4 (SD 0.5), $p < 0.001$], and anxiety/depression [from 1.6 (SD 0.6) to 1.4 (SD 0.5), $p < 0.001$]. For the pain/discomfort and anxiety/depression subcategories, changes occurred predominantly in terms of a shift in the median from level 2 to level 1 ($p < 0.001$).

Cerebrovascular accident patients with 1-year mortality or 14-day hospital readmission had a higher percentage of ischemic stroke (90.0%), of older age [median 78.0 years (IQR = 66.3–84.0)], with lower BMI of 22.2 kg/m^2 (IQR = 19.7–24.9), higher

TABLE 1 | Baseline characteristics of patients with cerebrovascular accident.

Cerebrovascular accident	*n* = 267
Ischemia (%)	222 (83.1)
Hemorrhage (%)	45 (16.9)
Demographic profile	
Age, median (IQR, years)	67.0 (58.0–79.0)
Gender, male (%)	172 (64.4)
Smoking (%)	86 (32.2)
Alcohol (%)	47 (17.6)
BMI, median (IQR, kg/m^2)	24.4 (22.1–27.3)
Comorbidity profile (%)	
Diabetes mellitus	97 (36.3)
Hypertension	225 (84.3)
Hyperlipidemia	159 (59.6)
Cardiovascular disease	106 (39.7)
COPD	7 (2.6)
ACCI, median (IQR)	4.0 (3.0–6.0)
Laboratory profile, median (IQR)	
Low-density lipoprotein cholesterol (mg/dL)	100.0 (85.0–125.0)
Fasting glucose (mg/dL)	123.0 (105.0–159.0)
Hba1c (%)	6.0 (5.6–6.6)
Albumin (g/dL)	3.9 (3.6–4.1)
eGFR (mL/min per 1.73 m^2)	82.9 (61.6–103.8)
Urine protein/creatinine ratio (mg/g)	0.1 (0.1–0.3)
NT-proBNP (pg/mL)	1333.0 (235.0–3450.0)
Assessment in general hospital, median (IQR)	
Modified Rankin Scale	4.0 (4.0–4.0)
ADLs	35.0 (20.0–55.0)
IADLs	1.0 (0.0–2.0)
Functional Oral Intake Scale	6.0 (3.0–6.0)
Mini-Nutritional Assessment	18.5 (14.5–21.0)
EQ-5D-3L	
Mobility	2.0 (2.0–3.0)
Self-care	3.0 (2.0–3.0)
Usual activities	3.0 (2.0–3.0)
Pain/discomfort	2.0 (1.0–2.0)
Anxiety/depression	2.0 (1.0–2.0)

Continuous data were expressed as median (IQR, interquartile range) and analyzed by the Kruskal–Wallis test. Categorical data were expressed as number and percentage and analyzed by the Chi-square test.
BMI, body mass index; COPD, chronic obstructive pulmonary disease; ACCI, age-adjusted Charlson Comorbidity Index; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal pro-B-type natriuretic peptide; ADLs, activities of daily living; IADLs, instrumental activities of daily living; EQ-5D-3L, 3-level 5-dimensional European Quality of Life questionnaire; eGFR, calculated by using modified modification diet of renal disease (MDRD) formula, was utilized to evaluate renal function.

CVD (75%), small numbers of improved functionality with a median 3.5 items (IQR = 1.0–6.0) vs. 6.0 items (IQR = 5.0–8.0), lower percentages of improved MRS, ADLs, IADLs, BBS, MMSE, and lower levels of improved EQ-5D-3L (**Supplementary Table 2**). Further, it was shown that an optimal cut-off values of improved PAC items to predict primary outcome was 5 with an AUC of 0.74 [95% confidence interval (CI) = 0.60–0.89, sensitivity: 82.2%, specificity: 65.0%, $p < 0.001$], and 7 for second outcome (LOS >42 days) with an AUC of 0.69 (95% CI = 0.62–0.76, sensitivity: 71.0%, specificity: 65.0%, $p < 0.001$) (**Figure 3**).

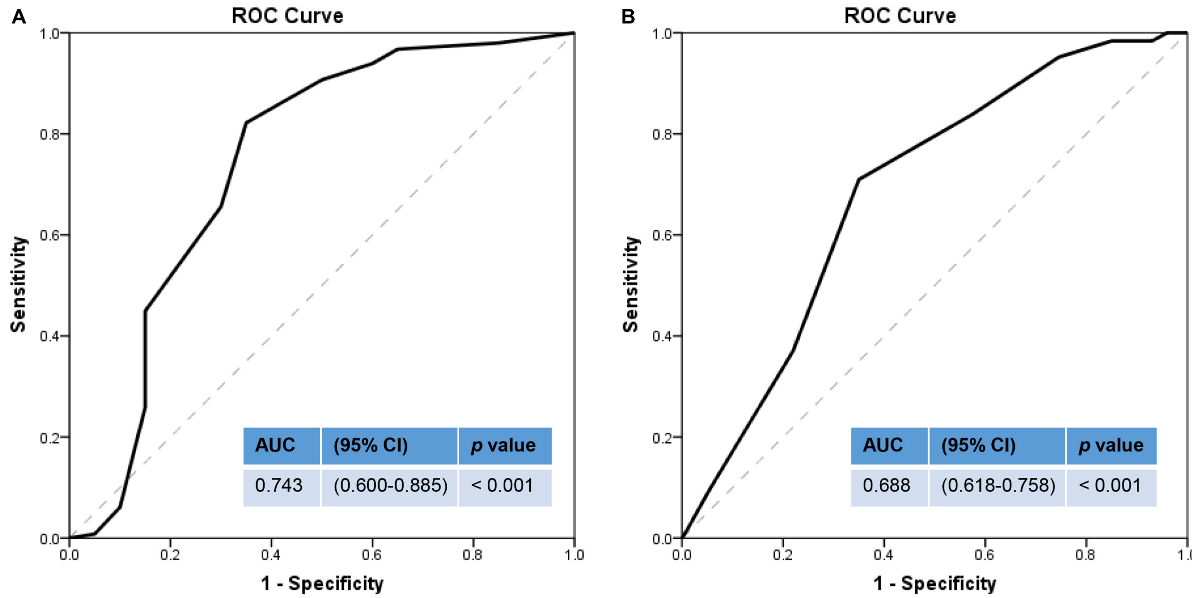
TABLE 2 | Effect of PAC on functional performance and quality of life in patients with stroke.

	Admission	Discharge	*p*-Value
MRS	4.0 (3.0–4.0)	3.0 (2.0–4.0)	<0.001
ADLs	40.0 (20.0–65.0)	70.0 (50.0–90.0)	<0.001
IADLs	1.0 (0.0–2.0)	2.0 (1.0–4.0)	<0.001
FOIS	6.0 (5.0–7.0)	7.0 (6.0–7.0)	<0.001
MNA	18.3 (14.0–22.5)	21.0 (16.5–24.0)	<0.001
BBS	20.0 (4.0–38.0)	40.5 (19.0–51.0)	<0.001
FMA-modified sensation	39.0 (24.0–44.0)	44.0 (36.0–44.0)	<0.001
FMA-motor	45.0 (15.5–59.0)	57.0 (33.5–62.0)	<0.001
MMSE	20.0 (12.0–26.0)	25.0 (19.0–29.0)	<0.001
CCAT	10.5 (7.3–11.5)	11.0 (8.9–11.9)	<0.001
EQ-5D-3L			
Mobility	2.0 (2.0–2.0)	2.0 (1.0–2.0)	<0.001
Self-care	2.0 (2.0–3.0)	2.0 (1.0–2.0)	<0.001
Usual activities	2.0 (2.0–3.0)	2.0 (2.0–2.0)	<0.001
Pain/discomfort	2.0 (1.0–2.0)	1.0 (1.0–2.0)	<0.001
Anxiety/depression	2.0 (1.0–2.0)	1.0 (1.0–2.0)	<0.001

Continuous data were expressed as median (IQR, interquartile range) and analyzed by the Wilcoxon signed ranks test.
MRS, Modified Rankin Scale; ADLs, activities of daily living; IADLs, instrumental activities of daily living; FOIS, Functional Oral Intake Scale; MNA, Mini-Nutritional Assessment; BBS, Berg Balance Scale; FMA, Fugl-Meyer Assessment; MMSE, Mini-Mental State Examination; CCAT, Concise Chinese Aphasia Test; EQ-5D-3L, 3-level 5-dimensional European Quality of Life questionnaire.

In the simple logistic regression, CVA patients with older age and CVD were significantly associated with increased risk of 1-year mortality or 14-day hospital readmission. On the other hand, higher BMI, higher numbers of improved function, improved functional number greater or equal to 5, improved MRS, ADLs, IADLs, BBS, and MMSE were all significantly associated with reduced risks of the primary outcome (**Table 3**). In the multivariate logistic regression model, improved functional number per item [model 1, **Table 3**, adjusted OR (aOR) = 0.69; 95% CI = 0.55–0.86; $p = 0.001$], improved functional numbers (≥5 vs. <5, model 2, **Table 3**, aOR = 0.16; 95% CI = 0.05–0.45; $p = 0.001$), and high MMSE (model 3, **Table 3**, aOR = 0.19; 95% CI = 0.05–0.68; $p = 0.010$) were significantly associated with reduced all-cause mortality or 14-day hospital readmission after adjusting for age, BMI, CVD, and different items of improved functionality.

Some CVA patients with prolonged LOS were female gender (46.8%), had lower serum N-terminal pro-B-type natriuretic peptide, higher disability [median MRS 4 (IQR = 4–4)], lower ADLs 25.0 (IQR = 15.0–40.0), lower IADLs 0.0 (IQR = 0.0–1.0), poorer FOIS 5.0 (IQR = 2.0–6.0), and lower MNA 16.5 (IQR = 13.0–19.8) in general hospitals. They had, however, a greater improved functional number with 71.0% ≥7, higher percentages of improved ADLs, FOIS, MNA, FMA-motor, MMSE, CCAT, and higher levels of improved anxiety/depression in EQ-5D-3L (**Supplementary Table 3**). In the multivariate logistic regression model in CVA patients within PAC units, improved functional number per item (model 1, **Table 4**, aOR = 1.46; 95% CI = 1.22–1.75; $p < 0.001$), improved functional



Improved functionality in PAC settings

	AUC	(95% CI)	*p* value	Cut-off point	Sensitivity	Specificity	Accuracy	PPV	NPV
Outcome 1	0.743	(0.600-0.885)	< 0.001**	≥5	82.19	65.00	80.90	96.67	22.81
Outcome 2	0.688	(0.618-0.758)	< 0.001**	≥7	70.97	65.00	66.41	38.60	87.84

FIGURE 3 | Outcome prediction assessed by numbers of improved functionality items in the area under the ROC curve (AUC) analysis. **(A)** For primary outcome (1-year mortality or 14-day readmission). **(B)** For secondary outcome (length of hospital stay >42 days). ROC, receiver operating characteristic curve; AUC, area under curve; PAC, post-acute care; CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value. ***p* < 0.01.

numbers (≥7 vs. <7, model 2, **Table 4**, aOR = 4.73; 95% CI = 2.48–9.02; $p < 0.001$), higher FOIS (model 3, **Table 4**, aOR = 2.33; 95% CI = 1.21–4.47; $p = 0.011$), and high MNA (model 3, **Table 4**, aOR = 3.51; 95% CI = 1.44–8.56; $p = 0.006$) were significantly associated with prolonged LOS after adjusting for age, gender, and different items of improved functionality. But in the multivariate logistic regression model on CVA patients with assessments in general hospitals, higher baseline FOIS (model 5, **Table 4**, aOR = 0.81; 95% CI = 0.66–0.999, $p = 0.049$) was significantly associated with reduced LOS after adjusting for age, gender, and different items of functionality.

DISCUSSION

Our principal findings of this retrospective, multi-center cohort of patients with CVA are MMSE being higher after PAC intervention, and that was significantly associated with reduced 1-year mortality or 14-day unplanned hospital readmission. Besides, greater functional improvements, especially ≥5 items, were associated more with the primary outcome. The mortality and 14-day readmission were typically high amongst individuals with low BMI and CVD. Finally, prolonged LOS in PAC settings was correlated with improved FOIS and MNA in the PAC units, whereas better baseline FOIS in the general hospital was significantly associated with reduced LOS.

Post-acute care services are well developed in the United Kingdom and United States, likely to reduce hospital readmission. Taiwan has only started to establish PAC services in 2014 from intermediate care, interchangeable with PAC. The first community hospital-based PAC program was launched in 2007 (Chen et al., 2010), and that was later extended to five major diseases, including CVA, burn injury, fragile fracture, traumatic nerve injury, and frailty. Compatible with several previous reports in Taiwan (Lai et al., 2017; Peng et al., 2017, 2019; Chien et al., 2020), our study provided additional evidence that intervention of the PAC program significantly had improved stroke patients regarding their general condition (MRS), ADLs, IADLs, nutritional status, quality of life, intake condition, balance, speech function, and mental status (MMSE).

In our study, the 1-year mortality rate was 3.7% which was lower than the 30% as reported in the literature (Mar et al., 2015). Age, gender, stroke type, stroke severity, comorbidities, rehabilitation, and social status are known predictors of stroke mortality (Chen et al., 2019). In line with other reports on early stroke disability and long-term mortality (Ganesh et al., 2017; Chen et al., 2019), we also found that baseline and improved MRS scores had predicted the 1-year mortality. Findings highlighted the importance of measuring stroke functional outcomes and suggested that reducing early disability lowers long-term mortality.

The AUC of the ROC curve of the 100-Barthel index score ≥48 for prolonged PAC hospital stay was 0.688 (95% CI = 0.617–0.759,

TABLE 3 | Predictors of 1-year mortality or 14-day readmission outcome in patients with PAC.

	Simple model	Model 1	Model 2	Model 3
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Age	1.05 (1.01–1.09)*	1.01 (0.98–1.05)	1.01 (0.97–1.05)	1.03 (0.98–1.08)
Female vs. male	0.76 (0.28–2.05)			
BMI	0.77 (0.66–0.90)**	0.74 (0.62–0.89)**	0.74 (0.62–0.89)**	0.70 (0.57–0.87)**
Cardiovascular disease	5.14 (1.81–14.62)**	4.90 (1.46–16.41)*	6.36 (1.82–22.19)**	3.53 (0.94–13.33)
ACCI	1.16 (0.95–1.42)			
Improved functional numbers	0.65 (0.54–0.79)**	0.69 (0.55–0.86)**		
Improved functional numbers (≥5 vs. <5)	0.12 (0.04–0.31)**		0.16 (0.05–0.45)**	
Improved functionality				
MRS	0.19 (0.06–0.60)**			0.73 (0.17–3.14)
ADLs	0.11 (0.04–0.28)**			0.52 (0.12–2.28)
IADLs	0.28 (0.09–0.89)*			0.66 (0.16–2.69)
FOIS	0.98 (0.39–2.48)			
MNA	0.47 (0.18–1.21)			
BBS	0.22 (0.08–0.61)**			0.46 (0.10–2.11)
FMA-modified sensation	0.74 (0.27–2.00)			
FMA-motor	0.53 (0.19–1.50)			
MMSE	0.25 (0.09–0.68)**			0.19 (0.05–0.68)*
CCAT	0.35 (0.07–1.71)			

**p < 0.05; **p < 0.001; Model 1: the logistic regression was used to evaluate the association of primary outcome with multivariate analysis among age, body mass index (BMI), cardiovascular disease (CVD), and numbers of functional improvement in patients with post-acute care (PAC). Model 2: the logistic regression was used to evaluate the association of primary outcome with multivariate analysis among age, BMI, CVD, and categorized functional improvement in patients with PAC. Model 3: the logistic regression was used to evaluate the association of primary outcome with multivariate analysis among age, BMI, CVD, and different functional improvement in patients with PAC.*

ACCI, age-adjusted Charlson Comorbidity Index; MRS, Modified Rankin Scale; ADLs, activities of daily living; IADLs, instrumental activities of daily living; FOIS, Functional Oral Intake Scale; MNA, Mini-Nutritional Assessment; BBS, Berg Balance Scale; FMA, Fugl-Meyer Assessment; MMSE, Mini-Mental State Examination; CCAT, Concise Chinese Aphasia Test.

$p < 0.001$). This showed its predictive value in the prognosis of acute CVA patients, a finding that is consistent with previous studies (Wade and Hewer, 1987; Martinsson and Eksborg, 2006; Lee et al., 2013; Li Q. X. et al., 2020). Results above suggest that the mortality of stroke patients is closely related to physical dependence, and that better basic care should be provided to stroke patients to reduce their mortality especially within a year after stroke onset. However, if the scale evaluation of daily activity function turns out to be unstable, prospective studies for several days or longer are needed to verify the findings.

Due to inactivity, diseases could worsen, and the ability of body balance often is impaired among older people. The impairment might lead to dramatic consequences such as dependency on ADLs, admission to nursing homes, falls and fractures, and even mortality (Conradsson et al., 2007; Keevil et al., 2018). We found that the BBS in the death group was significantly different from that in the survival group. The AUC of the ROC curve of the BBS scoring ≥37 for prolonged PAC hospital stay was 0.637 (95% CI = 0.562–0.711, $p = 0.001$). This showed its predictive value in the prognosis of acute stroke patients and suggested that training of static and dynamic balance control is of great importance in rehabilitation for old people.

After a stroke, cognitive impairment is common, ranging from 11.6 to 56.3% among hospital-based studies (Patel et al., 2002; Zietemann et al., 2018). Pre-stroke, any post-stroke, and new-onset post-stroke dementia is consistently related to poor survival. Cognitive impairment as measured by MMSE is associated with impaired survival up to 4-year follow-up, although two shorter studies of 1-year reported that MMSE is not an independent predictor of survival (Patel et al., 2002; Zietemann et al., 2018). Our present findings are in line with those findings on the association of global MMSE with survival. This means that patients with mild stroke executive dysfunction might be present. Even motor difficulties and management of basic daily tasks are minimal. Patients may have more difficulty performing complex activities. Therefore, accurate and appropriately timed assessment is essential. Related to this, we found that improvement of MRS, balance test, ADLs/IADLs, and MMSE scores were associated with reduced readmission risk.

In our study, the mortality in stroke patients with CVD was higher than in previous reports. We also found that those with lower BMI had higher 1-year mortality, whereas those with a higher BMI had lower 1-year mortality. Our result is consistent with a previous follow-up study (Ryu et al., 2011), in which the all-cause mortality rate is inversely related to BMI in patients with ischemic stroke. Low baseline BMI could reflect low muscle mass and malnutrition (Kimura et al., 2017), of which are detrimental to stroke patients (Kawase et al., 2017). Stroke patients with low BMI at admission might also not recover well with general hospital diets. They are therefore more likely to show post-stroke complications. It was thus suggested that underweight ischemic stroke patients should receive appropriate management, including nutrition and rehabilitation.

In our study, the 14-day readmission rate in acute stroke patients after the PAC program was 4.9%. This proportion created a significant burden on the healthcare system, and that is an important target for quality improvement efforts (Lichtman et al., 2010; Wen et al., 2018; Keawpugdee et al., 2021). Known common causes of readmission are their age and comorbid history of coronary heart disease, heart failure, renal disease, respiratory disease, peripheral arterial disease, and diabetes. Regarding stroke-related factors, LOS was associated with

TABLE 4 | Predictors of length of stay in patients with PAC.

	Simple mode	Model 1	Model 2	Model 3	Model 4
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Age	1.00 (0.98–1.02)	1.01 (0.99–1.03)	1.01 (0.99–1.03)	1.01 (0.98–1.03)	1.00 (0.98–1.03)
Female vs. male	1.91 (1.07–3.42)*	1.67 (0.90–3.07)	1.67 (0.90–3.10)	1.72 (0.88–3.36)	1.86 (0.84–4.13)
BMI	1.02 (0.94–1.10)				
Assessment in general hospital					
MRS	3.46 (1.50–7.96)**				2.21 (0.69–7.03)
ADLs	0.97 (0.96–0.99)**				1.00 (0.97–1.03)
IADLs	0.71 (0.53–0.95)*				0.86 (0.60–1.23)
FOIS	0.84 (0.73–0.96)*				0.81 (0.66–0.999)*
MNA	0.91 (0.86–0.97)**				0.97 (0.88–1.06)
Improved functional numbers	1.46 (1.22–1.75)**	1.46 (1.22–1.75)**			1.49 (1.17–1.89)**
Improved functional numbers (≥7 vs. <7)	4.54 (2.44–8.44)**		4.73 (2.48–9.02)**		
Improved functionality					
MRS	1.03 (0.58–1.83)				
ADLs	7.04 (1.65–30.07)**			5.60 (0.69–45.24)	
IADLs	1.30 (0.73–2.33)				
FOIS	3.12 (1.72–5.68)**			2.33 (1.21–4.47)*	
MNA	3.57 (1.71–7.43)**			3.51 (1.44–8.56)**	
BBS	1.53 (0.60–3.88)				
FMA-modified sensation	1.61 (0.89–2.88)				
FMA-motor	2.72 (1.16–6.38)*			1.83 (0.68–4.90)	
MMSE	2.41 (1.07–5.42)*			1.80 (0.74–4.38)	
CCAT	1.68 (0.78–3.63)				

**p* < 0.05; ***p* < 0.001; *Model 1: the logistic regression was used to evaluate the association of secondary outcome with multivariate analysis among age, gender, and numbers of functional improvement in patients with post-acute care (PAC). Model 2: the logistic regression was used to evaluate the association of secondary outcome with multivariate analysis among age, gender, and categorized functional improvement in patients with PAC. Model 3: the logistic regression was used to evaluate the association of secondary outcome with multivariate analysis among age, gender, and different functional improvement in patients with PAC in the PAC units. Model 4: the logistic regression was used to evaluate the association of secondary outcome with multivariate analysis among age, gender, and different baseline functional assessment of patients in the general hospital.*

MRS, Modified Rankin Scale; ADLs, activities of daily living; IADLs, instrumental activities of daily living; FOIS, Functional Oral Intake Scale; MNA, Mini-Nutritional Assessment; BBS, Berg Balance Scale; FMA, Fugl-Meyer Assessment; MMSE, Mini-Mental State Examination; CCAT, Concise Chinese Aphasia Test.

a higher readmission rate, followed by bowel incontinence, feeding tube, and urinary catheter (Rao et al., 2016). In addition, social, financial factors, discharge location/need for nursing care, advanced age, poor post-stroke physical functioning also contributed to readmission risk in these patients (Lichtman et al., 2010).

