ALTERNATE FORMAT RESEARCH ARTICLE

Alzheimer's & Dementia
**Translational Research**
*& Clinical Interventions*

# Moyamoya disease: A human model for chronic hypoperfusion and intervention in Alzheimer's disease

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## Abstract

**Introduction:** Chronic cerebral hypoperfusion has been considered the etiology for sporadic Alzheimer's disease (AD). However, no valid clinical evidence exists due to the similar risk factors between cerebrovascular disease and AD.

**Methods:** We used moyamoya disease (MMD) as a model of chronic hypoperfusion and cognitive impairment, without other etiology interference.

**Results:** Based on the previous reports and preliminary findings, we hypothesized that chronic cerebral hypoperfusion could be an independent upstream crucial variable, resulting in AD, and induce pathological hallmarks such as amyloid beta peptide and hyperphosphorylated tau accumulation.

**Discussion:** Timely intervention with revascularisation would help reverse the brain damage with AD hallmarks and lead to cognitive improvement.

**KEYWORDS**
Alzheimer's disease, cognitive impairment, hypoperfusion, metabolism, moyamoya disease, revascularization

# 1 | NARRATIVE

Vascular changes or pathologies are the earliest common precursors for subsequent catastrophic events, such as stroke and neurodegenerative processes leading to dementia and Alzheimer's disease (AD).[1] In recent years, the relationship between cerebrovascular pathology and AD has gained increasing attention. Evidence has emerged that vascular changes might accelerate the cognitive changes associated with AD pathology or take an active part in the earliest phase of AD pathogenesis.

## 1.1 | Cerebral blood flow reduction and AD

Brain functioning requires constant cerebral blood flow (CBF) for ensuring the adequate delivery of oxygen, glucose, nutrients, and removal of carbon dioxide and cellular waste.[2] Given the tight interactions between the CBF and neuronal activity, CBF provides critical insights into the proper functioning of the brain.[3] Moreover, the blood flow reduction is correlated with the increased risk for dementia as observed in normal, healthy aging.[4,5] In addition, the Alzheimer's Disease Neuroimaging Initiative (ADNI) has shown that lower resting CBF in AD-vulnerable regions, such as medial temporal, inferior temporal, and inferior parietal lobes, had faster rates of decline for everyday functioning in individuals without dementia.[6] Further, reduced CBF has been linked with increased amyloid beta (A$\beta$) deposition levels, with more severe white matter hyperintensities, and brain atrophy in AD patients.[7–9] Several brain regions in AD mouse models exhibited reduced CBF on high field arterial spin labeling magnetic resonance imaging (ASL-MRI; 7–11.4 Tesla) in the areas such as the occipital cortex, cerebral cortex, hippocampus, and thalamus. However, the brain regions most affected by CBF are very heterogeneous across the published literature.[10] Hypoperfusion mouse models indicated that chronic CBF reductions resulted in AD-like memory deficits and pathologies. However, this generally required more severe CBF deficits than seen in AD patients.[10]

## 1.2 | Existing hypotheses and pathological homeostasis in AD

Various hypotheses exist on the upstream causal events on the pathophysiology of sporadic AD. For example, vascular changes or pathologies may be the earliest common precursors for the subsequent neurodegenerative processes leading to dementia and AD.[1] According to the "two-hit hypothesis,"[11] vascular risk factors could lead to neurovascular unit (NVU) and blood-brain barrier (BBB) dysregulation and, subsequently, CBF reduction, initiating a cascade of events that precedes dementia. Other hypotheses such as the "amyloid cascade hypothesis" and "tau hypothesis" have also attained varying degrees of acceptance.[12,13] However, due to the long preclinical period of AD, the pathogenic hallmarks often evolve into a homeostasis state before becoming symptomatic.

**RESEARCH IN CONTEXT**

1. **Systematic review**: We carefully reviewed the relationship among typical sporadic Alzheimer's disease (sAD) hallmarks, as well as the comprehensive studies about moyamoya disease (MMD)–related brain damage and cognitive impairment.