As improved MRS, ADLs, IADLs, BBS, and MMSE can all reduce the risk of readmission, a routine plan with a continuous rehabilitation process is needed before discharge. Many factors influence subacute rehabilitation LOS, including stroke severity measured with the National Institute of Health Stroke Scale (NIHSS), ability to perform ADLs, or admission Functional Independence Measure (FIM) score (Garcia-Rudolph et al., 2020). This study showed that in the general hospital setting, CVA patients with higher baseline MRS, lower ADLs/IADLs, poorer FOIS, and MNA had longer LOS in PAC units. It was speculated that the more severe dysfunction was, the more complicated the rehabilitation process became, thus prolonging LOS. However, it should be noted that the greater the PAC LOS, the greater the number of improved rehabilitation assessments. The situation is similar to a previous study in Taiwan showing post-stroke patients having longer stay in a PAC institution have superior ADL function, balance and coordination, walking speed, and upper-limb dexterity and sensory function (Tung et al., 2021). Despite an upper limit in the PAC payment for LOS, it was suggested that the disability status of patients should be taken into account in planning PAC with preset rehabilitation goals (Tan et al., 2009, 2010).

Our findings that for prognostic prediction, larger numbers of improved assessment tools had discriminating power better than a single parameter are likely related to the following issues. First, patients with varying severity, different stroke subtype, and risk factors experience different recovery courses that plateau at different levels and times. This may limit the clinical utility of predictiveness in cases based on one characteristic variable at a specific time point, such as stroke severity at the onset of stroke. Therefore, using a combined patient-specific predictive model, one can generate individualized recovery profiles, assisting in tailored discharge planning for stroke survivors. Overall, we used a comprehensive statistical approach for data analysis to demonstrate the relationship between various rehabilitation tools and outcomes after PAC program in acute stroke patients for predicting clinical outcomes. Such prognostic information is important for clinicians, stroke survivors, and their carers.

There were several limitations in this study. First, this was a retrospective and single medical center-based study which would limit the generalization of results to the whole Taiwanese or the global population. Second, this study involved many PAC institutions, and some data bias can be introduced. For example, data were recorded by different personnel, and the efficacy of training was likely non-uniform among participants. Third, not all comorbidities were recorded, and thus only some possible factors were analyzed. Finally, the measurement scales used in our PAC might have inherent limitations. For example, the 6-min walking test cannot represent cardiopulmonary capacity in those bedridden patients. However, despite this, by combining various rehabilitation parameters, mortality and readmission in patients with stroke can be better predicted.

CONCLUSION

The PAC rehabilitation unit was beneficial for patients with acute strokes in terms of not only improvement in ADL function but also in the quality of life and balance function. Higher baseline and greater improvement of physical and cognitive function were significantly associated with less 1-year mortality and 14-day hospital readmission. The improved ADLs, FOIS, MNA, FMA-motor, and MMSE scores were related to LOS during PAC. Through classification by combined functional assessments, clinical outcomes can be better predicted. It is suggested that stroke patients with such conditions require better intensive care and risk-factor control at deciding discharge times for outcome improvements.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Institutional Review Board of Taichung Veterans General Hospital (No. CE21441B). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

S-CW: conceptualization, investigation, formal analysis, and writing – original draft. C-YH: data curation, formal analysis, and investigation. C-CS, J-AH, and P-LC: conceptualization, investigation, and funding acquisition. S-YL: conceptualization, investigation, formal analysis, writing – review and editing, and supervision. All authors reviewed and approved the manuscript prior to submission.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2022.834273/full#supplementary-material

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Sex dimorphism in isoproterenol-induced cardiac damage associated neuroinflammation and behavior in old rats

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Acute cardiac damage can be induced by isoproterenol injections in animals. The associated inflammatory response could be reflected in the brain as neuroinflammation, with potential consequences for brain function and behavior. Although cardiac responses are reported age and sex-related, for neuroinflammation and brain function this is virtually unknown. Therefore, cardiac damage and its consequences for neuroinflammation, brain function and behavior were compared in aged male and female rats. Wistar rats of 24 months of age were treated with isoproterenol (ISO, twice s.c.) or saline. Four weeks after injections, exploratory behavior and short-term memory were tested. Then, rats were sacrificed. Hearts were collected to measure cardiac damage. Brain tissue was collected to obtain measures of neuroinflammation and brain function. In male-, but not in female rats, ISO induced significant cardiac damage. Accordingly, mortality was higher in males than in females. Baseline hippocampal microglia activity was lower in females, while ISO induced neuroinflammation in both sexes, Hippocampal brain-derived neurotrophic factor expression appeared lower in females, without effects of ISO. In the open field test, ISO-treated males, but not females, displayed anxiety-like behavior. No effects of ISO were observed on short-term memory in either sex. In conclusion, sex dimorphism in effects of ISO was observed for cardiac damage and open field behavior. However, these effects could not be related to differences in hippocampal neuroinflammation or neuronal function.

KEYWORDS

advanced age, sex dimorphism, isoproterenol, cardiac damage, short-term memory, open field exploration, neuroinflammation, brain derived neurotrophic factor

Introduction

Acute sympathetic stress is associated with overactivation of the sympathetic nervous system, evoking inflammation and increased cytokine production in the heart, resulting in cardiac damage and consequently cardiac dysfunction (Alemasi et al., 2019). Although these cardiac effects are extensively investigated, effects on other organs, including the brain, are far less known. However, the peripheral inflammatory response could well be reflected in the brain as neuroinflammation (Quan, 2014; Gouweleeuw et al., 2017), and depending on the affected brain area, may result in behavioral changes associated with mood and cognition. Moreover, sex-differences were observed for depression as well as cognitive decline (Eastwood et al., 2012; Deckers et al., 2017). Finally, mental problems in cardiovascular disease are not harmless, as they are associated with increased morbidity and mortality (Meijer et al., 2013).

Acute administration of high dose of beta-receptor agonist isoproterenol (ISO) was used to mimic the clinical condition of acute sympathetic stress (Beznak and Hacker, 1964; Nichtova et al., 2012; Adamcova et al., 2019). ISO, administered twice with 24h in between, evoked inflammation and increased cytokine production resulting in cardiac fibrosis (Adamcova et al., 2019; Alemasi et al., 2019), that over a period of weeks developed into left ventricular hypertrophy and dilatation, and ultimately heart failure (Nichtova et al., 2012). In young male rats, this process was associated with reduced exploratory behavior (Tkachenko et al., 2018), depressive-like behavior (Hu et al., 2020) and cognitive decline (Ravindran et al., 2020).

Cardiac effects of ISO were shown dependent on age (Wexler, 1978; Woulfe et al., 2018) and sex (Wexler and Greenberg, 1979) of the animals. Mortality in old males was substantially higher than in young males (Wexler, 1978), while pathophysiology of cardiac damage also differed significantly (Wexler, 1978). In a study comparing adult male and female rats, female rats showed better survival and lower cardiac damage than males (Wexler and Greenberg, 1979). Moreover, gonadectomized adult male and female rats showed better survival and superior repair of their damaged hearts compared to their intact sex-matched controls (Wexler and Greenberg, 1979), supporting an important role of sex hormones. Although authors measured several circulating substances, including adrenocortical hormones, they did not investigate changes in the brain nor behavioral consequences. Behavioral studies, to our knowledge, were only performed in (according to their body weights < 300 g) young male rats (Tkachenko et al., 2018; Hu et al., 2020; Ravindran et al., 2020). Therefore, in the present study, effects of isoproterenol on the heart, neuroinflammation, neuronal function and aspects of behavior were compared in old male and female rats. We hypothesized that the inflammatory response due to high dose of isoproterenol would be reflected in the brain as neuroinflammation, resulting in altered neuronal function with behavioral consequences. Since sex dimorphism is reported for the response on isoproterenol, we anticipate different cardiac and brain responses in old male versus female rats.

Materials and methods

Subjects

Twenty-one male and twenty-two female Wistar rats of 24 months age were recruited from our own breeding colony (Semmelweis University, Budapest Hungary). Rats were group housed in a conventional animal facility (22 ± 2°C and humidity of 50 ± 10%). Light was provided from 6 a.m. to 6 p.m. CEST. Standard rodent chow (LT/R, Innovo Ltd., Gödöllõ, Hungary) and tap water were provided *ad libitum*. In case of male rats, 3 rats had to be housed individually due to aggressive behavior. Cleaning of the cages took place 2–3 times per week and was done by an animal caretaker. Bodyweight was measured twice a week. Experimental protocols were approved by the local animal committee of the University of Physical Education, Budapest, Hungary.

Experimental groups and protocol

Male (n = 21) and female rats (n = 22) were randomly divided into two groups regarding type of intervention. ISO groups (11 males and 12 females) received 70 mg/kg isoproterenol dissolved in 1 ml/kg saline, control groups (10 males and 10 females) were given 1 ml/kg saline (Toth et al., 2021). Although usually a higher dosage of ISO is used, 85–100 mg/kg, the 70 mg/kg dose was chosen to balance reliable studying effects of ISO and bias because of too high mortality (Toth et al., 2021). Substances were administered on two consecutive days with 24 h in between via subcutaneous injection (Ravindran et al., 2020). This resulted in 21 (10 saline + 11 ISO) females and 22 (10 saline + 22 ISO) male rats.The experimental protocol is summarized in **Figure 1**. Male and female 24 months old rats were injected with isoproterenol (ISO) or saline, twice with 24 h in between. Four weeks later, behavioral testing was performed, and rats were subsequently sacrificed to collect heart and brain tissue.

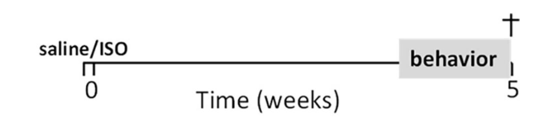

FIGURE 1
Experimental protocol. ISO, isoproterenol.

Behavior

Different aspects of behavior were assessed. Exploratory behavior and anxiety were tested in the open field. Effects on cognition were obtained from short-term memory in the novel object recognition test and the novel location recognition test. All tests were recorded with a digital video camera on memory card. Tests started 4 weeks after ISO/saline intervention.

Open field exploration test

For the open field test (OF), rats were placed in a round shaped arena (diameter of 80 cm), that was divided into an inner circle (diameter of 32 cm; center area), and an outer wall area. Rats were given 5 min to freely explore it. After removal of the animals, the arena was cleaned with 70% ethanol. Video recordings were analyzed with Eline software (University of Groningen, Netherlands). The time spent in the center and outer wall areas and number of entering of these areas were measured. More time spent in the wall area and less visits to the center area were regarded a measure for anxiety-related behavior, while total number of movements were seen as exploratory behavior.

Novel object- and novel location recognition tests

Effects on cognitive performance were tested using the short-term memory test of object and location. The two memory tests were combined in one protocol (Toth et al., 2021) and took place in a black box of 45*55*50 cm. The animal was placed in the box and stayed there for the whole test procedure. Two sets of objects with similar size, weight and shape were used. Animals were unable to replace and/or move the objects. The two sets were randomly rotated through the procedures. Rats were allowed 3 min to explore the box. Then, two identical objects were placed far apart into the arena. After again 3 min the objects were removed, cleaned and after 1 min, one familiar and one novel object were placed back at the same positions as previously; the novel object recognition test (NOR). Again, after 3 min objects were removed, cleaned, and after 1 min the objects were reintroduced with one object placed at a new location on the opposite site of the box; the novel location recognition test (NLR). The test was ended 3 min after exploration of the last setting. Arena and objects were cleaned with 70% ethanol after each animal. Video recordings were analyzed with Eline software (University of Groningen, Netherlands). Time spent exploring the objects was measured. Preference for the novel object or familiar object on a novel place was calculated as time spent on the novel or relocated objected divided by time spent exploring both objects. Data of rats that showed no interest in the objects were omitted from further analyses of these tests.

Tissue collection and processing

At the end of the experiment rats were terminally anaesthetized with 6% sodium pentobarbital solution injected intraperitoneally (2 ml/kg) and perfused with heparinized (1 ml/l) 0.9% saline via the heart, in order to remove blood. Heart and brain tissues were dissected, and fixated in 4% buffered formaldehyde freshly depolymerized from paraformaldehyde. After 4 days, tissue was washed in 0.01 M phosphate buffered saline (PBS), dehydrated using a 30% sucrose solution, and subsequently quickly frozen in liquid nitrogen and stored at −80°C. From the brain, coronal sections (25 μm) were cut and stored as free-floating sections in 0.01 M PBS containing 0.1% sodium azide at 4°C, till processing for immunohistochemical staining to visualize microglia or brain derived neurotrophic factor expression. Transvers sections (25 μm) of heart tissue at mid-ventricular level were paced on glass immediately after cutting, and processed for histochemical staining to measure collagen levels.

(Immuno)histochemistry

Microglia

To visualize microglia, immunohistochemical staining of ionized calcium binding adaptor molecule 1 (IBA-1) was performed, as described in detail previously (Hovens et al., 2014a). Briefly, sections were incubated with 1:2,500 rabbit-anti IBA-1 (Wako, Neuss, Germany), followed by incubation with 1:500 goat-anti rabbit secondary antibody (Jackson, Wet Grove, United States). After incubation with avidin-biotin peroxidase complex (Vectastain ABC kit, Vector, Burlingame, United States), labeling was visualized by diaminobenzidine (DAB). Sections were mounted onto glass slides. Photographs were taken from the prefrontal cortex-PrL (PFC) and the dorsal hippocampus (DH; CA1, CA3, Dentate Gyrus and Hilus areas) at 200 times magnification. Microglia morphology was analyzed by image analyses (Image Pro plus, United States), according to our previous publication (Hovens et al., 2014a), regarding coverage, density, cell size, cell body area and processes area. Microglia activity was calculated as cell body area/total cell size. Values for the overall dorsal hippocampus were obtained from the average of the values of the different hippocampal areas.

Brain-derived neurotrophic factor

Brain Derived Neurotrophic Factor (BDNF) antibody was used to obtain BDNF expression in the PFC and the different areas of the DH; CA1, CA3, Dentate Gyrus and Hilus. Sections were incubated with this first antibody with 1:1,000 dilution (Alomone Labs, Israel), followed by the incubation with 1:500 goat-anti rabbit secondary antibody (Jackson, Wet Grove, United States). Similar to IBA-1, sections were incubated with avidin-biotin peroxidase complex and were visualized by DAB.

BDNF expression was measured as corrected optical density (Image-J) compared to an underlying reference area was used as final outcome measure (Hovens et al., 2014b).

Cardiac collagen

Heart sections were stained with Sirius red (Sigma-Aldrich) and fast green as counterstaining (Hovens et al., 2016). Percentage collagen was used to measure cardiac damage. Color pictures were taken (20×) to visualized the whole left ventricle. Image analysis (Image Pro plus, United States) was used to measure the collagen positive (red) area and was expressed as percentage of total left ventricular tissue area.

Data analysis

Data are presented as mean ± standard error of the mean (S.E.M), unless indicated otherwise. Results outside twice the standard deviation of its group were considered outliers and were excluded before analyses (maximally 2 per experimental group). Results were compared using two-way analysis of variance (ANOVA) with least square difference (LSD) *post-hoc* test, with male/female and saline/ISO as factors. Association between selected parameters were analyzed with Pearson linear correlation. For the NOR/NLR tests, outcomes were also tested against change level (= 50%), using a single sample *t*-test. *P*-values of < 0.05 were considered statistically significant and presented as * or $^{\#}$. Potentially relevant tendencies ($p < 0.1$) were mentioned as well.

Results

General

For this experiment 21 male and 22 female Wistar rats were used. From the 11 injected male rats, 4 died within the first 24 h following the first injection and 2 additional premature death occurred later. From the 12 injected female rats, 2 died after the first injection, which this was similar to the spontaneous death in both control saline-treated groups (2 out of 10 rats each).

Male rats weighed significantly more than female rats ($p < 0.001$), irrespective of treatment. Whereas relative heart weight appeared slightly higher in females than in males ($p = 0.060$), relative brain weight was significantly higher in females (Table 1). No significant effects of ISO, nor interaction between sex and treatment were observed.

Cardiac collagen

Percentage of collagen in the left ventricle at midventricular levels was obtained to measure cardiac damage. Figure 2 illustrates collagen deposition (red) in saline and ISO treated male rats. According to the two-way ANOVA statistics, a significant effect of male/female, saline/ISO, as well as an interaction effect could be observed. However, in more detail (*post hoc* analyses), saline treated males did not differ from saline treated females, and ISO only increased collagen in male rats.

Neuroinflammation

Neuroinflammation was measured as microglia activity, obtained from morphological changes. In the prefrontal cortex, no sex-related differences, nor effects of ISO were observed in microglia activity (Figure 3A). In contrast, in the hippocampus, female rats had significantly lower microglia activity than males; significant sex-effect. Also, a significant effect of ISO was seen, which was most pronounced in female rats (Figure 3B).

Results in the hippocampus have been studied in more detail regarding the different hippocampal areas. Effects of overall hippocampal microglia activity (Figure 3B); significant sex differences and significant effects of ISO, were best reflected in the CA3 area (Figure 4 top pictures and panel Figure 4B), whereas in the other areas (Figures 4A,C,D), sex differences (significant) were more prominent than potential effects of ISO (non-significant) (Figure 4), with no interaction between these factors.

The underlying morphologic parameters of the microglia in these areas are presented in Table 2. In most areas, significant differences were observed between the sexes and/or ISO or saline treatment (two-way ANOVA), but no interactions between these factors were found. In all, but the Hilus, ISO increased the microglia cell body size in male as well as in female rats. Although in these areas processes size was consistently lower after ISO, it did not reach statistical significance. In the CA3, females showed lower density and larger microglia compared to male rats; the latter attributable to increased processes.

Neuronal function

Brain-derived neurotrophic factor (BDNF) expression was used as an indicator for neuronal function in the prefrontal cortex and hippocampus. Whereas in the prefrontal cortex, a tendency for declined expression in ISO treated rats was observed ($p = 0.068$), in the dorsal hippocampus, females showed a significantly lower BDNF expression than male rats. When looked into more detail to the different hippocampal areas (Figure 5), the above tendency was substantiated in all but the Hilus area.

Behavior

Effects on behavior were studied using exploration in the OF test and short-term memory in the NOR and NLR

TABLE 1 Bodyweight at sacrifice and relative organ weight in the experimental groups.

	Male saline (n = 8)	Male ISO (n = 5)	Female saline (n = 6)	Female ISO (n = 10)
Body weight (g)	438 ± 33	416 ± 37	**289 ± 12***	**276 ± 14***
Heart weight (%body weight)	0.33 ± 0.03	0.35 ± 0.04	0.38 ± 0.01	0.40 ± 0.02
Brain weight (%body weight)	0.50 ± 0.04	0.52 ± 0.05	**0.69 ± 0.02***	0.63 ± 0.07

ISO = isoproterenol. *Significant difference between corresponding female and male groups ($p < 0.05$). Bold values refer to statistically significant effects.

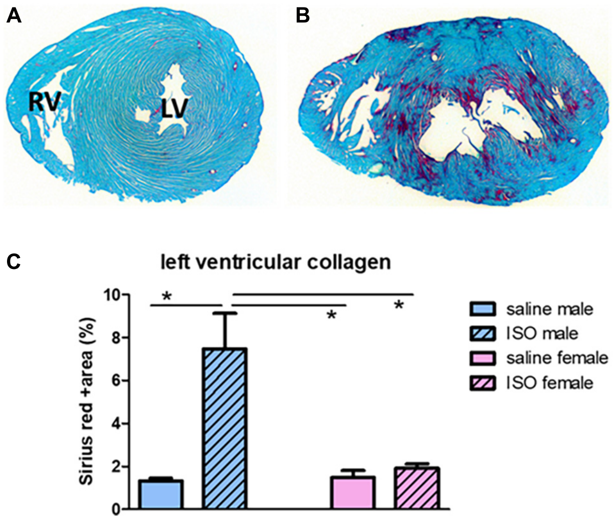

FIGURE 2
Illustration of transversal sections of the heart with Sirius red staining of cardiac collagen. Upper part shows the result of collagen staining (red) in a saline treated male rat **(A)** and an ISO treated male rat **(B)**. LV, left ventricle; RV, right ventricle. Lower graph **(C)** actual measurements of collagen percentage in the different experimental groups. ISO, isoproterenol. *Significant difference between indicated groups ($p < 0.05$).

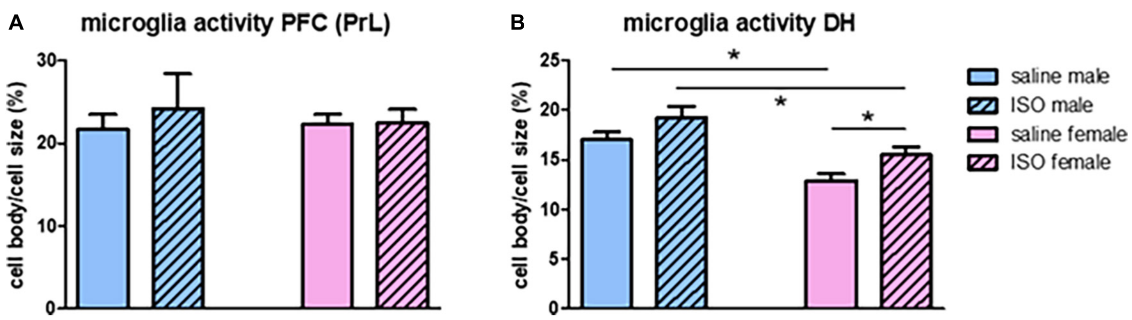

FIGURE 3
Microglia activity in the prefrontal cortex (PFC; **A**) and the dorsal hippocampus (DH; **B**) in the different experimental groups (n = 8,5,7,10 in saline male, ISO male, saline female and ISO female rats, respectively). ISO, isoproterenol. *Significant difference between indicated groups.

tests. In the OF, time spent at the wall showed significant sex differences; male rats spent more time in this area (Figure 6A). Similarly, male rats paid significantly less visits to the center area (Figure 6B). No significant effects of ISO were observed. However, a significant interaction between the two factors, sex and treatment, for both parameters indicated that male rats became more anxious after ISO, whereas females did not.

For the NOR/NLR tests, data of several rats had to be excluded as these rats did not show interest in the objects, resulting in reduced numbers of rats per group with high variation (Table 3). Consequently, results from these short-term memory tests did not reveal any statistical effects of sex and/or ISO, nor interaction (Table 3). In fact, only female rats with ISO treatment performed significantly about chance level in the NOR test (indicated by #).

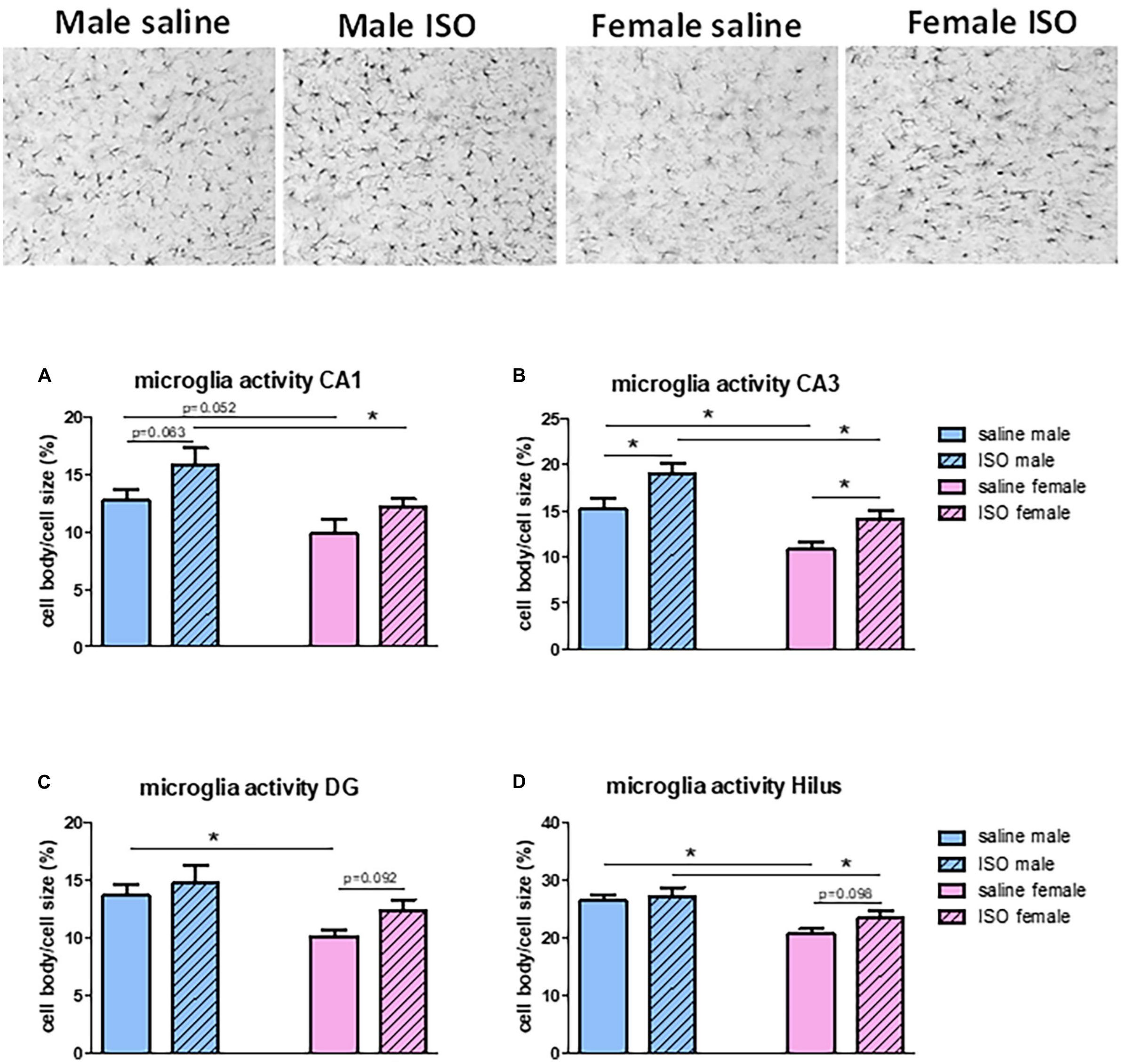

FIGURE 4
Top: typical pictures of microglia in the hippocampal CA3 area of rats from the different experimental groups (200×). **(A–D)** Measurements of microglia activity in the different areas of the hippocampus, CA1, CA3, dentate gyrus (DG) and Hilus, in the different experimental groups (n = 8,5,7,10 in saline male, ISO male, saline female and ISO female rats, respectively). ISO, isoproterenol. *Significant difference between indicated groups. Relevant tendencies with $p < 0.1$ are presented as well.

Discussion

General

Acute sympathetic stress in patients can be mimicked by high dose of isoproterenol in rats. Animal studies indicated age- and sex associated peripheral effects. The isoproterenol-associated peripheral inflammatory response could be reflected in the brain as neuroinflammation with consequently behavioral changes. So far behavioral changes are only sparsely investigated, and only in young male rats. Therefore, the aim of the present study was to investigate effects of isoproterenol in old male and female rats, regarding survival, cardiac damage, neuroinflammation, neuronal function and behavior.

Main findings were that aged male rats suffer more from ISO than old female rats. Male rats showed higher mortality, more cardiac damage and more anxiety/depressive-like behavior after ISO. Baseline hippocampal microglia activity and brain function were lower in females than in males. ISO induced significant neuroinflammation, but that appeared most pronounced in female rats. ISO did not distinguish between the sexes regarding neuronal function. In conclusion, indeed sex dimorphic effects

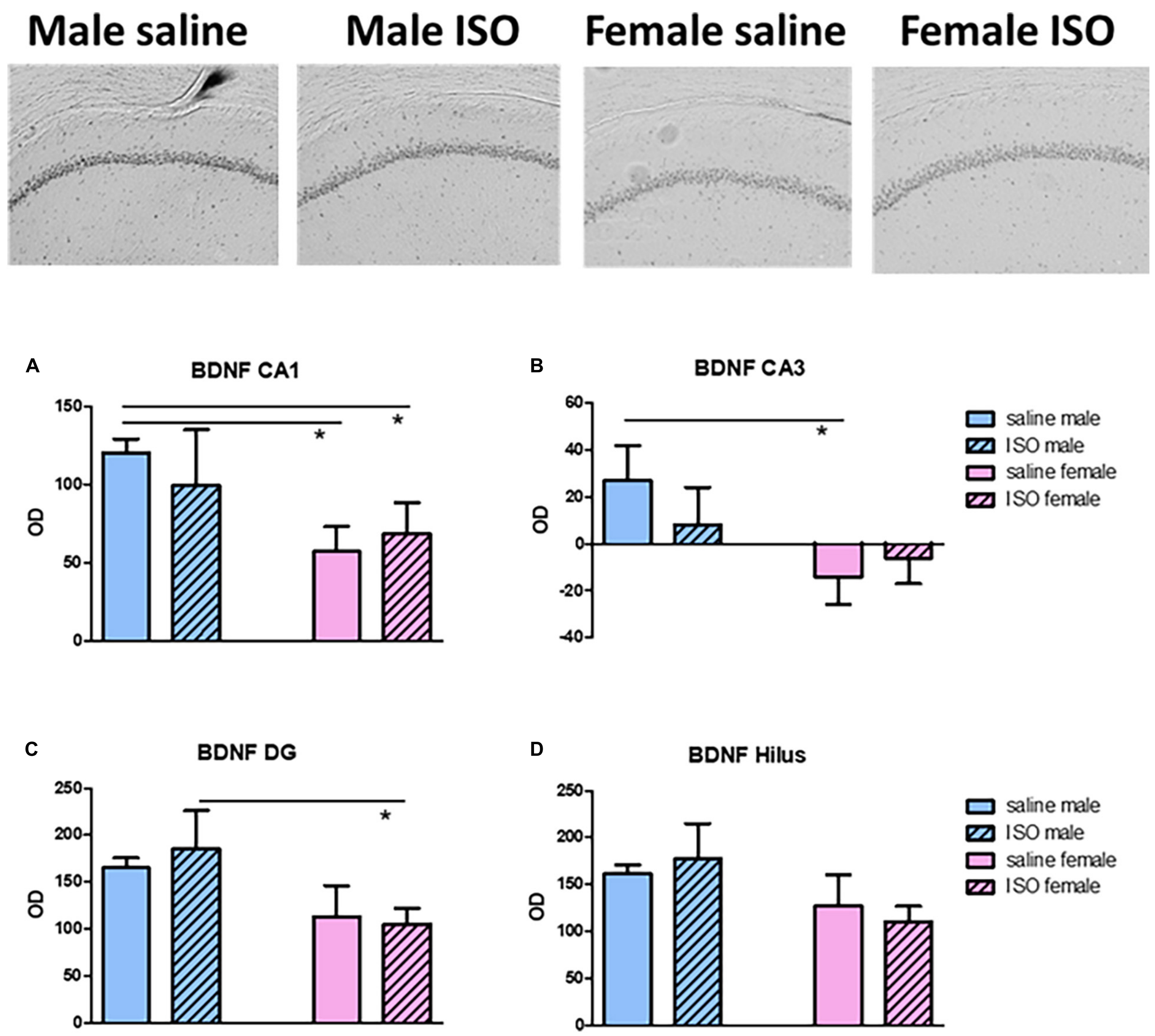

FIGURE 5
Top: typical pictures of the Brain-derived neurotrophic factor (BDNF) staining in the CA1 area of the different experimental groups. **(A–D)** BDNF expression, expressed as relative optical density (OD), in the different areas of the hippocampus, CA1, CA3, dentate gyrus (DG) and Hilus, in the different experimental groups (*n* = 8,5,6,10 in saline male, ISO male, saline female and ISO female rats, respectively). ISO, isoproterenol. *Significant difference between indicated groups.

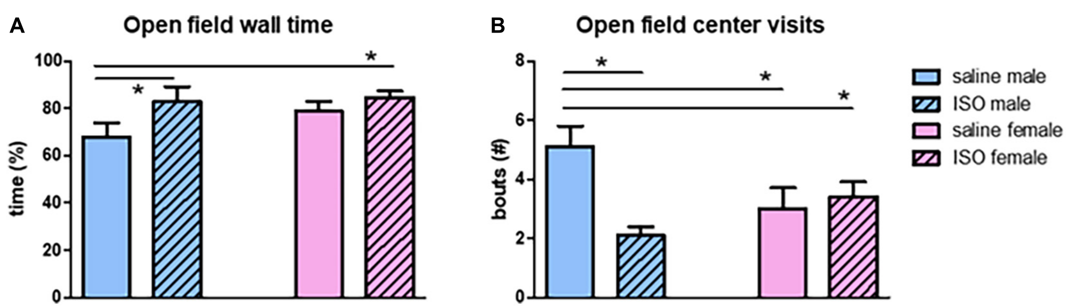

FIGURE 6
Behavior in the open field test in the different experimental groups (*n* = 8,7,7,10 in saline male, ISO male, saline female and ISO female rats, respectively). ISO, isoproterenol. *Significant difference between indicated groups ($p < 0.05$). **(A)** Time spent at the wall; **(B)** number of visits to the center.

TABLE 2 Morphological parameters of microglia in the different hippocampal areas, CA1, CA3, dentate gyrus (DG) and Hilus, in the different experimental groups.

Experimental group/Brain area	Male saline (n = 8)	Male ISO (n = 5)	Female saline (n = 7)	Female ISO (n = 10)
CA1				
Density (#/area)	46.9 ± 2.7	49.5 ± 2.5	40.2 ± 3.2	42.8 ± 2.0
Coverage (%)	12.1 ± 0.4	11.9 ± 0.9	13.5 ± 0.8	12.5 ± 0.5
Cell size (pixel)	2,896 ± 422	2,543 ± 284	3,702 ± 424	3,096 ± 222
Cell body size	317 ± 7	**363 ± 6***	318 ± 13	**343 ± 6***
Processes size	2,580 ± 425	2,180 ± 286	3,384 ± 422	2,753 ± 220
CA3				
Density (#/area)	59.4 ± 3.9	62.6 ± 1.8	**50.0 ± 3.2#**	**52.2 ± 2.4#**
Coverage (%)	11.9 ± 4.1	11.7 ± 6.9	13.1 ± 7.0	12.5 ± 5.4
Cell size (pixel)	2,139 ± 208	1,896 ± 77	**2,900 ± 140#**	**2,512 ± 197#**
Cell body size	299 ± 6	**349 ± 5***	294 ± 12	**326 ± 4*#**
Processes size	1,840 ± 210	1,547 ± 79	**2,606 ± 144#**	**2,186 ± 198#**
DG				
Density (#/area)	55.7 ± 3.1	54.3 ± 1.8	48.8 ± 1.7	51.5 ± 2.4
Coverage (%)	14.4 ± 1.2	13.5 ± 0.8	15.1 ± 0.6	14.1 ± 0.4
Cell size (pixel)	2,964 ± 632	2,583 ± 243	3,284 ± 202	2,894 ± 216
Cell body size	312 ± 6	**346 ± 8***	300 ± 9	**329 ± 4***
Processes size	2,651 ± 633	2,238 ± 244	2,985 ± 201	2,565 ± 217
Hilus				
Density (#/area)	101.5 ± 5.8	97.7 ± 5.7	86.5 ± 4.5	93.3 ± 3.9
Coverage (%)	12.8 ± 0.5	12.8 ± 0.9	13.4 ± 0.6	13.5 ± 0.5
Cell size (pixel)	1,294 ± 36	1,319 ± 38	**1,586 ± 56#**	1,487 ± 91
Cell body size	333 ± 6	353 ± 17	316 ± 11	331 ± 4
Processes size	961 ± 38	966 ± 40	**1,269 ± 54#**	1,156 ± 90

ISO, isoproterenol. *Significant effect of ISO compared to sex-matched saline ($p < 0.05$). #Significant difference between sexes with the same treatment (ISO/saline) ($p < 0.05$). Bold values refer to statistically significant effects.

TABLE 3 Outcome of short-term memory tests in the different experimental groups.

	Male saline	Male ISO	Female saline	Female ISO
Novel object preference (%)	62 ± 7 (n = 8)	78 ± 18 (n = 4)	63 ± 13 (n = 7)	63 ± 3 (n = 6)#
Novel location preference (%)	51 ± 10 (n = 6)	72 ± 10 (n = 5)	67 ± 11 (n = 7)	63 ± 10 (n = 9)

ISO, isoproterenol. #Significantly different from change level (= 50%); $p < 0.05$.

of ISO were observed, with old male rats being more susceptible than old females. However, these sex dimorphic ISO effects seemed not reflected in differences in neuroinflammation or brain function.

Effects of isoproterenol in aged rats

In 24 months old male rats, but not in female rats, ISO induced cardiac fibrosis, as seen by the increased collagen percentage 5 weeks later. The mechanism underlying the ISO-induced cardiac damage is widely investigated (reviewed by Nichtova et al., 2012). Briefly, ISO increased heart rate and contractility, causing an imbalance between oxygen demand and consumption, thereby irreversibly damaging cardiomyocytes. This process evokes wound healing and scar formation, with increased levels of cytokines (Alemasi et al., 2019), ultimately resulting in cardiac hypertrophy and heart failure. In the present study, only old rats have been included, hampering direct comparison with younger ones to establish an age effect. For the latter we have to rely on comparing present results to those obtained in our studies in adult 12 months old male (Toth et al., 2021) and female rats (under review for publication), showing that ISO caused significant cardiac damage in both male and female rats. Although in the 12 months old male rats, microglia morphology suggested ISO-induced hippocampal neuroinflammation, BDNF expression was not affected, and OF behavior even suggested lower anxious/depressive-like behavior, suggesting interaction between the time courses of age-related and ISO-related processes. The increased cytokine levels may be reflected in the brain as neuroinflammation. Several studies support the release of proinflammatory cytokines shortly after ISO treatment (Alemasi et al., 2019; Li et al., 2021; Al-Botaty et al., 2022). Moreover, the cytokines that appeared increased in plasma after ISO, TNFα, IL6, and IL1β (Li et al., 2021), are also the ones shared between depression and heart failure (Pasic et al., 2003). Specifically, TNFα may play a role in leakage of the blood brain barrier (Liu et al., 2013; Al-Botaty et al., 2022). Although this short-term inflammatory response may subsequently subside, its reflection in the microglia in the brain may be prolonged as neuroinflammation. Indeed, in the present study, ISO induced hippocampal neuroinflammation 5 weeks later. A direct effect of beta-adrenergic stimulation on microglia priming has been demonstrated (Johnson et al., 2013), but effects that persists for weeks after acute peripheral ISO administration has not been reported before. No significant effects of ISO were demonstrated on BDNF expression, indicating no effect on neuronal function. In the behavioral tests, specifically male ISO-treated rats may become more anxious. Similarly, depressive-like behavior was reported 7 weeks after ISO (Hu et al., 2020). Moreover, comparable to our NOR and NLR test outcomes, no effects on working memory 8 days after ISO were observed, but long-term learning and memory seemed impaired after ISO (Ravindran et al., 2020). However, effects on cognitive performance in the present study may remain inconclusive, because of low number of successful tests and high variability. In general, in the present study, similar effects of ISO were observed as seen in the literature in young male rats. However, substantial sex-related differences could be distinguished.

Sex dimorphism in isoproterenol response

ISO induced substantial mortality in male rats, whereas similar doses in female rats did not exceed mortality in saline treated rats. This is in general agreement with literature (Wexler, 1978). Five weeks after ISO, cardiac collagen was still increased in male-, but not in female rats. Similarly, chronic ISO stimulation causing fibrosis in male but not female rat hearts was reported, which seemed attributable to different responses of cardiac fibroblasts (Peter et al., 2021). Male cardiac fibroblasts were more activated than female cardiac fibroblasts, consistent with elevated fibrosis in male rat hearts, and may be attributed to higher β-adrenoceptor expression and phosphokinase-A activation in male fibroblasts (Peter et al., 2021). The observation that gonadectomized male and female rats showed better survival and superior repair of their damaged hearts compared to their intact sex-matched controls (Wexler and Greenberg, 1979), supported an important role of sex hormones.

Consistent with these findings, male rats, but not female rats, showed more anxious behavior. Although this anxious/depressive-like behavior has been reported before in literature (Hu et al., 2020), no sex dimorphism was investigated here. Moreover, all behavioral studies on the effects after ISO-induced cardiac damage were only performed in young male rats (Tkachenko et al., 2018; Hu et al., 2020; Ravindran et al., 2020). However, our previous study in rats with myocardial infarction induced by coronary artery ligation also showed behavioral changes in male, but not in female rats (Gouweleeuw et al., 2016).

We hypothesized that the ISO-induced peripheral inflammatory response would be reflected in the brain as neuroinflammation, potentially leading to declined neuronal functioning and consequently behavior changes (Quan, 2014). From above observations, male rats would be anticipated to display more neuroinflammation and further declined BDNF expression than female rats. However, BDNF expression was lower in females than in males, and not significantly affected by ISO. Indeed, male rats showed higher control microglia activity in the hippocampus than female rats, but the responses to ISO were comparable in both sexes. Moreover, these responses were best reflected in the CA3 area of the hippocampus, an area involved in pattern separation (Stevenson et al., 2020), rather than in the CA1 area involved in learning and memory (Stevenson et al., 2020). This would be consistent with the lack of differences in the short-term memory (NOR and NLR) tests. Therefore, the effects of ISO that were predominantly seen in male rats, could not be directly attributed to differences in neuroinflammation or neuronal function in the investigated brain areas. Other mechanisms may be involved, including glucose- and lipid metabolism (Wexler and Greenberg, 1979). Nevertheless, the older studies of Wexler and coworkers (Wexler, 1975; Wexler and Greenberg, 1979) clearly indicated sex differences in the response of peripheral parameters that could be linked to behavioral changes, such as depression and cognition (Keller et al., 2017). For instance, the corticosterone response during the first week after ISO appeared much higher in female rats than in male rats (Wexler and Greenberg, 1979), suggesting different hypothalamic–pituitary–adrenal (*HPA*) *axis* activity. Compared to males, female rats show a more robust HPA axis response, as a result of circulating estradiol levels which elevate stress hormone levels during non-threatening situations as well as after stressors (Oyola and Handa, 2017), with distinct behavioral consequences (reviewed by Packard et al., 2016).