2. **Interpretation**: By demonstrating the relationship among typical sAD hallmarks, we considered the pathogenic burdens would evolve into a homeostasis state before becoming symptomatic, which will bring difficulties for sAD treatment. An alternative therapeutic strategy is to focus on the pre-homeostasis period, or a more widely targeted intervention. Showing the similarities between MMD and sAD, we drew the hypothesis that chronic cerebral hypoperfusion can be an independent upstream variable resulting in sAD, and MMD can be considered an early-stage model in that case.

3. **Future directions**: Future work should focus on the MMD cohort studies and the possibility of revascularization treatment for sAD.

"Pathological homeostasis" is a stable systemic state, consisting of various feedback loops and cascade reactions among sporadic AD (sAD) pathologic burdens (A$\beta$, phospho-tau [p-tau], and impaired NVU components, etc.). Broadly, the homeostasis contains at least three of the alteration scales (Figure 1). The medium scale includes interactions among AD pathologic burdens. For example, A$\beta$ deposition and pathological tau trigger NVU dysfunctions,[14,15] affecting vessel architecture, CBF, and vascular permeability.[16,17] Dysfunction of the NVU furthers triggers A$\beta$ accumulation and tau hyperphosphorylation.[18] A$\beta$ induces tau oligomer formation and directly promotes tau aggregation.[19–23] In addition, A$\beta$, pathological tau, and NVU interactions can be intermediated by the local inflammatory environment alteration (outer scale), including A$\beta$,[24–26] tau,[27–31] and NVU/BBB[17,32–37] interaction with various inflammatory molecules and cells. Moreover, in the inner scale, intracellular alterations contribute to pathological homeostasis by dysregulated calcium, subcellular components, energy metabolism, and so on, which are summarized as the "calcium hypothesis,"[38] highlighting the core role of cytosol $Ca^{2+}$ as receptor (e.g., metabolic crisis, $Ca^{2+}$ dyshomeostasis induced by free radical oxidative damage), amplifier (e.g., calcium-dependent second and third messenger changes), and effecter (e.g., mitochondria breakdown, caspase-dependent apoptosis, etc.). A recent update of this hypothesis focused on the small and prolonged $Ca^{2+}$ concentration dyshomeostasis equivalence to large transient $Ca^{2+}$ increase damage.[39]

## 1.3 | The need for a chronic hypoperfusion model

Current mouse models do not capture the full spectrum of pathogenic factors that contribute to AD. These studies mainly rely on the
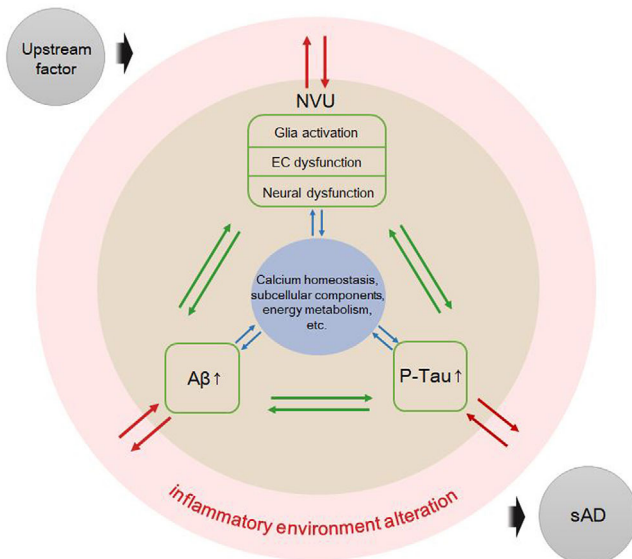
**FIGURE 1** Pathological homeostasis in AD. A stable systemic state consists of various feedback loops and cascade reactions in the three biological alteration scales. Inner scale is the intracellular alteration. The medium-scale includes interactions among the sAD pathologic burdens (Aβ, p-tau, impaired NVU components, etc.). The outer scale is the local inflammatory alteration. Aβ, amyloid beta peptide; AD, Alzheimer's disease; EC, endothelial cell; NVU, neurovascular unit; p-tau, phosphorylated tau; sAD, sporadic Alzheimer's disease