Limitations

In the present study, only old rats have been included, hampering direct comparison with younger ones to establish an age effect. Comparison with results from our studies in

12 months old rats (Toth et al., 2021) may indicate interaction between ISO-induced effects and age-related processes. Although selected carefully, effects were studied at single time points, limiting the overview of time courses of these ongoing processes.

In accordance with the lack of ISO-induced cardiac fibrosis in old female rats, the increased ISO-induced mortality in male rats was absent in female rats. For the male rats, but not for the females, this could have led to selection of the "better" old rats for analyses. Analyses of survivors may have led to underestimation of effects, hence biasing proper comparison between the sexes.

On the other hand, since ISO was dosed based on body weight, female rats with significantly lower body weights and higher relative heart (ns) and brain weights, could have received too less ISO to cause an effect. However, in our previous studies in 12 months old male (Toth et al., 2021) and female rats (Toth et al., 2022), using the same dose per body weight as used in the present study, led to a significant and similar magnitude of cardiac damage and reduced cardiac function in both sexes.

Finally, in hindsight, collecting blood samples to measure circulating (inflammatory) factors could have further elucidated on the mechanism of the inflammation/neuroinflammation process.

Conclusion

Our data indicated that old male rats appeared more susceptible to ISO than old female rats, by displaying higher mortality, more cardiac damage and more anxious/depressive-like behavior, indeed supporting sex dimorphism in ISO responsiveness. Since ISO did not distinguish between the sexes regarding microglia activation or BDNF expression, mechanisms other than neuroinflammation and/or altered neuronal function seemed to underly this sex dimorphism.

Data availability statement

The original contributions presented in this study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The animal study was reviewed and approved by Animal Ethical Committee of University of Physical Education, Budapest, Hungary.

Author contributions

KT, RS, EZ, and CN contributed to the conception and design of the study. KT and TO performed the animal experiment. KT and RS analyzed and organized the data. RS did the statistical analysis and wrote the first draft of the manuscript. All authors contributed to the final version of manuscript and approved the final version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Electroencephalogram signals emotion recognition based on convolutional neural network-recurrent neural network framework with channel-temporal attention mechanism for older adults

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Reminiscence and conversation between older adults and younger volunteers using past photographs are very effective in improving the emotional state of older adults and alleviating depression. However, we need to evaluate the emotional state of the older adult while conversing on the past photographs. While electroencephalogram (EEG) has a significantly stronger association with emotion than other physiological signals, the challenge is to eliminate muscle artifacts in the EEG during speech as well as to reduce the number of dry electrodes to improve user comfort while maintaining high emotion recognition accuracy. Therefore, we proposed the CTA-CNN-Bi-LSTM emotion recognition framework. EEG signals of eight channels (P3, P4, F3, F4, F7, F8, T7, and T8) were first implemented in the MEMD-CCA method on three brain regions separately (Frontal, Temporal, Parietal) to remove the muscle artifacts then were fed into the Channel-Temporal attention module to get the weights of channels and temporal points most relevant to the positive, negative and neutral emotions to recode the EEG data. A Convolutional Neural Networks (CNNs) module then extracted the spatial information in the new EEG data to obtain the spatial feature maps which were then sequentially inputted into a Bi-LSTM module to learn the bi-directional temporal information for emotion recognition. Finally, we designed four group experiments to demonstrate that the proposed CTA-CNN-Bi-LSTM framework outperforms the previous works. And the highest average recognition accuracy of the positive, negative, and neutral emotions achieved 98.75%.

KEYWORDS

electroencephalogram (EEG), emotion recognition, channel-temporal attention, CNN-RNN, older adults

Introduction

Background

Japanese family norms based on the traditional culture of filial piety form a social support network centered on kinship ties, which differs sharply from the individual-centric social networks of Western countries (Sugisawa et al., 2002; Knight and Sayegh, 2010). As a result, Japanese older adults are more likely to feel socially isolated at a rate of 15.3% compared to 5.3% in the UK (Noguchi et al., 2021). Poor interaction and lack of social participation are among the contributing factors to social isolation which are closely associated with depression, one of the major risk factors for the development of Alzheimer's dementia (Santini et al., 2015). Many studies (Westermann et al., 1996; Thierry and Roberts, 2007; Sitaram et al., 2011; Iwamoto et al., 2015; Leahy et al., 2018) have shown that reminiscence and communication about past photographs between older adults and younger volunteers, healthcare workers, or families encourage positive interaction and social engagement. And therefore, they are highly effective in improving the emotional state and alleviating depression in older adults. However, it is necessary to evaluate the emotional state of the older person when talking about the photographs to (a) ensure that the communication is positive, as long-term negative emotions may cause changes in feelings and state of mind (**Figure 1A**) leading to various mental illnesses (Van Dis et al., 2020). For example, mania is easily caused by a prolonged state of ecstasy (high positive) and euphoria (high arousal) as shown in **Figure 1B** and (b) estimate whether the photographs in the conversation are effective in improving the emotion of the older person, and replace them with other photographs if they are not effective. While numerous studies focus on the evaluation of emotions in older adults, earlier studies generally used self-assessment in the form of verbal or questionnaires and were found to be intermittent and influenced by social expectations or demand characteristics (the idea that participants or stimulators will develop similar or specific emotions in response to perceived expectations) (Orne, 1962). Later developments use smart wearable devices (physiological signals) (Kouris et al., 2020), facial expression (Caroppo et al., 2020), and speech recognition (Boateng and Kowatsch, 2020) to monitor and recognize emotions. However, variances and continuities such as facial aging in older adults and differing accents among various groups of people (e.g., different dialects spoken throughout Japan) make it difficult to distinguish and unify such features and expressions. These inevitably result in unreliable emotion recognition results for older adults.

Thus, while physiological signals to monitor emotions seem to be a more suitable approach for older adults, not all physiological signals are suitable for distinguishing between different emotional experiences. For example, although excitement and panic are different emotions generated in response to different stimuli of award and threat, both exhibit the same physiological changes (i.e., increased heart rate, increased blood pressure, body shaking, etc.). Moreover, time is also necessary for the autonomic and sympathetic nervous systems to switch on and off, resulting in outward physiological changes that are slow-acting and insufficient in keeping up with the emotional changes (Liu and Cai, 2010). By conducting the EEG signals through the electrodes on the scalp we can collect EEG signals with a high temporal resolution that reflect different emotional states and variances between these moments (Alarcao and Fonseca, 2017) (Note: all commercially available acquisition devices have a sampling rate of at least 160 Hz/s). As we know from the widely accepted cognitive-evaluation theory of emotions (two-factor theory) (Cornelius, 1991), when we are stimulated by the external environment, we immediately generate physical reactions and simultaneously evaluate them with past knowledge and experience (cognitive process) and finally integrate them into the cerebral cortex obtaining the emotional state (the whole process shown in **Figure 1C**). Therefore, we can say that EEG signals have a significantly stronger association with emotions than other physiological signals. They are also objective, non-invasive, and safe.

The general process and principles of EEG signals for the emotion recognition system (shown in **Figure 1D**) are (1) stimulus materials elicit emotions in the subject while collecting EEG signals, (2) the computer sequentially preprocesses and extracts features from the received EEG signals, and (3) an EEG-based emotion recognition classifier is trained using task-relevant EEG features. The emotion label of EEG features in training emotion classifiers is based primarily on the SAM scale using the valance-arousal emotion model proposed by Posner et al. (2005). The subject is exposed to stimuli and their emotional state is evaluated by oneself using the SAM scale (Valence: positive to negative emotional state; Arousal: difference in the level of physiological activity and mental alertness), which is mapped to the valence-arousal emotion model (**Figure 1B**) to obtain a corresponding "emotion label." In this way, the subjective experience of different emotions (emotion labels) and subjects' objective physiological responses (EEG signals) are matched one-to-one. Nowadays, many inexpensive solutions for portable EEG acquisition devices are available on the market (Stytsenko et al., 2011; Surangsrirat and Intarapanich, 2015; Athavipach et al., 2019), and thus EEG signal-based emotion recognition has a promising application and research value. For this study in the conversation scenario using EEG signals for emotion recognition is extremely challenging. Especially, as the facial muscle activity during the conversation will evoke high-energy artifacts that may distort the intrinsic EEG signal. Such artifacts will hide the rhythm of the real EEG signal and cause perturbation in an EEG system that makes EEG signal processing difficult in all respects (Kamel and Malik, 2014). Therefore, in EEG-based emotion

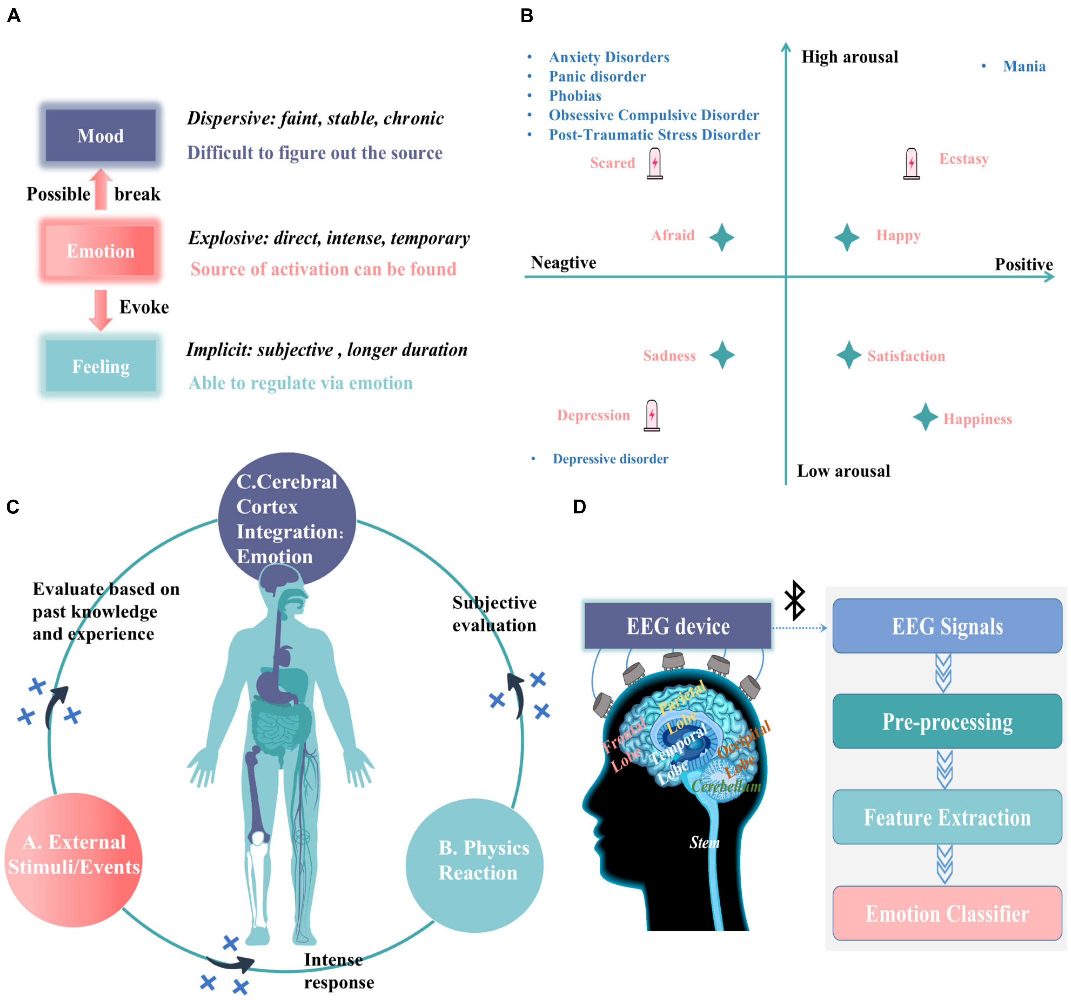

FIGURE 1
Overview of the causes and methods of monitoring individual (subject) emotions. **(A)** Characteristics of mood, emotion, and feeling. **(B)** Expression of emotions space model and mental disorders. **(C)** The formation of emotion. **(D)** EEG emotion recognition system.

recognition, appropriate signal pre-processing methods must be first adopted to remove artifacts and make the EEG data as clean as possible simply reflects the brain's activity. Meanwhile, the challenge to reduce the number of dry electrodes to improve user comfort while ensuring a high emotion recognition rate remains.

In this paper, we propose a CNN-RNN framework combined with a channel-temporal attention mechanism (CTA-CNN-Bi-LSTM) for EEG emotion recognition inspired by the channel-spatial attention module (CBAM) proposed in the field of computer vision research (Woo et al., 2018). The primary contributions of this study are summarized as follows.

(1) In the EEG signal pre-processing stage, due to the EMG and EOG artifacts contribute differently to different brain regions and attenuate as the distance from the scalp gets more remote. We divided the 8-channel EEG signals into Frontal, Temporal, and Parietal groups according to brain regions. And then remove multiple biological artifacts from raw EEG signals in each group separately based on the MEMD-CCA method (Xu et al., 2017; Chen et al., 2018).

(2) In the phase of assigning emotional labels to EEG signals, the emotion labels (positive, neutral, and negative) of EEG signals were automatically obtained by the K-means method based on the ratings of the emotion scale [Valence (-4,4), Arousal(-4,4) and Stress (1,7)] of each participant. The advantage of using this method is not to use the same rating classification criteria for all participants, but to use each participant's rating to classify their own emotions.

(3) For data-driven EEG-based emotion recognition without feature engineering, we developed a CTA-CNN-Bi-LSTM framework. This framework integrates the channel-temporal attention mechanism (CTA) into the CNN-Bi-LSTM module to explore using spatial-temporal information of different important channels (channel attention) and time points

(temporal attention) of EEG signals to achieve EEG-based emotion recognition. And the proposed framework achieved average emotion recognition accuracy of 98%, 98%, and 99% in the negative, neutral, and positive emotions.

(4) We conducted four group experiments on the OCER dataset to explore the contribution of each module to EEG-based emotion recognition. The experimental results indicate that the CNN module provided the largest contribution to the accuracy improvement (21.29%) of the proposed framework, the Bi-LSTM module after the CNN module provided little enhancement (8%) of the framework and the addition of the Channel-Temporal attention module before the CNN-RNN module led to a further significant improvement (11%).

Related works

In this part, we first describe the artifacts that typically emerge during EEG acquisition and existing effective methods to remove them. Then we introduce EEG emotion recognition systems which have evolved from traditional hand-crafted feature extraction to end-to-end deep learning frameworks with channel selection mechanisms.

Electroencephalogram artifacts and removal methods

Due to the potential technical and biological artifacts (**Figure 2**) in the EEG acquisition process will cause the oscillating discharge larger than the neuronal discharge (Kamel and Malik, 2014). Before proceeding with electroencephalography (EEG) data analysis, it is important to make sure that the EEG data is as clean as possible, meaning that the data collected simply reflects the brain's activity.

Technical artifacts mainly include three types: impedance fluctuation (Rodriguez-Bermudez and Garcia-Laencina, 2015), line interference (Huhta and Webster, 1973), and wire movement (Urigüen and Garcia-Zapirain, 2015). Technical artifacts can be avoided by paying attention during the acquisition of the EEG signals. Biological artifacts mainly include two types: muscular artifacts [Electromyogram (EMG), Electrocardiogram (ECG)], ocular artifacts [Electrooculogram (EOG)] including eye movement and eye blinking. Such biological artifacts are inevitable contaminations due to the conductivity of the scalp (Kamel and Malik, 2014), and the closer the artifact's sources are to the electrodes, the more significant is their effect on the EEG data. In particular, the activity of the facial muscles (forehead, cheeks, mouth), neck muscles and jaw musculature (EMG) have a serious effect on the EEG, with a broadband frequency distribution of 0–200 Hz (Halliday et al., 1998; Van Boxtel, 2001). In addition, the heart also is muscular (ECG) and continuously active, which also affects the quality of the EEG data. The artifact has a broadband frequency distribution of 0–75 Hz (Lee and Lee, 2013), but has less effect on the EEG because of the large distance between the scalp and the heart. The eyes have a powerful electromagnetic field, which is formed by millions of neurons in the retina, thus eye movement (horizontal, vertical, and rotation) and eyeblink will affect the electric field received by the electrodes resulting in electrooculogram (EOG) artifacts. Similar to eye movements, eye blinking can interfere with brain signals to a large extent, one, due to the proximity of the eye to the brain, two, as individuals would blink 20 times per minute to keep the ocular moisture of their eyes (Karson, 1983), and these artifacts are unavoidable for prolonged tasks.

Therefore, for our task, the removal of EMG and EOG artifacts from raw EEG signals can be considered the top issue to address. There are already many algorithms (Narasimhan and Dutt, 1996; Jung et al., 2000; Schlögl et al., 2007; Ferdousy et al., 2010; Vos et al., 2010; Safieddine et al., 2012; Sweeney et al., 2012; Teng et al., 2014; Zhao et al., 2014; Chen et al., 2017; Paradeshi et al., 2017; Yang et al., 2017) for removing these two artifacts (summarized in **Table 1**), the BSS-based techniques are widely proposed because they do not require a priori knowledge and reference electrodes for EMG/EOG signals acquisition and they could separate related artifacts from EEG signal by statistical inference. Among them, CCA-based methods which more effective than ICA-based methods and other filters, taking advantage of the fact that the autocorrelation coefficient of EEG is larger than that of EMG, so it is possible to separate task-related EEG and EMG artifacts. Moreover, relevant studies (Vos et al., 2010; Urigüen and Garcia-Zapirain, 2015) have demonstrated the effectiveness of the CCA method in removing muscle artifacts during speech. EEMD-CCA (Sweeney et al., 2012) is one of the best methods the for removal of EMG and EOG artifacts for single-signals EEG signals. Although for non-single channel EEG signals, EEMD-CCA can be applied channel-by-channel, the inter-channel correlation is not captured. The later proposed MEMD-CCA (Chen et al., 2017) addressed the challenge by decomposing all channels together and then aligning the same frequency components of each channel to form multivariate IMFs before applying CCA (by setting the autocorrelation coefficient threshold, generally less than 0.9 components are set to 0) to remove the artifacts to reconstruct the EEG signals. However, it does not take into account the different degrees of influence on the EEG signals due to the distance of the artifact source from the location of the scalp electrodes (shown in **Figure 2**). Therefore, it is necessary to group the EEG channels based on brain areas and then use MEMD-CCA on each group separately.

Electroencephalogram emotion recognition systems

Electroencephalogram emotion recognition systems, mainly differ in their approach to feature extraction and choice of classifiers: a step-by-step machine learning framework (hand-crafted feature extraction, feature fusion, modeling

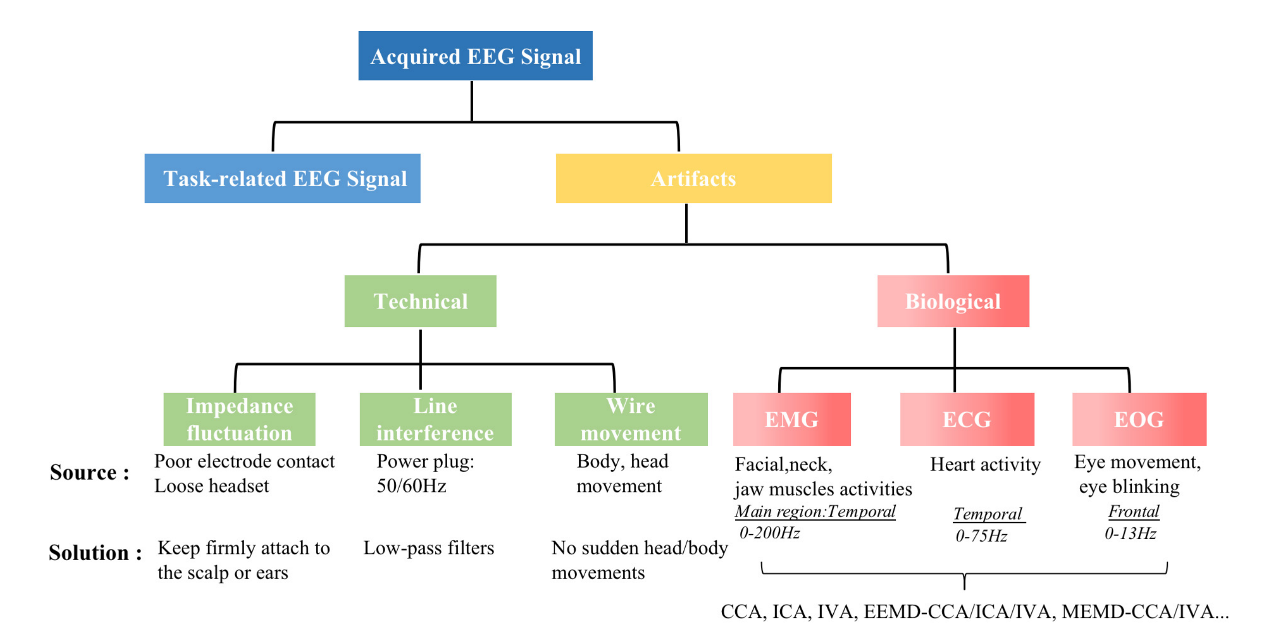

FIGURE 2
The sources of artifacts in EEG signal and the removal methods.

TABLE 1 Comparison of EMG and EOG artifacts removal techniques.

Methods		Ref. E	Channel	Comparison results
PK	**NPK (BSS-based)**			**(Better than)**
Adaptive filtering		√	All	EMG: Low-pass filter EOG: WPT, ICA, DWT, ANC (Narasimhan and Dutt, 1996; Zhao et al., 2014)
Linear regression		√	All	EOG: Visual identification (Schlögl et al., 2007)
	ICA	×	Multi	PCA, LR, Wavelet (Jung et al., 2000; Paradeshi et al., 2017)
	CCA	×	Multi	EMG: low-pass filter + Robust ICA; EOG: equivalent to ICA (Ferdousy et al., 2010; Vos et al., 2010)
	EMD	×	Single	ICA, CCA, WT (Safieddine et al., 2012)
	EEMD-CCA	×	Single	EMD, EMD-ICA, EMD-CCA, EEMD, EEMD-ICA (Sweeney et al., 2012)
	MEMD	×	Few	ICA (Teng et al., 2014)
	MEMD-CCA	×	Few	EMG: ICA, EEMD-ICA, MEMD-ICA CCA, EEMD-CCA (Chen et al., 2017)
	CCA-MEMD	×	Few	EOG:ICA, CCA (Yang et al., 2017)

PK, prior knowledge; NPK, no prior knowledge; BSS, blind source separation; Ref. E, reference electrode; ICA, independent component analysis; CCA, canonical correlation analysis; EMD, empirical mode decomposition; EEMD, ensemble empirical mode decomposition; MEMD, multivariate empirical mode decomposition.

classification) and an end-to-end deep learning framework (automatic feature extraction, feature fusion, modeling classification).

Step-by-step machine learning framework

The performance of machine learning frameworks largely depends on the quality of hand-crafted extracted features (Hosseini et al., 2020). Generally, researchers extract the EEG features from parts of the brain regions considered to contribute the most to emotions based on *a priori* knowledge of the combinatorial design. Of the most used in emotion recognition are the following two theories based on asymmetric behavior: (1) the right hemisphere dominance theory which posits right hemispheric dominance over the expression and perception, and (2) the valence theory which asserts that the right hemisphere predominantly processes negative emotions and left hemisphere predominantly processes positive emotions (Coan and Allen, 2003; Demaree et al., 2005). For example, in the study (Wang et al., 2014), the authors subtracted the power spectrum (PSD) of obtained brain waves collected from 27 pairs of symmetrical electrodes in the left and right brain regions to obtain 27 asymmetrical PSD features input to SVM classifiers. The negative and positive emotion recognition accuracy average rate was 82.38%. Later studies

(Duan et al., 2013; Zheng et al., 2014, 2017) demonstrated that the following six features: PSD, differential entropy (DE), DASM (DE(L_{eft})-DE(R_{ight})), RASM (DE(L_{eft})/DE(R_{ight})), ASM ([DASM, RASM]), DCAU(DE(F_{rontal})-DE($P_{osterior}$)) were robust and effective for EEG emotion recognition. However, the DE features achieved the highest recognition accuracy of 91.07% which is higher than the other four asymmetric features. This demonstrates ambiguity as to what degree the stimuli (pictures, music, videos, etc.) elicit neuronal processes similar to those occurring in real-life emotional experiences; making it difficult to cover all the implied features by hand-extracted features.

End-to-end deep learning framework

Recently studies began to focus on end-to-end deep learning frameworks (Craik et al., 2019). In a study (Alhagry et al., 2017), the authors proposed the use of LSTM models to automatically learn features of emotions from the context of EEG signals. They achieved average recognition accuracy of 85.65% in the valence dimension. Later in a study (Zhang et al., 2020) the authors further considered that the spatial information in the EEG signal could be used to improve the accuracy of emotion recognition and thus proposed a CNN-LSTM model. EEG raw data was first input into a CNN module (1-dimensional convolutional layer, maximum pooling layer) to extract the local spatially features which were then input into a two-layer LSTM to learn the temporal information in the spatial features. The result was an average recognition accuracy of 94.17% with a four-emotion classification. In addition, the authors input EEG raw data separately into CNN (four-layer of two-dimensional convolution; spatial features) and LSTM (four-layer; temporal features) to achieve accuracies of 90.12% and 67.47%, respectively. A later study (Sheykhivand et al., 2020) also proposed the use of CNN-LSTM for EEG raw data with the main structure of 10-1D convolutional layers plus 3 LSTM layers, achieving a recognition average accuracy of 97.42% with a two emotion classification.

From the results of the above-related studies, it was found that (a) the model automatically learns emotional features from EEG raw data better than hand-crafted extracted features, and (b) the model emotion classification recognition performance using EEG spatial-temporal features demonstrates improvements across a wide range. In addition, there are also studies that combine feature extraction and deep learning models, such as a DECNN model (Liu et al., 2020) was proposed that focuses on subject-independent emotion recognition and used extracted DDE (dynamic differential entropy) features fed into the CNNs for emotion classification. Finally, the average accuracy achieved 97.56% in EEG subject-independent emotion recognition on the SEED public dataset.

Channel selection mechanism

The number of dry electrodes used in the EEG emotion recognition systems studied above is, in general, excessive and not conducive to prolonged wear from a comfort perspective. Moreover, the EEG signals obtained with multichannel EEG devices often contain redundant, irrelevant, or interfering information (noise, overlapping/interference of signals from different electrodes) for affective analysis (Alotaiby et al., 2015). Thus, selecting the most relevant channel for emotion analysis is essential for enhancing comfort and emotion recognition accuracy.

A study (Tong et al., 2018), utilized the Relief algorithm to calculate the weight values of each channel according to the time-domain features of the EEG signal. At the cost of losing 1.6% accuracy, 13 channels with the highest contribution to emotion classification under time-domain features were selected from the initial 32 channels. Later, a study (Dura et al., 2021) used the reverse correlation algorithm applied to the band-time-domain features of 32 channels to construct a subset of electrodes with the smallest band correlation for each subject. The number of occurrences of each subset in each subject was then calculated to obtain the most common subset of channels. The smallest subset contained only four electrodes and accuracy was not affected. However, the accuracy of such channel selection methods would depend entirely on the quality of hand-extracted features. In response, the latest has research proposed to apply an attention mechanism to channel selection to prompt the network to automatically learn the most important information and improve the performance of important features. In a study (Tao et al., 2020), the authors added the channel attention module before the CNN-LSTM model to automatically learn the importance of each channel to the EEG emotion signals and then assigned weights to each channel. It was found that the FC5, P3, C4, and P8 channels contributed the most to emotion classification on the DEAP dataset (32 channels) and had an average accuracy improvement of 28.57% compared to the CNN-LSTM model without the channel attention. Later, a 3DCANN (Liu et al., 2021) framework was proposed, in which five consecutive 1s-62-channel EEG signals were fed as 3D data inputted to a CNNs module with two convolutional layers to extract spatial features, which were later output to two attention modules in the channel dimension to enhance or weaken the effect of different electrodes on emotion recognition. The model achieved an average accuracy of 96.37% for positive, negative, and neutral emotions. It is demonstrated that the attention mechanism enhances the information of the important channels and suppresses the information of the irrelevant channels for emotion analysis. However, the shortcoming is that, to get the global perspective of the temporal dimension (Time × Sample point) of the EEG signals (Time × Sample point × Channel), the channel attention module pools the EEG signals globally into 1 × 1 × Channel to get the weight matrix of the channel. This directly ignores the specific temporal information of the EEG signals, if a channel contains more noise/artifacts, it may get larger weight values instead of being conducive to the later model learning.

As our purpose is to perform emotion recognition during the conversation, even if the removal of artifacts is implemented in EEG signals, some artifacts may be still present. Therefore, attention mechanisms need to be applied simultaneously in the temporal dimension. The temporal attention mechanism will play an important role in determining "where" the need to focus attention exists. It can improve the expressiveness of the time points of changing emotional states in the EEG signal while suppressing noise/artifacts information.

Materials and methods

In this section, first, we describe the EEG dataset, the method of division of the EEG dataset, and the preprocessing of EEG signals. Then, we describe in detail the structure of each module of the proposed CTA-CNN-Bi-LSTM.

The division and preprocessing of electroencephalogram dataset

Our experiments were conducted on the dataset from the previous study (Jiang et al., 2022). Eleven older adults (six males and five females) and seven younger adults (five males and two females) were randomly pair-matched into 11 groups, and each group engaged in 36 photo conversations. The young person guided the older adult in a 1-min conversation around each photo during which time the EEG signals from the older adult were collected. After each photo conversation, the older adult also filled out an emotion evaluation form (rating of valence, arousal from −4 to 4, and the level of stress from 1 to 7). A detailed description of the EEG dataset (here named OCER) is presented in **Table 2**.

As individual differences in gender, age, economic, educational, and life circumstances would result in differences in the benchmarks for evaluating emotions, we did not classify samples by uniformly setting thresholds for the rating values on each dimension. Instead, in our experiments, the ratings of valence, arousal, and stress were first standardized using the standard deviation standardization method (Z-score). And the K-means method (Likas et al., 2003) was then applied to the three standardized scores for each individual, and the 36 samples were divided into three groups of positive, neutral, and negative emotions samples. Finally, the pre-processing was applied to the EEG signals in the dataset:

TABLE 2 Summary of experiment dataset (OCER).

Conversation experiment	
Trails	36 trails × 60 s
Subject	Older: 11 (M = 71.25 ± 4.66) Young: 7 (M = 22.4 ± 1.51)
Rating	Valence (−4,4), Arousal (−4,4), Stress (1,7)
EEG dataset	
Device	OpenBCI Cyton board (250 Hz/s)
Channel	F3, F4, F7, F8, T7, T8, P3, P4 (10–20 system)
Array	396(Samples) × 60 (s) × 250(Hz/s) × 8 (Channels)

Removal of technical artifacts

Electroencephalogram signals used a 1–45 Hz bandpass filter (removal of the line interference) and a Chebyshev I high-pass filter to remove baseline drift (Jiang et al., 2022).

Removal of biological artifacts

Electroencephalogram signals were divided into three groups: The frontal group (F7, F8, F3, F4), the temporal group (T7, T8), and the parietal group (P3, P4). And then each group used MEMD-CCA (Xu et al., 2017; Chen et al., 2018) methods to remove multiple artifacts (detailed in **Figure 3A**).

Segmented data

Used a 3s-non-repetitive window for segmentation of each sample (60 s trail) in the dataset. The reason is that normally the duration of an adult's emotional state does not exceed 12 s and in studies (Li et al., 2017; Tao et al., 2020) a 3s-non-repetitive sliding window applied to the EEG signals achieved excellent results for the emotion recognition task.

Preprocessing of proposed framework

First of all, before inputting the raw clean EEG dataset into the first module of the proposed framework, we normalized each raw EEG sample along the channel direction with zero-mean normalization to eliminate subject and channel differences in EEG signals and reduce computational complexity. Thus, the mean value of the processed raw EEG signals sample for each channel is 0 and the standard deviation is 1. The normalization formula for each channel is as follows:

$$X_{i,j}^{k*} = \frac{X_{i,j}^{k} - \overline{X^k}}{\sigma^C}. \quad (1)$$

Where $X_{i,j}^{k}\left(i = 1, 2, 3\ Time\left(second\right); j = 1, 2, \ldots, 250\ Sample\ Point\ \left(250Hz/s\right); k = 1, 2, \ldots, 8\ EEG\ Channel\right) \in R^{T\times P}$ represents the data of the k-th channel of a 3s-EEG sample. T and P are the time length and the sample point of the 3s-EEG sample respectively. $\overline{X^k}$ and $\sigma^C$are the mean and standard deviation of the k-th channel respectively.

Modules of proposed CTA-CNN-Bi-LSTM framework

The proposed framework consists of the following three modules: channel-temporal attention module, spatial feature

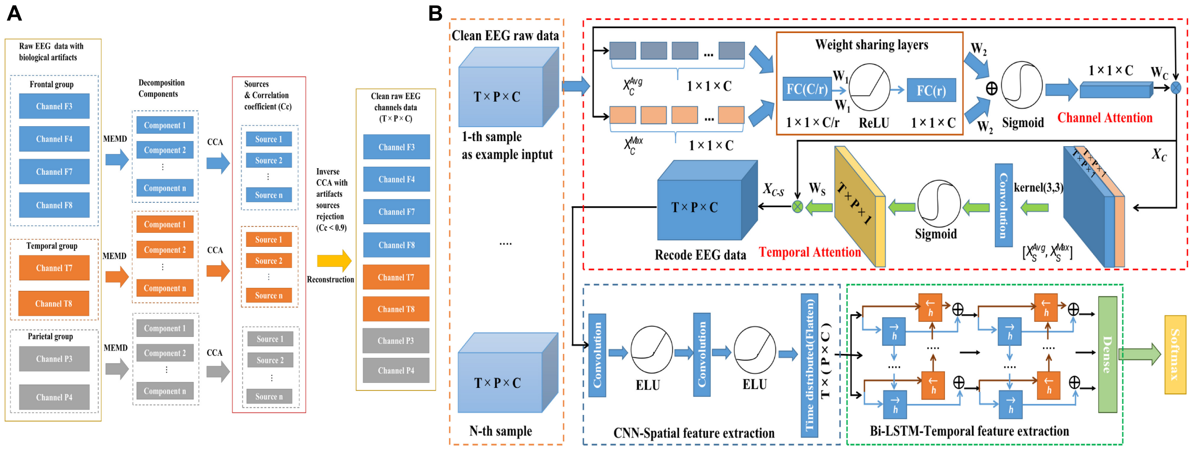

FIGURE 3
Illustration of the proposed framework based on raw EEG data for emotion recognition. **(A)** Removal of biological artifacts by MEMD-CCA. **(B)** CTA-CNN-Bi-LSTM framework.

extraction module (CNNs) and bi-directional temporal feature extraction module (Bi-LSTM). The structure of the proposed CTA-CNN-Bi-LSTM framework is shown in Figure 3B. The specific calculation process and description are as follows.

Channel-temporal attention module

An EEG sample is defined as $X \in R^{T \times P \times C}$ whereby T denotes the time duration of one EEG sample, P is the sampling points per second and C denotes the number of EEG channels. The output after the channel-temporal attention module is $X_{c-s} \in R^{T \times P \times C}$, and the specific calculation process and descriptions are as follows. Here for our EEG dataset, the T is 3 s, P is 250 Hz/s, and C is 8 channels.

Channel attention

The global average pooling and maximum pooling are performed separately in the temporal dimension on the channel direction of X to obtain two channel statistical descriptions $X_C^{\text{Avg}}, X_C^{\text{Max}} \in R^{1 \times 1 \times C}$. They are then fed into a two-layer weight-sharing multi-layer perceptron (MLP): the first layer is the compression layer (the number of neurons is set to C/r to get the weight $W_1 \in R^{1 \times 1 \times C/r}$ and ReLU is used as the activation function. r represents the reduction ratio and here r is set to 2); The second layer is the excitation layer (the number of neurons is set to C to get the weight $W_2 \in R^{1 \times 1 \times C}$). Finally, these two combined features are mapped using a sigmoid activation function to generate the channel attention mapping matrix $W_c \in R^{1 \times 1 \times C}$ as follows:

$$W_c(\mathrm{X}) = \mathrm{Sigmoid}(W_2(\mathrm{ReLu}(W_1 \cdot X_c^{Avg}) + W_2(\mathrm{ReLu}(W_1 \cdot X_c^{Max}))). \quad (2)$$

And the output of channel attention $X_c \in R^{T \times P \times C}$ is as follows:

$$X_c = \mathrm{W}_c(X) \otimes X. \quad (3)$$

Temporal attention

Average pooling and maximum pooling are used along the channel dimension on the temporal direction to obtain $X_s^{\text{Avg}}, X_s^{\text{Max}} \in T \times P \times 1$ to stitch them together, and convolutional layers (a convolutional kernel of size 3 × 3, $K^{3 \times 3}$). The sigmoid activation functions are used to generate the temporal ($T \times P$, Time × Sample Point) attention mapping matrix $W_s \in R^{T \times P \times 1}$ as follows:

$$W_s(X) = Sigmoid(K^{3 \times 3}([X_s^{Avg}, X_s^{Max}])). \quad (4)$$

Thus, our final output $X_{c-s} \in R^{T \times P \times C}$ is as follows:

$$X_{c-s} = W_s(\mathrm{X}_c) \otimes X_c. \quad (5)$$

In this way, the output shape of $X_{c-s} \in R^{T \times P \times C}$ remain unchanged and has learned what channels are important and at which time points in the channel and temporal dimension.

Convolution neural networks module

The convolution neural networks (CNNs) and their essential characteristics (spatially dependencies/local connection and weight sharing) have been widely used in various fields, especially for image tasks (object segmentation, image classification, style conversion, etc.) (Hijazi et al., 2015; Rawat and Wang, 2017). All of these applications were built based on the feature maps after the CNNs performed feature extraction for the task. Thus, essentially the role of CNNs models is to extract local spatial features of EEG signals. The specific steps of our CNNs module are as follows.

Step 1: Convolution layer

The input recorded EEG signals $X_{c-s} \in R^{T\times P\times C}$ and the convolution kernel of CNNs is defined as $filter^{k}_{(i,j)}$. k represents the number of filters, which is the same as the number of EEG channels. (i, j) is the size of the convolutional sliding window in the temporal-spatial ($T \times P$, Time $\times$ Sample Point) dimension of multi-channel EEG signals. More specifically, the k-th filter is convolved with the corresponding region in $T \times P$ dimension of the k-th channel of X_{c-s} with a window size of $i \times j$ sliding in step 1 (direction from left to right and top to bottom). The output value is obtained by adding the sum of the k channels. Finally, the feature map X^{f}_{C-S} is as follows:

$$X^{f}_{C-S} = \mathrm{f}\left(\sum X_{C-S} \otimes K + b\right). \tag{6}$$

The bias term is represented by b. A convolution kernel produces a feature map, and the closer the value in X^{f}_{C-S} is to 1, the more it is associated with the feature, and the closer it is to −1, the less it is associated.

In our dataset for EEG emotion recognition, the k was set 8 corresponding to the number of EEG channels. And the size of the sliding window (i, j) was set "1×10" and sliding in step 1, where the "i" was set 1 in order not to destroy the temporal features of the EEG signals at different seconds and the convolutional window to constantly move at the same second as the sampling points when sliding. Therefore, later the generated spatial feature maps have the following characteristics: (a) different spatial locations on the same channel were sharing convolutional kernel parameters (spatial independence), and (b) different convolutional kernels were used on different channels (channel specificity). This allowed each feature map of the output CNNs to learn different spatial emotion features with temporal information preserved.

Step 2: Exponential linear units layer

The exponential linear units (ELU) was selected as the activation function after the convolution layer because it is continuous and differentiable at all points and its gradient is non-zero for all negative values, meaning it does not encounter the problem of exploding or disappearing gradients during deep network learning. It achieves higher accuracy compared with other activation functions such as ReLU, Sigmoid, and tanh (Clevert et al., 2015). The ELU activation function can be written as:

$$f(x) = \begin{cases} e^{x} - 1, & x < 0 \\ x, & x \geq 0 \end{cases}. \tag{7}$$

As can be deferred from (7), the ELU function retains the values greater than or equal to 0 in the feature map X^{f}_{C-S} and assigns $e^{x} - 1$ to all the remaining values less than 0. This further suppresses the uncorrelated data in the feature map using a non-linear activation function.

To ensure that the temporal information contained in the extracted spatial feature maps is not reduced during the input temporal feature extraction module (Bi-LSTM), we did not use the pooling layer often used in CNN structures. Thus, our spatial feature extraction module used two convolution-ELU layers.

Bi-directional long short-term memory module

LSTM networks (Hochreiter and Schmidhuber, 1997) have been widely used in time series related tasks, such as disease prediction (Chimmula and Zhang, 2020) and air quality prediction (Yan et al., 2021). This is because, unlike previous feedforward neural networks (one-way propagation, where the input and output are independent of each other), LSTM networks have internally inclusive memory units (the state of the current time step is jointly determined by the input of that time step and the output of the previous time step). LSTM is, effectively, a gating algorithm added to the memory unit of a traditional RNN which solves the problem of long sequences in which the gradient disappears and explodes during the training process of the RNN model (Bengio et al., 1994). The memory unit of LSTM is as follows:

$$Z_{forget} = sigmoid(W_{f}\left[h_{t-1}, X_{t}\right] + b_{f}), \tag{8}$$

$$Z_{input} = sigmoid(W_{i}\left[h_{t-1}, X_{t}\right] + b_{i}), \tag{9}$$

$$Z_{output} = sigmoid(W_{o}\left[h_{t-1}, X_{t}\right] + b_{o}), \tag{10}$$

$$Z = tanh(W\left[h_{t-1}, X_{t}\right] + b_{c}), \tag{11}$$

$$C_{t} = Z_{forget}C_{t-1} + Z_{input}Z, \tag{12}$$

$$h_{t} = Z_{output}tanh(C_{t}), \tag{13}$$

$$y_{t} = \sigma\left(W_{t}h_{t}\right). \tag{14}$$

where Z_{forget}, Z_{input}, Z_{output} are vectors of data input from the current state and input data received from the previous node multiplied by the weights and then converted to values from 0 to 1 by a sigmoid activation function which acts as a gating function (0 means complete discard of information, 1 means complete retention of information). Thus Z_{forget} determines which information in C_{t-1} needs to be forgotten; Z_{input} determines which new information in X_{t} needs to be recorded; Z_{output} determines which information is the output of the current state. Z is converted to a value between −1 and 1 by the tanh activation function as the input data for C_{t}. In addition, C_{t} (cell state) and h_{t} (hidden state) represent the two transmission states of the memory cell to the next cell of the LSTM. y_{t} is obtained from h_{t} by σ transformation and represents the output of the memory cell.

However, for the EEG emotion recognition task, the current emotional state is correlated with both previous and subsequent information due to the latency of the device during signal acquisition. Bi-LSTM (Schuster and Paliwal, 1997) is an extension of LSTM consisting of a forward LSTM layer (fed the sequence, left to right) and a backward LSTM layer (reversed fed the sequence, from right to left) which can solve this problem. The out layer of the memory unit of Bi-LSTM is as follows:

$$y_t = \sigma(W_t(\overrightarrow{h_t} + \overleftarrow{h_t})). \tag{15}$$

TABLE 3 Division of OCER into three motions by K-MEANS.