**FIGURE 2** Vasculopathy features and surgical procedures for MMD. A, Difference between the growing features of normal and moyamoya vessels. Bifurcation of normal brain vessels is generally per the Fibonacci sequence, while the moyamoya vessels are more aggressive, showing exponential growth; (B) STA-MCA bypass. The MMD patient has left MCA stenosis and moyamoya vessels of the skull base. After bypass, the blood flow of the left hemisphere increased with the disappearance of moyamoya vessels. Such sutures are usually performed on the 1 mm wide vessels. MCA, middle cerebral artery; MMD, moyamoya disease; STA, superficial temporal artery

mouse models that overexpress the mutant form of amyloid precursor protein (APP) or tau. Thus, the results obtained from these studies may be challenging to transfer to the clinic, although some studies have layered onto AD mice.[40] On the other hand, no direct casual evidence in human subjects has been associated with decreased CBF. Also, it is an independent predominant factor for inducing AD pathogenesis because chronic cerebrovascular disease and AD share the same risk factors, for example, aging,[41,42] smoking, diabetes, and atherosclerosis.[43] Additionally, vascular and neurodegenerative pathologies interact and are synergistic, even in asymptomatic individuals.[44] This evidence clarifies whether vascular changes can be the earliest AD pathogenesis or contribute to accelerating AD pathology's cognitive changes. Therefore, a human hypoperfusion model with pure etiology is required to investigate the causal mechanism from chronic cerebral hypoperfusion to AD and the possibility of a revascularization strategy for prevention and the intervention of AD.

## 1.4 | Moyamoya disease and cognitive impairment

Moyamoya disease (MMD) is a rare cerebrovascular disease, having a feature of chronic hypoperfusion. In 1969, Dr. Suzuki named the disease "moyamoya," a Japanese word meaning a "puff of smoke," due to the appearance in angiography,[45] breaking the "Fibonacci gene" in creatures (Figure 2A). The initial pathological changes include only chronic stenosis of the main arteries. Unusually, the compensatory ves-
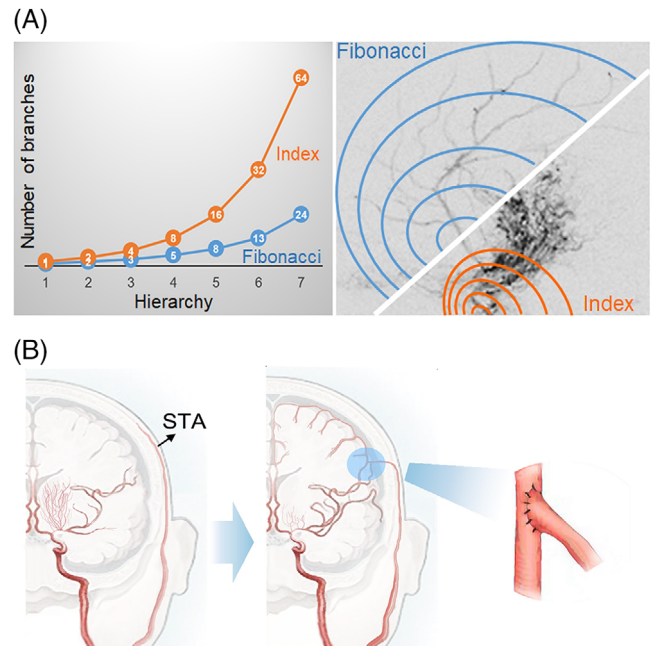
sel's extension forms in a reticular shape, which is its unique feature. MMD is found worldwide; however, it is more common in Asian countries, particularly in Japan, South Korea, and China, with a prevalence of 0.3 to 0.6/100,000. The specific genetic backgrounds of those populations might be one of the contributing factors.[46] Notably, most MMD patients are young to middle-aged, different from those with ischemic stroke caused by cerebrovascular atherosclerosis, which occurs primarily in later life. The smoke vessel's appearance is the only criteria to distinguish it from other cerebral hemadostenosis. However, it's unclear if this typical feature is caused only by chronic hypoperfusion or other reasons. The etiology of MMD is still under investigation, except for specific genetic mutations, for example, ring finger protein 213 (RNF213) association.[47] With progressive stenosis from intracranial carotid arteries to the anterior/middle/posterior cerebral arteries, patients are at an increased risk for ischemic stroke. Meanwhile, as the disease progresses, the weak moyamoya vessels continue developing and tend to bleed.