Subject ID	Rating scale	Clustering center (Z-score) 1	2	3
1	Valence	−1.58	0.26	1.27
	Arousal	−0.98	0.65	1.85
	Stress	−0.90	−0.90	−0.90
2	Valence	−1.58	0.55	1.16
	Arousal	−0.98	−1.12	1.08
	Stress	−0.90	−0.90	−0.90
3	Valence	0.63	0.61	0.63
	Arousal	−2.40	−0.96	0.44
	Stress	0.23	−0.80	−0.90
4	Valence	−0.20	0.63	1.02
	Arousal	−0.41	−0.56	0.62
	Stress	0.23	0.46	0.38
5	Valence	−1.58	−1.53	−0.11
	Arousal	−3.11	−1.07	−0.98
	Stress	0.23	0.78	1.36
6	Valence	−0.35	0.22	0.63
	Arousal	−0.63	0.44	0.60
	Stress	2.30	0.73	2.01
7	Valence	−3.05	−1.58	−0.48
	Arousal	−0.98	−0.98	−0.98
	Stress	−0.90	−0.83	−0.90
8	Valence	0.14	−0.11	0.35
	Arousal	0.91	−0.27	0.44
	Stress	1.36	−0.90	0.23
9	Valence	−1.39	−0.45	0.51
	Arousal	−0.81	−0.60	−0.20
	Stress	2.78	1.10	0.41
10	Valence	−0.48	0.49	1.36
	Arousal	−0.27	0.91	1.69
	Stress	−0.90	−0.85	−0.90
11	Valence	−0.11	0.63	1.36
	Arousal	0.40	0.76	1.14
	Stress	0.23	0.23	0.23

All results are retained to 2 decimal places. The larger the score of Valence indicates the more positive; the larger the score of Arousal indicates the greater emotional intensity (no positive or negative directionality); the larger the score of Stress indicates the greater stress (negative directionality).

In addition, the LSTM contains overly numerous parameters, and the Bi-LSTM is twice as large as the LSTM, so it is easy to overlearn to produce the overfitting problem. The most common solution in deep learning is the utilization of dropout regularization (Hinton et al., 2012) which temporarily disconnects the input-hidden layer-output layer with a certain probability. However, temporarily dropping layer-to-layer connections in recurrent neural networks may cause direct loss of some of the previous memory. Therefore, we use the recurrent dropout method (Semeniuta et al., 2016) to act on the memory units; temporarily dropping a part of the links in h_t (hidden state) with probability p at each time step. This ensures that the output y_t does not lose the earlier important information while simultaneously solving the overfitting problem. Therefore, the features of past and future emotion information through this structure were combined in the out layer. Here, our temporal feature extraction module consists of two layers of internal memory cell units (32 and 16 respectively) with a 0.2 recurrent dropout rate of the bidirectional LSTM.

In summary, our proposed framework can automatically extract meaningful features for emotion classification from raw clean EEG data. Firstly, a channel-temporal attention mechanism is used to infer attention weights for raw EEG signals X successively along the channel and temporal dimensions and got re-coded EEG signals X_{c-s} , which improves the points of time representation of significant channel and emotional state changes. Next, CNNs (including two convolution-ELU layers) are used to extract spatial features of X_{c-s} to get feature maps X^f_{C-S}. Finally, all spatial feature maps X^f_{C-S} were packaged in time series input into a two-layer Bi-LSTM with a recurrent dropout function to learn temporal information from the spatial features maps for EEG emotion recognition.

Results and analysis

Firstly, we describe the division and preprocessing of the EEG dataset. Secondly, we displayed the result of the channel attention weights in the channel-temporal attention module. Finally, we introduce designed four groups of deep learning methods for demonstrating the validity of each module of our proposed method.

The division and preprocessing of electroencephalogram dataset

The standardization of the scores of the rating scale [Valence (−4,4), Arousal (−4,4) and Stress (1,7)] and the classification of emotions using K-means for 36 samples of each participant was completed in IBM SPSS Statistics (version 26). The related results were displayed in **Table 3**. Each participant's 36 trials were divided into three categories respectively: Clustering "1"

TABLE 4 The emotion classification of OCER and the data arrays.

Emotion classification	
Negative	72 samples (60 s)
Neutral	180 samples (60 s)
Positive	138 samples (60 s)
3s-dataset arrays	
Dataset	7800(seg) × 3(s) × 250(Hz/s) × 8(channels)
Label	7800 × 3(Negative, Neutral, Positive)

represented the "negative emotion"; Clustering "2" represented the "neutral emotion"; and Clustering "3" represented the "positive emotion". The advantage of using this method is that instead of using the equal criteria for all participants, each participant's criteria was used to classify the emotions. Therefore, there are 73 negative samples, 182 neutral samples and 141 positive samples in the EEG dataset (OCER). Then, after removing the technical and biological artifacts in the EEG dataset by using the method mentioned in section the division and preprocessing of electroencephalogram dataset, we found that artifacts of the 36-th trail from subject 4, the 11-th trail from subject 6, the 31-th and 32-th trails from subject 8, the 23-th trail from subject 9 and the 35-th trail from subject 10 could not be removed cleanly (the amplitude of EEG signals more than 200 μV) and they were excluded. Finally, we cut each clean trail using a 3-s non-repeating window. Therefore, the array of the EEG dataset became 7800 (390 × 20 segments) × 3 (seconds) × 250 (sample points/s) × 8 (channels). The details were shown in Table 4.

Electroencephalogram channel attention weights

To illustrate the different degrees of importance of each EEG signal channel for emotion recognition, the mean of ten times weight calculations of the channel attention in the channel-temporal attention module for OCER are shown in Figure 4. As shown, the weights of the channels for different emotions were significantly different. The EEG signals of the channels corresponding to the right brain regions (except F4 is less than 0.5) contributed more to positive emotions. The EEG signals the channels corresponding to the left brain regions (except P3 less than 0.5) contributed more to negative emotions. And the weights of channel F4 and channel F3 achieved significant advantages in neutral emotion. Further to demonstrate the contribution of different channels to the emotions, the one-way ANOVA was implemented on the 8-channel weights of the three emotions respectively. The weights of channel F8 and F7 had a significant ($F = 3.55$, $p < 0.01$) in negative emotion, channel P4 and T7 had a significant ($F = 3.39$, $p < 0.01$) in positive emotion, a non-significant for 8-channel in neutral emotion. This suggests that there are variances in the contribution of channels to different emotions and utilizing channel attention mechanisms could enhance the ability to discriminate between different emotions.

Parameters of proposed and baseline methods

The proposed framework mainly was implemented with the Keras module based on the TensorFlow framework and trained on NVIDIA GeForce GTX GPU. At first, each batch size (here denoted by None) of samples defined as (None, 3,250,8) was input into the CTA module and the output shape was the same as (None, 3,250,8). The samples were then fed into the CNN module which used the AdaBelief optimizer (Zhuang et al., 2020) with a learning rate of 1e-3 and the epsilon of 1e-7 to minimize the cross-entropy loss function. In order not to destroy the temporal information in the EEG signals, the size of the convolution kernel was set to 1×10×8 (height, width, depth) and the number of kernels was 8 the same as the number of EEG signal channels. This makes the number of channels of the feature maps of the output CNNs consistent with the number of channels of the EEG raw data. This causes each feature map in the input Bi-LSTM with a shape of (None, 3,250,8), which means that the time step is 3 and the features map was split up into three feeds that can be expressed as (None, 3,250 × 8). Therefore, the Bi-LSTM module further extracts the temporal features from the spatial feature maps containing temporal information. In the Bi-LSTM module, the dimension of the hidden states of the LSTM in each direction (forward/backward) of the two layers were 32 and 16, respectively. In addition, in every LSTM the recurrent dropout rate was set as 0.2. Initially, the input batch size is 10 and the epoch is set at 200. And the early stopping technique (Prechelt, 1998) is used during the training process: the training is stopped when the loss value of the test set no longer decreases in two epochs.

To demonstrate the validity of the three modules in the proposed framework, four groups of experiments were implemented: **Group A:** LSTM, Channel Attention-LSTM (CA-LSTM) and Channel-temporal Attention (CTA)-LSTM;

TABLE 5 Baseline and proposed method for EEG dataset emotion recognition.

	Channel attention	**Temporal attention**	**CNN**	**LSTM/Bi-LSTM**
RNN	×	×	×	√
C-RNN	√	×	×	√
CTA-RNN	√	√	×	√
CNN-RNN	×	×	√	√
C-CNN-RNN	√	×	√	√
Proposed method	√	√	√	√

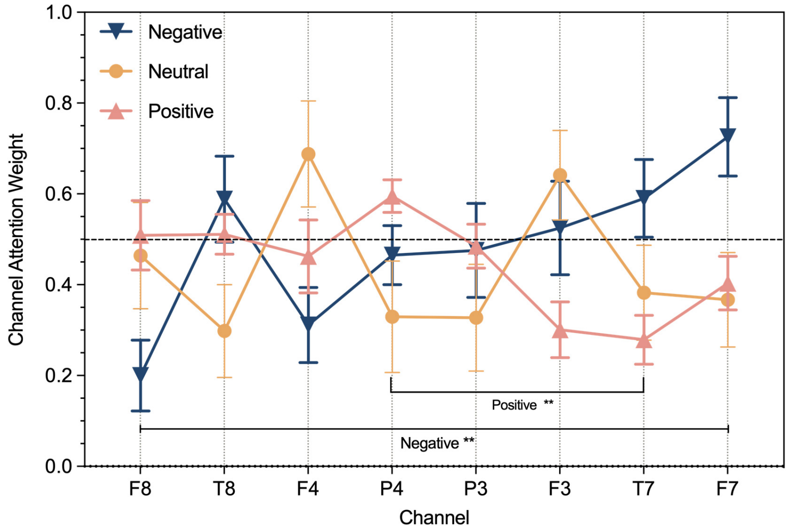

FIGURE 4
The result of channel weight on OCER dataset respectively for negative, neutral, and positive emotions. $^{**}P < 0.01$.

Group B: Bi-LSTM, CA-Bi-LSTM, and CTA-Bi-LSTM; **Group C:** CNN-LSTM, CA-CNN-LSTM, CTA-CNN-LSTM; **Group D:** CNN-Bi-LSTM, CA-CNN-Bi-LSTM and CTA-CNN-Bi-LSTM. Here the LSTM and Bi-LSTM are referred to generically as RNN. Except for the different number of RNN layers, the model including the CNN-RNN module used two layers of LSTM/Bi-LSTM with hidden states of dimensions 32 and 16. The model including the RNN module used 3 layers of LSTM/Bi-LSTM with hidden states of dimensions 64, 32, and 16. Because each layer of Bi-LSTM is combined with two directions of LSTM, the training parameters are twice as large as the LSTM. All models use the same parameter settings as the proposed method. Specific structures and parameters were shown in Tables 5, 6.

Results of experiments

Our work aimed to evaluate individuals' emotions during the periodic implementation of reminiscence therapy, in which our focus was on the individual's emotion recognition accuracy, rather than an emotional recognition model to accommodate all older adults. Therefore, the subject-dependent method was utilized for EEG emotion recognition. All samples of the OCER dataset (Table 4) were divided into training sets and test set based on the 10-fold cross-validation method. This method randomly divided the dataset into ten equal parts (nine parts as the training set and one part as the test set) and this process repeated 10 times. Finally, the number of samples in the training set was 7020 and the number of samples in the test set was 780.

The average accuracy of the results of the 10 test sets was used as the evaluation metric for the performance of the proposed framework and baseline methods. Further, a one-way ANOVA was performed on the results of average emotion recognition accuracy rate for four groups of 12 models to explore whether there was a significant in EEG emotion recognition across models. The detailed results were shown in Figure 5. As seen from the figure, for the average accuracy of emotion recognition on the OCER dataset: (1) Significance among groups A, B, C, D ($F = 372.8$, $p < 0.0001$); (2) Significance among the models within groups A, B, C, D ($p < 0.01$ or $p < 0.0001$), except between the CNN-LSTM model and the CA-CNN-LSTM model in group C ($p = 0.7756$, non-significant). (3) The proposed framework CTA-CNNN-Bi-LSTM in group D achieved the best emotion recognition accuracy with 98.75% on three emotions.

To demonstrate the contribution and performance of each module of the proposed framework on the recognition of negative, neutral, and positive emotions, we implemented confusion matrices on all models (see Figure 6). As can be seen, vertically, from the base models (LSTM, Bi-LSTM, CNN-LSTM, CNN-Bi-LSTM) to the front of the models adding the channel attention mechanism (CA) and adding the channel-temporal module (CTA), the recognition accuracy improves for almost in the three emotions. Specifically, the recognition accuracy of negative, neutral and positive emotions improved by at least 18%, 2%, and 9%, respectively. It proved the effectiveness of the CTA module in improving the model's performance in distinguishing between different emotions. Horizontally, from left to right, from the LSTM series models to the CNN-Bi-LSTM series models (except for the CA-CNN-LSTM model), the recognition accuracy improves for almost the three emotions. Specifically, the recognition accuracy of negative, neutral and positive emotions

TABLE 6 Array and total parameters of 3s-dataset (OCER) fed into different models.

Model	Input array	Main layers	Total params
RNN	None × 3 × 2000	3 Unit (64,32,16)	544,243/1108,963
C/CTA-RNN	(None × 3 × 250 × 8)reshape (None × 3 × 2000)	3 Unit (64,32,16)	544,243/1108,963
-CNN-RNN	(None × 3 × 250 × 8)reshape (None × 3 × 2000)	2 Conv (K = 8(1,10))2 Unit (32,16)	648 × 2 + 263411/530915

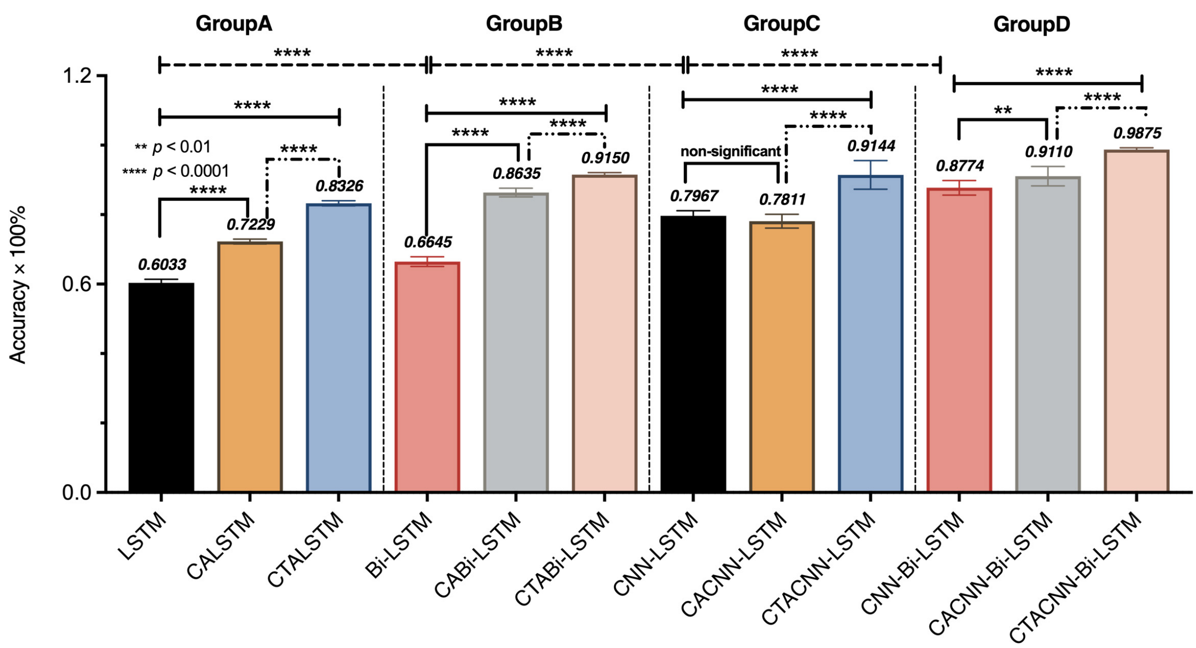

FIGURE 5
The results of mean accuracy (%) and one-way ANOVA in baseline and proposed methods on 3s-data set. The symbol ** means that $P < 0.01$ and is a statistically significant difference. The symbol **** means that $P < 0.0001$ is an extremely significant statistical difference.

improved by at least 21%, 9%, and 10%, respectively. It sufficiently demonstrated the superiority of CNN-Bi-LSTM in integrating the bi-directional temporal features (past and future information features) on the spatial features information in the EEG signals information to determine the current emotional state. The CTA-CNN-Bi-LSTM model achieved the best accuracy of emotion recognition for negative, neutral, and positive emotions.

Furthermore, to indicate the performance of the proposed framework on the emotion recognition of each individual, we conducted experiments on each individual. As Figures 7–9 show, the proposed framework CTA-CNN-Bi-LSTM almost achieved the best accuracy of emotion recognition for negative, neutral and positive emotions on each subject. In addition, for the base models, the RNN models did not perform well below 60% for each individual on negative emotions, but after adding the CTA module before the RNN models the individual's negative emotion recognition rate with an accuracy of more than 80%. And the CNN-RNN series models perform better than the RNN series in terms of positive emotion for each subject. There was no such significant tendency in negative emotion and neutral emotion for each subject. For the negative emotion, the CA-Bi-LSTM model performed better than the CA-CNN-Bi-LSTM on subjects 5, 6, and 11. For the neutral emotion, the CTA-Bi-LSTM model performed better than the CTA-CNN-LSTM model on subjects 1, 5, 6, 7, and 8. However, the proposed framework performed best on each individual for the three emotions.

Discussion

Principal results and limitations

The experimental results reveal that the CTA-CNN-Bi-LSTM framework performs better in EEG emotion recognition as the proposed framework combined consideration of the spatial features and two directions' temporal features which were extracted from the channels and temporal dimension of EEG signals most relevant to emotions.

In the first module of our proposed framework, the channel-temporal attention module applied to the clean EEG

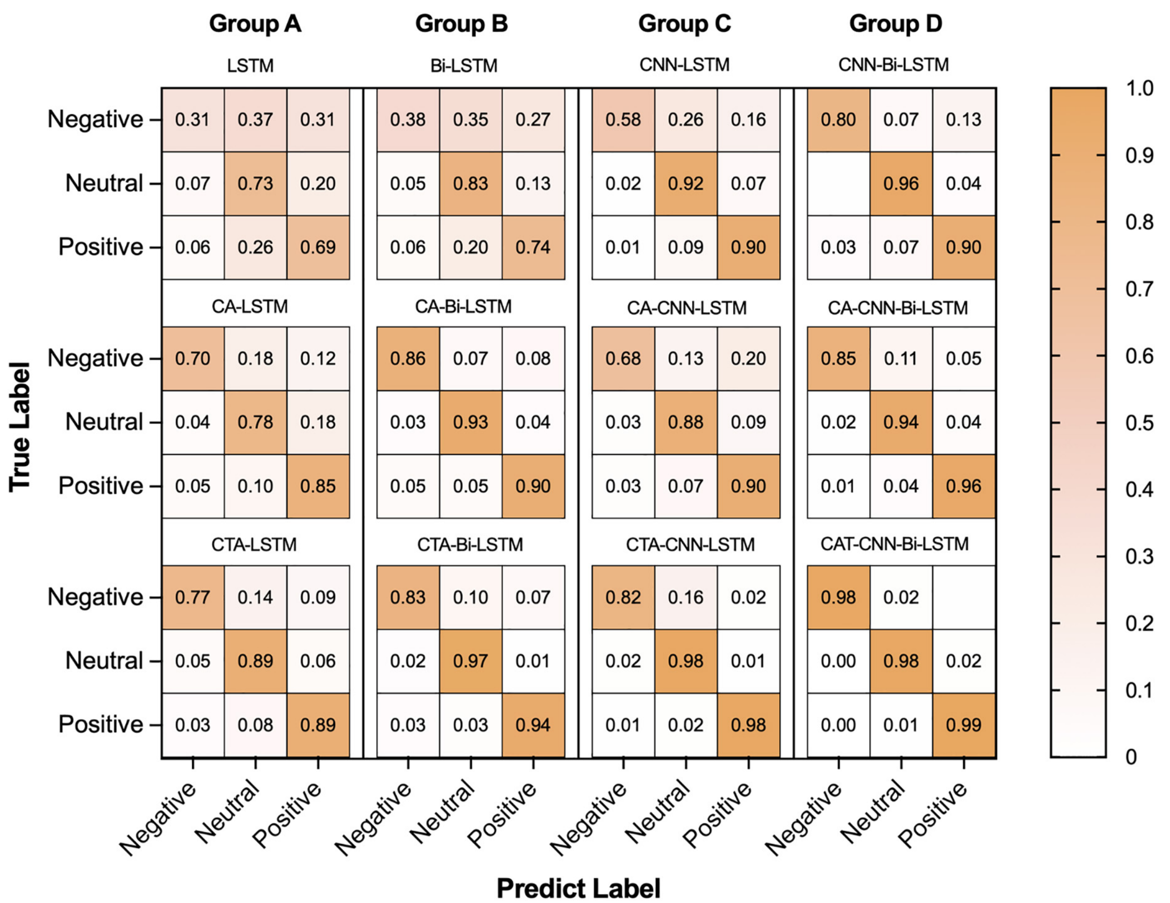

FIGURE 6
The result of confusion matrixes of negative, neutral, and positive emotions in baseline and proposed method.

raw data emphasized meaningful feature information and suppresses irrelevant information in both channel and temporal dimensions. Firstly, the channel weights were calculated under the global average pooling and global maximum pooling in the temporal dimension to obtain two channel statistical descriptions (two different angles of the global field of view). In contrast, the channel attention module in the previous study (Tao et al., 2020) only conducted global average pooling on the temporal dimension (T8 and F8 dominated among 14 electrodes in the DREAMER dataset; FC5, P3, C4, and P8 dominated among 40 electrodes in DEAP), which may have resulted in the inability to distinguish the contribution of channels to different emotions. The channel weights in this study were calculated so that the weights of F3 and F4 achieved significant advantages in neutral emotion. For negative emotions, channel weights greater than 0.5 are F3, T7, F7, and T8, meanwhile the weights of channels F8 (0.2) and F7 (0.73) had a significant ($F = 3.55$, $p < 0.01$) in negative emotion, which both suggested that they played a major role in the channels corresponding to the left-brain area. For positive emotions, the channel weights greater than 0.5 were F8, T8, and P4, and channel P4 (0.6) and T7 (0.28) had a significant ($F = 3.39$, $p < 0.01$) in positive emotion, which indicate that the right-brain area corresponding to the channel was dominant. These findings are consistent with previous studies: (1) The valence theory stated that left-brain areas predominantly process negative emotions and right-brain areas process positive emotions (Demaree et al., 2005); (2) EEG signals in the frontal lobe, lateral temporal lobe, and parietal lobe brain regions of the brain were the most informative on different emotions (Lin et al., 2010; Zheng et al., 2017; Özerdem and Polat, 2017; Tong et al., 2018). If it is necessary to reduce electrodes while ensuring a high recognition rate of emotions, the intersection of all emotion-dominated channels or channels with significant differences can be selected. This means that F3, F4, F7, and F8 can be chosen for the task of our study. Other tasks can recalculate channel weights according to this method.