The clinical symptom of cognitive impairment in MMD was first reported in 2008.[48] As evaluated by neuropsychological tests, 30% to 40% of MMD patients had moderate to severe impairment in cognitive domains such as executive function, orientation, comprehension, calculation, and memory.[48,49] Moreover, the cognitive impairment in MMD can occur in the absence of cerebral infarction or hemorrhage

or might even show normal brain appearance in MRI.[50] Brain functional remodeling leads to more insidious impairment such as neuronal activity decline,[51] brain network dysfunction,[52] and network interaction abnormalities.[53] The existing evidence supports that hypoperfusion of MMD is an association with brain tissue degeneration and cognitive impairment.

## 1.5 | Revascularization as the intervention

According to the initial hypoperfusion nature, bypass surgery is the only surgical treatment for MMD, as angioplasty is unsuitable for progressive Willis's circle stenosis. Superficial temporal artery (STA) to middle cerebral artery (MCA) bypass can help in augmenting or restoring CBF into the ischemic territory. However, the suture on the 1 mm wide vessels is extremely meticulous needlework (Figure 2B), and therefore the recipient territory can be determined as needed. Moreover, compared to medication, bypass surgery effectively reduces 5-year recurrent stroke risk by 25%.[54]

In MMD patients, revascularization improves cognitive function and brain network connectivity.[55] In AD studies, recovered vascular transport is a probable contributor to the removal of A$\beta$. This effect could be mediated by binding transport proteins such as apolipoprotein E/J (apoE/J), BBB receptors such as lipoprotein receptor-related protein 1/2 (LRP1/2), and receptor for advanced glycation end products (RAGE) that clears A$\beta$ away from the brain interstitial fluid across the BBB.[56,57] Some anti-diabetic agents such as glucagon-like peptide 1 (GLP-1) analogs and peroxisome proliferator-activated receptor (PPAR) agonists can also benefit the NVU because of their vasoactive abilities to regulate CBF. These agents promote glucose uptake, protect against oxidative injury, reduce neuro-inflammation and mitochondrial dysfunction, and even reduce the A$\beta$ oligomers and plaque load in a mouse model.[58–60] By increasing CBF by their vasodilator effects, some antihypertensive drugs can also improve NVU function. They show antioxidant and neuroprotective effects, improve endothelial function, reduce vascular inflammation, and attenuate the neuronal deterioration induced by A$\beta$.[61,62] Therefore, it's possible that recovered CBF could reverse AD pathology and cognitive impairment; thus, revascularization may be a potential therapeutic strategy for selected AD patients.

Microsurgical techniques can help neurosurgeons perform delicate bypass and achieve significant blood influx. However, acute hyperperfusion can result in temporal or even permanent impairment.[63] As a result, some patients with MMD experience cognitive decline after the revascularization surgery.[63] However, redistribution of blood flow after the bypass can have long-term improvement although the prognosis of the procedure is widely debatable and unclear. Therefore, we combined several techniques for precision bypass in our center. With the assistance of intraoperative electrocorticogram (ECoG) and indocyanine green (ICG) flow analysis, we could locate the aridest area and choose the proper recipient vessels.

Of note, chronic brain hypoperfusion is not the only independent factor underlying the pathology of AD. Future studies are required to

validate the upstream event, but it would only provide limited mechanisms of molecular signal cascades that mediate cognitive impairment. One speculative strategy is to link our hypothesis to testable pivot pathophysiology events discussed below.

## 2 | CONSOLIDATED RESULTS AND STUDY DESIGN

### 2.1 | Pathological vascular morphology in MMD and AD brain

MMD and AD share similar pathological vascular morphology to some extent. For example, *post mortem* studies in AD brains have demonstrated several vascular alterations, such as fragmented string vessels, irregularities in the capillary surface, changes in vessel diameter, thickening, vacuolization, and local rupture of the capillary basement membrane, are associated with vascular A$\beta$ accumulation.[64] Further, brain tissue remodeling similarities such as gray matter density, white matter alteration, and dendrite density loss are other features reported in MMD imaging studies.[50,65,66]