When the recoded EEG data obtained directly using the channel attention is used for subsequent model learning, as shown in **Figure 5**, the average accuracy of the CA-RNN/CA-CNN-RNN model improved only slightly compared to RNN/CNN-RNN, except the CA-CNN-LSTM model was slightly lower than the CNN-LSTM model. However, from

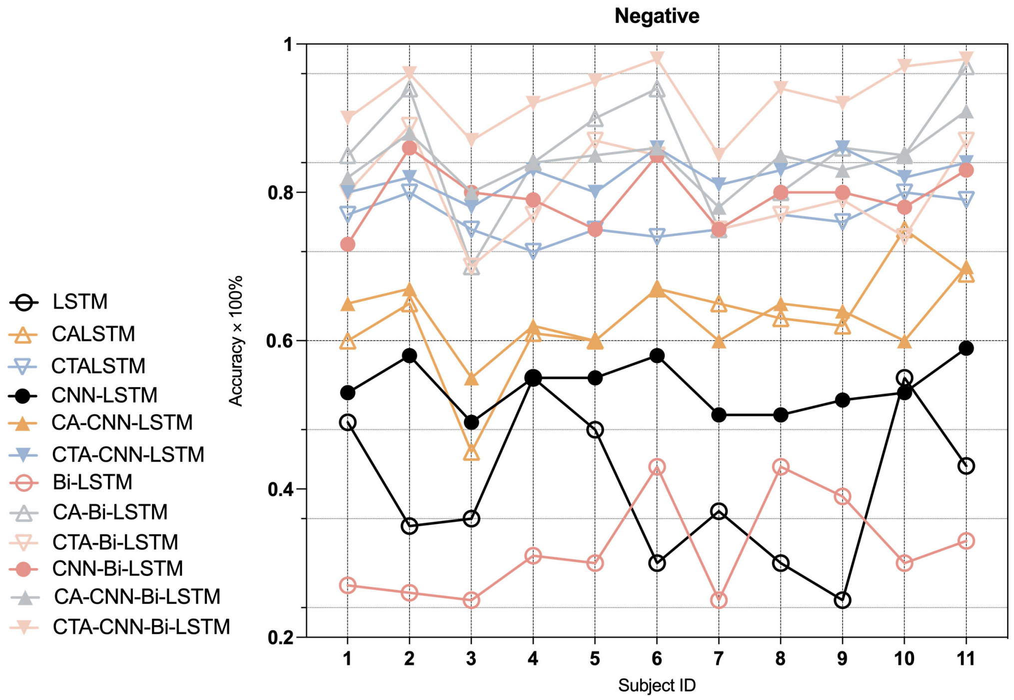

FIGURE 7
Average accuracy (%) of baseline and proposed method on the recognition of negative emotion in each individual.

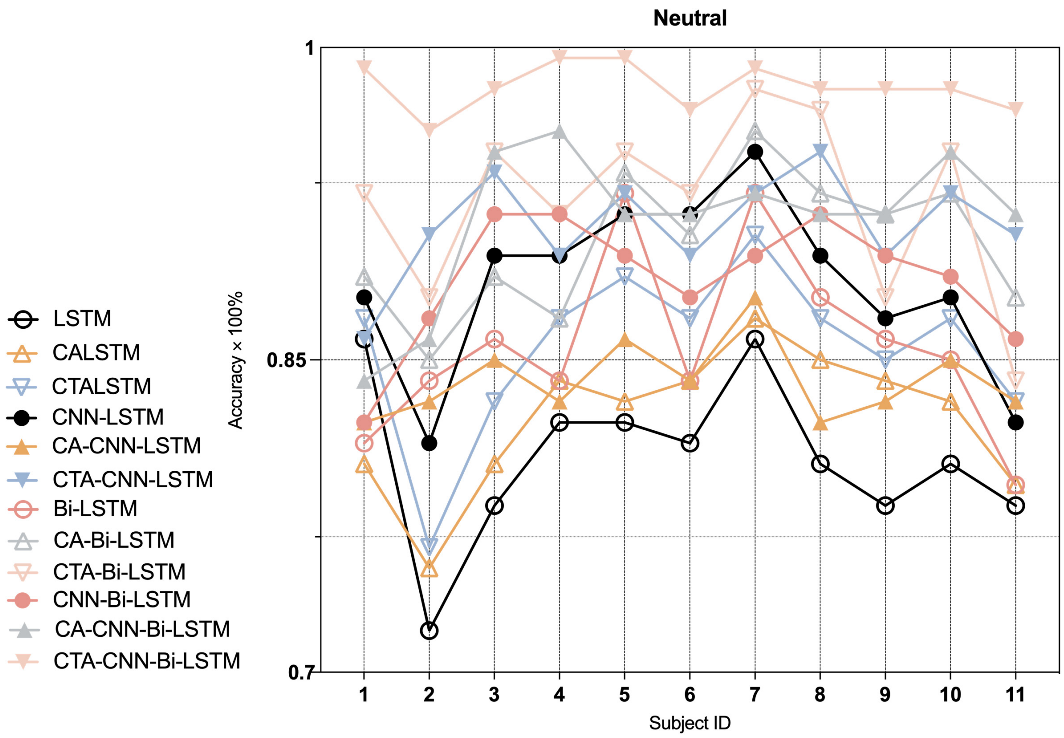

FIGURE 8
Average accuracy (%) of baseline and proposed method on the recognition of neutral emotion in each individual.

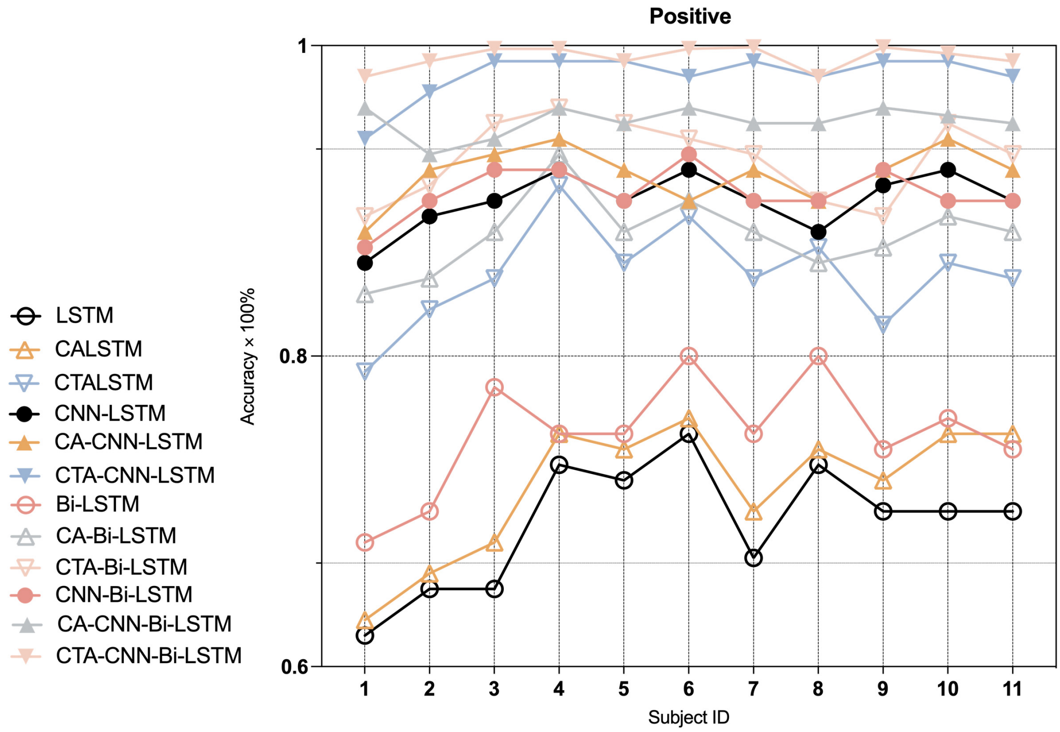

FIGURE 9
Average accuracy (%) of baseline and proposed method on the recognition of positive emotion in each individual.

Figure 6, the CA-CNN-LSTM improved the recognition accuracy of negative emotion by 10% over the CNN-LSTM model. The average accuracy of CTA-RNN/CTA-CNN-RNN not only increased but also achieved the minimum variance, demonstrating that the temporal attention mechanism did improve the representation of emotional state change time points in EEG signals while further suppressing the noise/artifact information. And the results were higher than the accuracy results of the previously mentioned related studies using channel selection (Alotaiby et al., 2015; Tong et al., 2018; Tao et al., 2020; Dura et al., 2021). Therefore, the EEG raw data was processed by the channel-temporal attention module to emphasize meaningful feature information and suppress irrelevant information in both channel and temporal dimensions.

In the second and third modules of our proposed framework, the recoded EEG signals (containing information on the most relevant channel and temporal dimensions to the task) from the channel-temporal attention module were fed into the CNNs and RNN to extract spatial and temporal features for emotion recognition. As Table 6 and Figure 5 shown, the training parameters of CNN-RNN without the channel-temporal attention mechanism (264,707/532,211) were much smaller than those of RNN (544,243/1108,963), while the average accuracy was substantially higher than that of RNN (19.34% and 21.29% improvement). This, as has been shown in previous studies (Sheykhivand et al., 2020; Zhang et al., 2020; Ramzan and Dawn, 2021), demonstrates that it is necessary to consider both spatial and temporal information of EEG signals for emotion recognition. And the CA-CNN-RNN models achieved an average accuracy of 78.11% (1.56% lower than CNN-LSTM model and 10% improvement on negative emotion) and 91.11% (3.37% improvement over CNN-Bi-LSTM model), respectively. It was further demonstrated that channel attention suppresses the information of irrelevant channels and enhances emotional information. Finally, the results of the CTA-CNN-Bi-LSTM model proposed in this study achieved the highest average accuracy of 98.75%. It further demonstrated that channel-temporal attention suppresses both the information of irrelevant channels and the irrelevant information of temporal dimensions. The CTA-CNN-Bi-LSTM model with an improvement of 7.25% over the CTA-CNN-LSTM model. The reason is that Bi-LSTM model learned the temporal information on the spatial feature map from both forward and reverse directions while LSTM model learned from only one direction in the forward direction. This is consistent with the conclusions in the study (Siami-Namini et al., 2019): Bi-LSTM model outperforms the LSTM model on temporal series forecasting tasks. As our experiments also employed 10-fold cross-validation, the average accuracy standard deviation values can more objectively demonstrate that the proposed framework has a high emotion recognition performance. From the result of confusion matrixes of negative emotion (**Figure 6**), it was found that the recognition rate of the basic RNN and CNN-RNN models on negative emotion was far lower than the other two emotions, firstly, the number of samples of negative emotion was lower than the other two emotions, and secondly, negative emotion seemed to be easily misclassified as neutral emotion. However, through the channel attention mechanism (CA) and the channel-temporal attention (CTA), the recognition of negative emotions with small samples is enhanced and the accuracy rate is further improved. Finally, we conducted experiments on each individual, and the proposed framework CTA-CNN-Bi-LSTM almost achieved the best accuracy of emotion recognition for negative, neutral, and positive emotions on each subject.

In summary, EEG raw 3s-dataset achieved the highest accuracy of 98.75% by the proposed method CTA-CNN-Bi-LSTM. It included channel-temporal attention module (CTA), spatial feature extraction (CNNs) and Bi-LSTM. The proposed method improved the average accuracy by 38.42% compared to the LSTM model. Of which, the channel-temporal attention module (CTA-CNN-Bi-LSTM) led to an average accuracy improvement of 11.01% for CNN-Bi-LSTM. The convolutional module (CNN-Bi-LSTM) resulted in an average accuracy improvement of 21.29% for Bi-LSTM. And the bi-directional LSTM module (CNN-Bi-LSTM) led to an improvement of 8.07% in CNN-LSTM. It indicates that the convolution module (spatial information of the EEG signal) provides the largest contribution (21.29%) to the accuracy improvement of the framework. The bi-directional LSTM module after the CNN module provides little enhancement (8.07%) to the framework. However, the addition of the channel-temporal attention module before the convolution module (by suppressing the irrelevant channel information and temporal dimensional noise) led to a further significant improvement (11.01%) in the accuracy of the model while reducing the std. dev. to a minimum. Thus, our proposed framework was demonstrated to be effective in extracting spatial and temporal information from recoded EEG signals (including most relevant channels and temporal dimensional information to emotion) for emotion recognition. However, our framework used the dataset divided using the subject-dependent method as the usage scenario of our task, and it has not been demonstrated whether the same high performance of emotion recognition can be achieved on the dataset divided by the subject-independent method.

Conclusion and future work

The proposed framework in this paper used clean raw EEG signals (removal of muscle artifacts by MEMD-CCA) as input to an end-to-end deep learning method (without feature engineering) for emotion recognition. The proposed CTA-CNN-Bi-LSTM framework considered both spatial features and bidirectional temporal features in the channel dimension and temporal dimensions that were most relevant to emotions in the raw EEG signals. At first, the channel-temporal attention module suppresses the channel information in both the EEG signal that is not related to emotion and the noise in the spatial dimension in each channel. Later, the CNN-RNN module first extracts the spatial features in the recoded EEG signals and then feeds them into the Bi-LSTM network in order. Therefore, the Bi-LSTM learned the temporal information simultaneously from two directions (forward LSTM for previous information and reverse LSTM for future information) on the spatial feature maps. Finally, the results of four group experiments have demonstrated that CTA-CNN-Bi-LSTM improved EEG emotion recognition compared to other methods and achieved the highest average accuracy of 98.75% for negative, positive, and neutral emotion recognition. Therefore, the proposed framework reduces the emotion-independent information and noise in the channel and temporal dimensions, CTA-CNN-Bi-LSTM significantly improved the accuracy of emotion recognition in the dataset compared with existing methods.

However, this work may not achieve high emotion recognition accuracy for new individuals and requires retraining the model/fine-tuning the model to achieve it, which is not conducive to later applications of real-time emotion monitoring. In future work, after collecting EEG signals from more individuals, perhaps self-supervised learning models such as a contrastive learning model which learns knowledge on its own from unlabeled data, could be used to potentially realize a plug-and-play real-time EEG emotion recognition system. It focuses on learning the common features between similar examples and distinguishing the differences between non-similar examples to construct an encoder. This encoder has the ability to encode similar data of the same category and make the encoding results of different categories of data as different as possible.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Author contributions

LJ and NK designed the experiments. LJ carried out the experiments. LJ, PS, and FZ analyzed the results. LJ and DC prepared the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Association of time to groin puncture with patient outcome after endovascular therapy stratified by etiology

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Background: Randomized clinical trials and large stroke registries have demonstrated a time-dependent benefit of endovascular treatment (EVT) in patients with acute ischemic stroke (AIS) due to large vessel occlusion (LVO). The aim of this study was to investigate whether this could be applied to different stroke subtypes in a real-world single-center cohort.

Materials and methods: Consecutive ischemic stroke patients with LVOs presenting within 24 h after symptom onset were prospectively registered and retrospectively assessed. Baseline multimodal imaging was conducted before EVT. Independent predictors of functional independence [90-day modified Rankin scale (mRS), 0–2] and any incidence of intracranial hemorrhage (ICH) were explored using a stepwise logistic regression model in the entire cohort and in stroke subtypes.

Results: From 2015 to 2020, 140 eligible patients received EVT, of whom 59 (42%) were classified as large artery atherosclerosis (LAA)-related. Time from last known normal to groin puncture was identified as an independent predictor for functional independence in patients of cardioembolic (CE) subtype [odds ratio (OR) 0.90 per 10 min; 95% CI 0.82–0.98; P = 0.013] but not in the LAA subtype and the whole cohort. Groin puncture within 6 h after the time of last known normal was associated with a lower risk of any ICH in the whole cohort (OR 0.36, 95% CI 0.17–0.75, P = 0.007). Sensitivity analysis of patients with complete imaging profiles also confirmed the above findings. Besides, compared with patients of the CE subtype, the LAA subtype had a smaller baseline ischemic core volume, a better collateral status, a slower core growth rate, and a numerically smaller final infarct volume.

Conclusion: Faster groin puncture has a more pronounced effect on the functional outcome in patients of CE subtype than those of LAA subtype.

Reducing time to groin puncture is of great importance in improving the prognosis of patients after EVT, especially those of CE subtype, and reducing the incidence of any ICH in all patients.

KEYWORDS

acute ischemic stroke, endovascular treatment, time to treatment, collateral circulation, perfusion imaging

Introduction

Endovascular treatment (EVT) has become a routine clinical practice in the early management of acute ischemic stroke (AIS) due to large vessel occlusion (LVO). With the assistance of advanced imaging, patients with a favorable imaging profile can be treated with EVT up to 24 h after the time of last known normal (LKN) (Albers et al., 2018; Nogueira et al., 2018). Previous studies have demonstrated a strong time dependency on treatment benefits. With every hour saved for the time from onset to groin puncture, there is an absolute increment of the probability of functional independence by 3.4–5.3% (Saver et al., 2016; Mulder et al., 2018; Jahan et al., 2019), an absolute decline of the risk of symptomatic intracranial hemorrhage (ICH) by 0.88% (Jahan et al., 2019), and an absolute decrease of mortality at 90 days by 5.3% (Mulder et al., 2018). This time-dependent relationship exists across both randomized clinical trials (RCTs) (Saver et al., 2016) and registry studies (Mueller-Kronast et al., 2017; Mulder et al., 2018; Jahan et al., 2019), conservative therapeutic time window (Saver et al., 2016; Mulder et al., 2018; Jahan et al., 2019), and emerging tissue window (Mundiyanapurath et al., 2017; Snyder et al., 2020).

Nevertheless, these studies (Saver et al., 2016; Mueller-Kronast et al., 2017; Mundiyanapurath et al., 2017; Mulder et al., 2018; Jahan et al., 2019; Snyder et al., 2020) are limited to the Western population, among whom the prevalence of large artery atherosclerosis (LAA) is much lower than their Asian counterparts (Kim and Kim, 2014). Accumulating evidence has suggested that LAA-related stroke has a distinct etiology and pathophysiology from cardioembolic (CE) stroke. Unlike the abrupt onset of cardiac embolism, patients with LAA are subjected to a chronic period of hemodynamic instability during which collaterals have been recruited (Liebeskind et al., 2011), compensating for the deficient blood supply and preserving more salvageable tissue at the time of treatment (Kim et al., 2009). Based on the finding that ischemic core growth rate is dependent on collateral status (Lin et al., 2021), it is thus assumed that patients with LAA-related stroke may be less time-sensitive in terms of the benefit of EVT.

To address this hypothesis, we present here a real-world single-center experience of EVT from China, investigating the association of time to groin puncture with functional outcome after endovascular therapy stratified by two major stroke subtypes, namely, LAA and CE.

Materials and methods

Study population

Consecutive patients with AIS presenting within 24 h of LKN at Huashan Hospital between April 2015 and December 2020 were recruited prospectively for the institutional stroke registry. Written informed consent was obtained from all participants, and the study was approved by the Huashan Ethics Committee (No. 2013002).

At our institution, patients with suspected AIS presenting within 24 h of LKN routinely underwent emergent multimodal imaging studies including non-contrast computed tomography (NCCT), CT angiography of the head and neck, and perfusion CT, if there were no contraindications to the contrast agent. Candidacy for EVT was conformed to the latest Chinese guidelines and high-quality evidence (Albers et al., 2018; Nogueira et al., 2018). Endovascular intervention may consist of a simple angiography, stent thrombectomy maneuver, angioplasty, or a combination of the above. Further details regarding EVT candidacy and treatment are provided in the **Supplementary material**.