### 2.2 | Metabolism alteration in MMD and AD brain

A long period of chronic hypoperfusion can alter brain metabolism and may be related to hypoperfusion severity. Our preliminary study showed two examples of metabolism alteration in earlier and later stages of ischemia (Figure 3A). In a patient with earlier-stage MMD, decreased right parietal perfusion and impaired glycometabolism were detected by ASL analysis and $^{18}$fluorodeoxyglucose positron emission tomography computed tomography ($^{18}$FDG PET-CT), respectively. However, increased proteometabolism was seen by in situ proteometabolism, as indicated by amide proton transfer-chemical exchange saturation transfer (APT-CEST). In contrast, in the later-stage MMD patients with bilateral internal carotid artery occlusion, proteometabolism was also impaired along with global perfusion and glycometabolism. Thus, the dual-phase change of proteometabolism may be correlated with the pathophysiologic progression of brain hypoperfusion. Intriguingly, the dual phase of metabolism alteration was also seen in animal and clinical AD studies.[67] For example, in MR-CEST studies, cerebral glucose metabolism was decreased in both A$\beta$ and tauopathy models.[68,69] However, variable levels of proteometabolism, even in negative correlation, are also detected for cognition in AD patients.[67,70,71] Thus, the dual phase of protein metabolism alteration in AD progression may be similar to MMD (Figure 3B).

### 2.3 | Cognitive impairments in MMD patients and correlations with CBF

As a pilot study, we enrolled twelve female and eight male MMD patients and five female and five male controls (diagnosed as
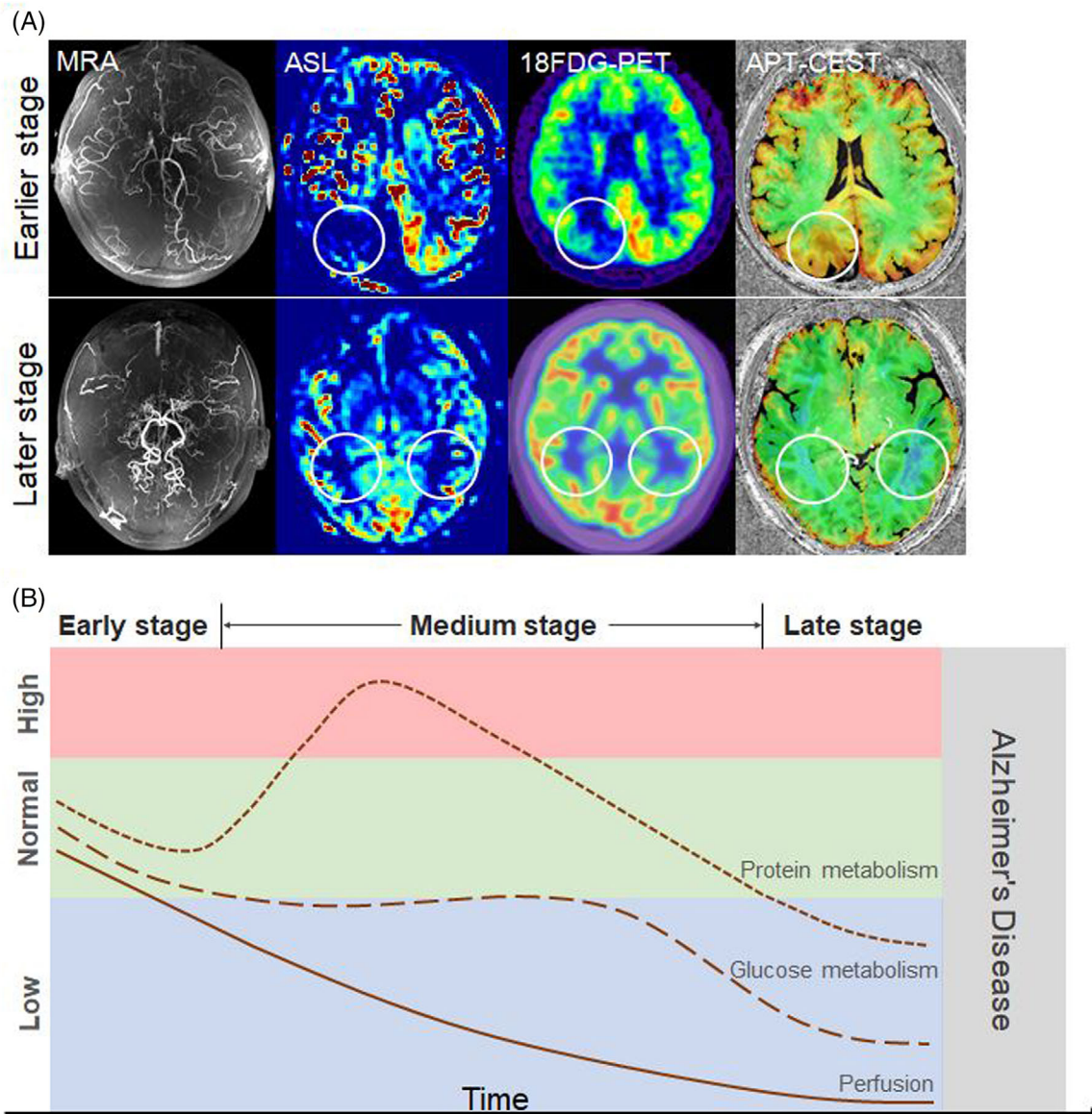
**FIGURE 3** Metabolism alteration in MMD and AD brain. A, Metabolism alteration in MMD patients with early and late stage disease. Upper: earlier stage imaging showed impaired 3D-TOF-MRA; perfusion (ASL), and glycometabolism ($^{18}$FDG PET) in the right parietal lobe; however, proteometabolism (APT-CEST) was increased. Lower: later stage imaging showed impaired 3D-TOFMRA, perfusion, and glycometabolism, and probe metabolism in the bilateral posterior temporal lobe. B, The dual phase of protein metabolism alteration in sAD progression might be having similarities to MMD. AD, Alzheimer's disease; APT-CEST, amide proton transfer-chemical exchange saturation transfer; ASL, arterial spin labelling; FDG, fluorodeoxyglucose; MMD, moyamoya disease; PET, positron emission tomography; sAD, sporadic Alzheimer's disease; TOF-MRA, time of flight magnetic resonance angiography

intracranial aneurysm, arachnoid cyst, cavernous malformation) with of comparable age. The onset manifestations of MMD patients were asymptomatic or transient ischemic attack (TIA) without image-confirmed stroke history. Cognitive function was evaluated by a battery of neuropsychological tests. CBF images were standardized with a cerebellum standardization method to obtain a relative CBF (rCBF) value.[72] We extracted the mean rCBF of regions of interest (ROIs) of frontal, parietal, temporal, and occipital lobes of each hemisphere for ROI-based analysis. Scores of Auditory Verbal Learning Test (AVLT),

Digit Symbol Substitution Test (DSST), Boston Naming Test (BNT), Trail Making Test (TMT), and Verbal Fluency Test (VFT) of 20 MMD patients were all significantly lower than controls (Figure 4A). Correlations between the mean rCBF from each lobular ROI and scores of neuropsychological tests were also significant. For instance, lower VFT scores (language function) were remarkably related to the rCBF decline in right temporal, parietal, occipital, and left temporal lobe, while lower TMT scores (executive function) were correlated with right frontal temporal and parietal hypoperfusion (Figure 4B).

(A)
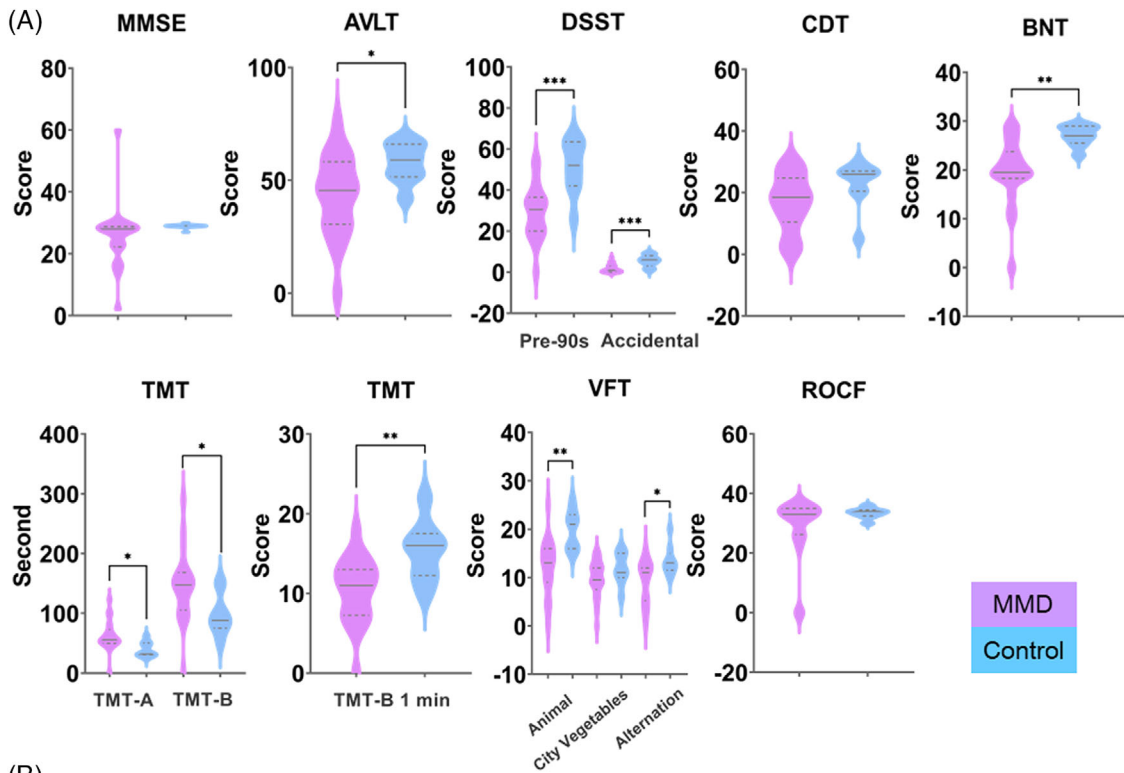


(B)



|  |  | LF | LP | LO | LT | RF | RP | RO | RT |
|---|---|---|---|---|---|---|---|---|---|
| MMSE |  | 0.005 | 0.000 | 0.019 | 0.012 | 0.044 | 0.011 | 0.051 | 0.057 |
| AVLT |  | 0.002 | 0.020 | 0.001 | 0.082 | 0.077 | 0.102 | 0.136 | 0.174 |