In this study, patients were included if they met the following criteria: (1) those had LVO or severe stenosis in the anterior cerebral circulation, confirmed by CT angiography (e.g., extracranial or intracranial segment of internal carotid artery and M1/M2 segment of the middle cerebral artery and anterior cerebral artery; severe stenosis was defined as $\geq$ 70% lumen narrowing); (2) aged $\geq$ 18 years; and (3) underwent EVT upon admission (i.e., entry into the angiography suite and initiation of groin puncture). Patients were excluded if they (1)

Abbreviations: EVT, endovascular treatment; LKN, last known normal; LAA, large artery atherosclerosis; LVO, Large Vessel Occlusion; LPT, last known normal to groin puncture time; CE, cardioembolic; mTICI, modified thrombolysis in cerebral ischemia scale; mRS, modified rankin scale; NIHSS, National Institute of Health Stroke Scale; NCCT, non-contrast CT; ICH, intracranial hemorrhage; sICH, symptomatic intracranial hemorrhage.

had no CT scan within 2 weeks after EVT; (2) lost to 90-day follow-up; and (3) had missing data on hospital arrival time or groin puncture time.

Data collection and imaging assessment

Demographic data, medical history, stroke subtypes, imaging features, procedural time metrics, and treatment details were recorded. Stroke subtypes were determined using the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classification (Adams et al., 1993). Patients with atrial fibrillation were grouped into the LAA subgroup if there was a fixed focal stenosis greater than 50% after thrombus retrieval (Jia et al., 2018), multiple/multistage ischemic lesions in a single internal carotid artery (ICA) territory, contrast-enhanced plaque upon high-resolution magnetic resonance imaging (MRI), or a previous history of stereotyped ischemic attacks (Zotter et al., 2021).

Imaging features derived from baseline CT, CT angiography, perfusion CT, digital subtraction angiography, and postprocedural NCCT were independently assessed by 2 neuroradiologists (YZ and LH). A third experienced neuro-interventionist (YL) was consulted in cases of discrepancy. Perfusion CT was post-processed by the commercial software MIStar (Apollo Medical Imaging Technology, Melbourne, Victoria, Australia) with singular value deconvolution with delay and dispersion correction. Infarct core (relative cerebral blood flow $< 30\%$) and acute hypo-perfused lesion [delay time (DT) > 3 s] were defined according to the previously validated thresholds (Bivard et al., 2014, 2017). Penumbra volume was calculated by subtraction of infarct core volume from acute hypoperfused lesion volume. The volume ratio of DT > 6 s/DT > 3 s was used to quantify collateral status (Hong et al., 2019), with a lower DT > 6 s/DT > 3 s ratio indicating better collateral flow. The collateral index ratio was deemed zero if the volume of DT > 3 s was equal to zero. Successful recanalization was determined by the modified thrombolysis in cerebral ischemia (mTICI) score of 2b or 3 on the final angiography run. The core growth rate was estimated by the core infarct volume on baseline perfusion CT divided by the time from LKN to perfusion imaging (Vagal et al., 2018; Lin et al., 2021). Follow-up MRI scans were obtained preferably within 3–7 days after EVT and were semi-automatically measured for the final infarct volume using the MIStar Region of Interest (ROI) tool by 2 neuroradiologists (YZ and LH) blinded to recanalization grade. In cases where follow-up MRI diffusion-weighted imaging was unavailable, follow-up NCCT was used as an alternative. If present, hemorrhagic transformation was incorporated in the final infarct volume.

The presence of ICH on CT was determined by an NCCT scan routinely performed 24-h post-procedure or anytime when a clinical deterioration was observed. A repeated CT scan was performed to distinguish petechial hemorrhage from contrast staining when there was uncertainty over a postprocedural hyperdensity on NCCT. Symptomatic ICH (sICH) was defined according to the Second European-Australasian Acute Stroke Study (ECASS-II) criteria (Hacke et al., 1998).

Study outcomes

The primary outcome was functional independence, defined as a modified Rankin scale (mRS), 0–2 at 90 days. The 90-day follow-up was assessed *via* telephonic interview by a trained nurse who was blinded to the clinical data. The secondary outcome was any incidence of intracranial hemorrhage post-EVT.

Statistical analysis

All statistical analyses were performed on Stata/SE 15.1 (StataCorp, College Station, TX, USA). Mean and standard deviation (SD) were used to describe continuous variables if normally distributed; otherwise, median and interquartile range (IQR) were displayed. Frequency and percentage were used to describe categorical variables. Differences in baseline characteristics were compared using Student's *t*-test or Wilcoxon rank-sum test for continuous variables, and chi-squared or Fisher's exact test for categorical variables. Variables with $P < 0.05$ in the univariate analyses or with clinical relevance [age, baseline National Institute of Health Stroke Scale (NIHSS) score, sex, successful recanalization, and for the imaging cohort, infarct core (Campbell et al., 2019) and final infarct volume (Boers et al., 2019)] were entered into a stepwise logistic regression analysis with a removal probability of 0.05. Adjusted odds ratios (ORs) with their 95% CIs were presented. To adjust for imaging features and account for potential selection bias caused by contraindication to perfusion study or follow-up imaging scan, a sensitivity analysis was conducted in patients with complete imaging data. Additional analysis was restricted to patients with pure LVO to exclude the effect of residual anterograde collateral flow in patients with severe stenosis. A two-sided $P < 0.05$ was considered statistically significant.

Results

Of 191 patients with AIS receiving EVT at our tertiary stroke center between April 2015 and December 2020, 140 (92.7%) were included in the primary analysis (**Supplementary Figure 1**), of whom 129 had pure LVO. The median (IQR) age was 71 (61–78) years with a mean (SD) baseline NIHSS score of 15 (6). Patients arrived at the emergency room with a median

(IQR) of 159 (78–300) min after LKN, and the median (IQR) door to puncture time was 159 (126–191) min. The median (IQR) LKN to puncture time was 337 (235–480) min with 79 (56%) patients being punctured within 6 h. A total of 57 (41%) patients achieved functional independence (mRS, 0–2) at 90-day follow-up and any ICH occurred in 54 (39%) patients of whom 18 (13%) had sICH according to ECASS-II criteria (Hacke et al., 1998). Baseline demographic, clinical, and imaging data of patients with mRS of 0–2 and 3–6 were listed in the **Supplementary material** (**Supplementary Table 1**).

A total of 59 (42%) patients were classified as LAA subtype according to the TOAST criteria, whereas 56 (40%) patients were diagnosed as CE subtype. Patients in the LAA group were younger and had a milder symptom. A significantly higher proportion of patients was treated with EVT outside the 6-h time window in the LAA group with a more delayed LKN to puncture time. However, there were no significant differences regarding the rate of successful recanalization, functional independence, and any ICH between the two groups (**Table 1**).

Multivariate logistic regression showed that for the entire cohort, younger age, successful recanalization, and absence of any ICH but no time to groin puncture were independent predictors of 90-day good functional outcome (**Table 2**). However, for patients punctured within 6 h after the time of LKN, every 10-min delay from hospital arrival (door) to puncture was associated with a 16% decline in the OR of functional independence (OR 0.84; 95% CI 0.74–0.96; $P = 0.008$; **Table 2**).

An explorative analysis revealed a significant association between LKN to groin puncture time (LPT) and functional independence (OR 0.94; 95% CI 0.89–1.00; $P = 0.04$) as well as a significant multiplicative interaction between stroke subtypes and LPT ($P = 0.031$) when restricting patients to LAA and CE subgroups. Subgroup analyses were subsequently performed. In the subset of patients diagnosed with CE-related stroke, a shorter LPT (OR 0.90; 95% CI 0.82–0.98; $P = 0.013$; **Table 2** and **Figure 1A**) was identified as an independent predictor of a good outcome, as well as younger age, absence of the history of diabetes mellitus, and absence of any ICH. Nevertheless, in patients with LAA-related stroke, the association of LPT and clinical outcome did not show a statistical significance (OR 1.01; 95% CI 1.00–1.01; $P = 0.635$; **Table 2** and **Figure 1B**).

In addition, LPT within 6 h was also independently associated with a lower risk of any ICH [OR 0.36; 95% CI (0.17–0.75); $P = 0.007$; **Supplementary Table 2**] in the entire cohort.

For the sensitivity analysis confined to patients with complete imaging data, 23 patients were excluded from the primary study (**Supplementary Figure 1**), while similar results were shown for a logistic regression model on 90-day functional outcome and any ICH (**Supplementary Tables 2**, **3**). In addition, the imaging cohort demonstrated two distinct imaging profiles classified as LAA and CE stroke subtypes. Compared with patients of CE subtype, patients of the LAA subtype had a smaller baseline ischemic core volume [median (IQR), 5 (1, 22) vs. 11 (5, 27) ml, $P = 0.044$], a better collateral status [DT6/DT3, median (IQR), 0.17 (0.08, 0.38) vs. 0.31 (0.15, 0.45), $P = 0.016$], and a slower core growth rate [median (IQR), 1.2 (0.3, 3.6) vs. 4.9 (2.0, 9.8) ml/h, $P < 0.001$]. On follow-up imaging, a numerically smaller final infarct volume was shown in patients of the LAA subtype [median (IQR), 13.5 (3.8, 79.9) vs. 33.8 (13.3, 97.3) ml, $P = 0.057$]. The two distinct imaging profiles between LAA and CE stroke subtypes may explain the discrepant time-dependent benefit of EVT observed in these two subtypes. Additional analysis restricting patients with pure LVO yielded similar results (**Supplementary Tables 4**, **5**).

TABLE 1 Characteristics and outcomes of patients with LAA vs. CE.

	LAA ($n = 59$)	CE ($n = 56$)	P-value
Demographics			
Age, median (IQR)	67 (12)	72 (10)	**0.03**
Female	17 (29%)	30 (54%)	**0.01**
NIHSS, mean (SD)	12 (8, 17)	17 (14, 19)	**< 0.001**
Medical history			
Smoking	26 (45%)	13 (24%)	**0.02**
Hypertension	42 (71%)	35 (62%)	0.32
Atrial fibrillation	8 (14%)	40 (71%)	**< 0.001**
Diabetes mellitus	17 (29%)	19 (34%)	0.55
Stroke	16 (27%)	11 (20%)	0.34
Antiplatelet	8 (14%)	12 (21%)	0.27
Statin	8 (14%)	3 (5%)	0.13
Imaging features			
Occlusion site			0.25
M1	33 (56%)	40 (71%)	
M2/ACA	3 (5%)	4 (7%)	
ICA	17 (29%)	9 (16%)	
Tandem	6 (10%)	3 (5%)	
Treatment details			
General anesthesia	28 (47%)	29 (52%)	0.64
IVT	23 (39%)	29 (52%)	0.17
LDT (min), median (IQR)	213 (127, 502)	96.5 (49.5, 234.5)	**< 0.001**
DPT (min), median (IQR)	165 (126, 212)	141 (120, 174.5)	**0.05**
LPT (min), median (IQR)	368 (305, 625)	247.5 (191.5, 386.5)	**< 0.001**
LPT within 6 h	28 (47%)	39 (70%)	**0.02**
Technical efficacy			
mTICI ≥ 2b	42 (71%)	37 (66%)	0.55
Outcome			
90 days mRS, 0–2	29 (49%)	22 (39%)	0.29
Any ICH	22 (37%)	22 (39%)	0.83
sICH-ECASS-II	9 (15%)	10 (18%)	0.71
90 days mortality	8 (14%)	15 (27%)	0.08

LAA, large artery atherosclerosis; CE, cardioembolism; LDT, last known normal to hospital arrival time; LPT, last known normal to puncture time; DPT, door to puncture time.

TABLE 2 Predictors of functional independence (mRS, 0–2) at 90 days.

	OR (95% CI)	*P*-value
All patients (*n* = 140)		
Age	0.94 (0.91, 0.98)	0.001
mTICI ≥ 2b	3.27 (1.32, 8.06)	0.001
Any ICH	0.12 (0.04, 0.31)	< 0.001
Patients punctured within 6 h after LKN (*n* = 79)		
NIHSS	0.86 (0.76, 0.96)	0.011
mTICI ≥ 2b	4.80 (1.30, 17.67)	0.018
Any ICH	0.06 (0.01, 0.28)	< 0.001
DPT[†]	0.84 (0.74, 0.96)	0.008
LAA patients (*n* = 59)		
Age	0.91 (0.86, 0.97)	0.002
Any ICH	0.17 (0.04, 0.67)	0.011
CE patients (*n* = 56)		
Age	0.85 (0.77, 0.95)	0.004
Any ICH	0.01 (0.00, 0.19)	0.002
LPT[†]	0.90 (0.82, 0.98)	0.013
Diabetes mellitus	0.08 (0.01, 0.69)	0.021

[†]Odds ratios are scaled per 10 min of delay in the listed intervals. LPT, last known normal to puncture time; DPT, door to puncture time.

Discussion

In this study, we report our single-center analysis of patients with LVOs of anterior circulation undergoing EVT within 24 h after time LKN. We demonstrate that in a real-world clinical setting where the LAA subtype accounted for 42% of all patients and groin puncture time was mostly delayed, EVT could still be effectively performed with a 41% functional independence rate at 90 days. The time-dependent benefit of EVT was observed in patients treated within 6 h after onset and in patients with CE-related stroke, rather than in the overall population and in patients with LAA-related stroke. Our study highlights the discrepancy in the time-dependent benefit of EVT stratified by stroke etiology.

Of note, 41% of patients in our cohort achieved 90-day functional independence (mRS of 0–2), which is within the range of 38–56% functional independence rate reported in other real-world registries with an extended therapeutic time window (Zi et al., 2017; Jansen et al., 2018; Huo et al., 2019; Jahan et al., 2019; Flottmann et al., 2021; Jia et al., 2021). However, the rate of functional independence was lower than that in other Asian cohorts (Zi et al., 2017; Huo et al., 2019; Jia et al., 2021). Meanwhile, the mortality rate and sICH rate were much higher than those in Endovascular Therapy for Acute Ischemic Stroke Trial (EAST) (Huo et al., 2019) and another Chinese nationwide registry (Jia et al., 2021). This may be in part due to an elderly population in our cohort with a median age of 71 years as opposed to 62–65 years in others (Zi et al., 2017; Huo et al., 2019; Jia et al., 2021). Apart from that, a significant treatment delay was observed in our cohort. This delay was even more obvious when compared with Western registries (Jansen et al., 2018; Jahan et al., 2019), whereas the rate of functional independence was comparable. Since no remarkable difference regarding age or stroke severity was noticed among our cohort and the Western registries, one possible explanation could be the different stroke subtype compositions across ethnicity and the less pronounced time effect in patients with LAA-related stroke.

Intracranial atherosclerosis is a major cause of ischemic stroke in Asian populations (Kim and Kim, 2014). In line with the Endovascular Treatment for Acute Anterior Circulation Ischemic Stroke Registry (ACTUAL) (Hao et al., 2017), our study demonstrated a 42% of patients classified as LAA subtype, while LAA only accounts for 19% in the German Stroke registry (Flottmann et al., 2021) and 13% in a large-scale Dutch registry (Boodt et al., 2020).

With a limited sample size, our study demonstrated a pronounced time-dependent benefit of EVT in patients with CE-related stroke, while no such association was observed in the overall cohort and in the subset of patients classified as LAA-related stroke. This is in accordance with one recent finding that patients with LAA have similar functional outcomes after EVT with CE patients despite a delay in symptom onset to recanalization (Lee et al., 2020). This discrepancy in the association between time and outcome may be explained by the robustness of collaterals and the resultant infarct growth in different subtypes. Along with other studies, our study showed that patients of the LAA subtype had significantly better collateral status (Zhang et al., 2018) and milder symptoms at presentation (Lee et al., 2020) than those of the CE subtype. Rather than a sudden occlusion in CE-related stroke, patients with LAA-related stroke suffer from a chronic period of steno-occlusive status and hemodynamic instability (Liebeskind et al., 2011). Previous studies (Lee et al., 2017) have demonstrated that angiogenic factors such as vascular endothelial growth factor (VEGF) were induced as a result of transient cerebral ischemia, building collateral pathways, thus improving collateral recruitment in patients of the LAA subtype. Our study further connected collateral status with both tissue outcome and clinical outcome. Accumulating evidence suggests that, besides a larger ischemic core at baseline (Chen et al., 2019), patients with poorer collateral status also have a faster infarct growth rate (Vagal et al., 2018; Lin et al., 2021), both of which have been reported to be independent predictors of poor clinical outcomes (Campbell et al., 2019; Chen et al., 2019). Similarly, by demonstrating distinct collateral profiles possessed by patients of CE subtype vs. those of LAA subtype, our study further found differences in core growth rate and final infarct volume in between. The status of collateral flow has been shown to modify the time-dependent benefit of EVT. Hwang et al. demonstrated

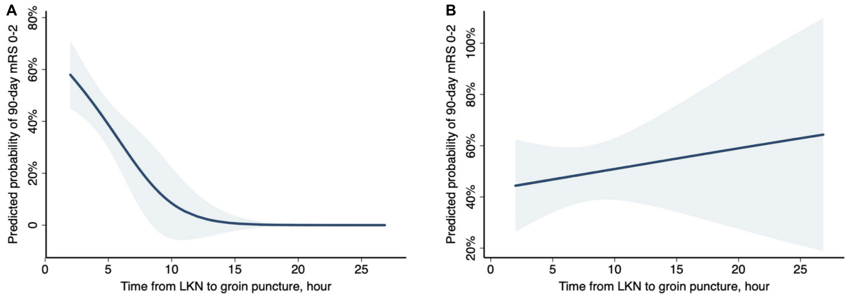

FIGURE 1
Probability of functional independence (90-day mRS, 0–2) by time from last known normal (LKN) to groin puncture in stroke subtypes. Curves (blue shading indicates 95% CIs) represent the predicted probabilities of functional independence under logistic regression models. **(A)** In CE-related strokes, after adjustment for age, baseline NIHSS, diabetes, and any ICH, there was a 47% decreased probability of functional independence per hour treatment delay (aOR, 0.53; 95% CI, 0.32–0.88; $P = 0.013$). **(B)** In LAA-related strokes, after adjustment for age, baseline NIHSS, and any ICH, the association between LKN to puncture time and functional independence did not reach a statistical significance (aOR, 1.05; 95% CI, 0.91–1.21; $P = 0.528$).

that the OR of favorable outcome in patients with a poor collateral status significantly dropped as onset to reperfusion time or puncture to reperfusion time increased, while no such association was found in patients with good collaterals (Hwang et al., 2015). Shirakawa et al. (2021) previously reported the discrepancy in time-dependent benefit by stroke etiology in a Japanese Registry. However, without complete perfusion evaluation at baseline, the study was not able to explore further behind the phenomena. Assisted by detailed imaging analysis, our study was capable of validating the hypothesis and highlighted again the role of collateral status (Hwang et al., 2015; Vagal et al., 2018; Lin et al., 2021) in the fast-saving-brain track.

Furthermore, the association between earlier treatment and better clinical outcome was significant in patients punctured within 6 h from LKN, but this association became insignificant when including patients treated beyond 6 h from LKN. This is consistent with one single-center analysis (Snyder et al., 2020). Similar findings have also been reported in larger registries (Jahan et al., 2019; Nogueira et al., 2022), with a rapid loss of EVT benefit with treatment delay in the initial hours, transitioning to a slower loss of benefit in the periods later. Early after onset, regardless of infarct growth rate, most patients could have a small to moderate infarct core unrestricted by imaging criteria, while later after onset, patients with poor collaterals and fast infarct growth rate could proceed with large infarcts inappropriate for further intervention and were thus excluded. In other words, the remaining patients who received EVT in the late time window were selected to be with better collaterals and slower infarct growth, attenuating the association between LPT with outcomes. This is also reflected by the temporal distribution of different stroke subtypes. With less robust collaterals and potentially faster infarct growth, CE-related stroke presenting in the late time window was less likely selected out and only accounted for 35% of strokes beyond 6 h after LKN in contrast to 58% in the early 6-h time window.

Despite not being selected as an independent predictor for functional outcome in the overall population, LKN to puncture within 6 h was associated with a lower rate of ICH, which stood as an independent predictor for poor functional outcome. Similar findings have been reported in a pooled analysis of RCTs (Raychev et al., 2020) as well as registry studies (Hao et al., 2017; Jahan et al., 2019), reflecting the increased vulnerability to reperfusion injury with prolonged ischemia (Raychev et al., 2020). These findings serve as a strong reminder that rapid treatment should always be pursued even if time-dependent benefit is less pronounced in the LAA subtype.

Our study has several limitations. First, the data reported in this study are from a single-center endovascular database with a limited sample size. It is thus possible that with a larger sample size, the time-dependent benefit from EVT in the LAA subtype would be identified. Further validation in a larger cohort is warranted. Second, there was missing of perfusion imaging data and follow-up imaging, which accounted for 16% (23/140) either due to the absence of imaging scan or reconstruction failure. Nonetheless, the primary study cohort and the sensitivity analysis with complete perfusion data demonstrated similar results.

Conclusion

Our single-center cohort of EVT with LVO of anterior circulation has a distinct composition of stroke subtypes in comparison with Western registries, with a higher proportion of patients with LAA-related stroke. Delay of groin puncture has a more pronounced effect on functional outcome in patients of CE subtype than those of LAA subtype. Reducing treatment delay is of great importance in improving the prognosis of patients after EVT, especially in those of CE subtype, and reducing the incidence of any ICH in all patients.

Data availability statement

The data that support the findings of this study are available from the corresponding authors upon reasonable request.

Ethics statement

The studies involving human participants were reviewed and approved by the Huashan Ethics Committee. The patients/participants provided their written informed consent to participate in this study.

Author contributions

LH, XC, and QD contributed to conception and design of the study. LY and SL organized the database. YZ, LH, and YL assessed the imaging. YZ performed the statistical analysis and wrote the original draft. LH and XC reviewed and edited the draft. XC and QD supervised the whole investigation. All authors have read and approved the submitted manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2022.884087/full#supplementary-material

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