| DSST | Pre-90s | 0.020 | 0.045 | 0.093 | 0.092 | 0.052 | 0.112 | 0.336 | 0.255 |
|  | Accidental memory | 0.277 | 0.092 | 0.138 | 0.049 | 0.008 | 0.010 | 0.049 | 0.003 |
| CDT |  | 0.034 | 0.095 | 0.083 | 0.115 | 0.009 | 0.089 | 0.150 | 0.180 |
| BNT |  | 0.006 | 0.007 | 0.001 | 0.002 | 0.026 | 0.068 | 0.129 | 0.145 |
| TMT | TMT-A | 0.003 | 0.001 | 0.007 | 0.038 | 0.089 | 0.072 | 0.315 | 0.337 |
|  | TMT-B | 0.012 | 0.023 | 0.002 | 0.008 | 0.077 | 0.052 | 0.065 | 0.083 |
|  | TMT-B-1min | 0.003 | 0.002 | 0.003 | 0.000 | 0.265 | 0.121 | 0.254 | 0.228 |
| VFT | Animal | 0.004 | 0.000 | 0.013 | 0.003 | 0.037 | 0.014 | 0.204 | 0.187 |
|  | City vegetables | 0.003 | 0.034 | 0.078 | 0.203 | 0.080 | 0.235 | 0.428 | 0.402 |
|  | Alternation | 0.010 | 0.035 | 0.023 | 0.113 | 0.126 | 0.074 | 0.195 | 0.302 |
| ROCF |  | 0.001 | 0.002 | 0.047 | 0.080 | 0.025 | 0.024 | 0.242 | 0.281 |

0.0 — 0.5 R squared    P<0.05

**FIGURE 4** Cognitive impairments in MMD patients and the correlations to rCBF. A, Index scores of cognition scales in MMD patients and normal controls. *$P < .05$, **$P < .01$, ***$P < .001$ compared to control. Two-tailed Student's t-test was used. B, R-squared between lobular rCBF and index scores of cognition scales. Simple linear regression was used, presented with R-squared. Correlations with statistical significance are emphasized with green frames. F, frontal; L, left; MMD, moyamoya disease; O, occipital; P, parietal; R, right; rCBF, relative cerebral blood flow; T, temporal
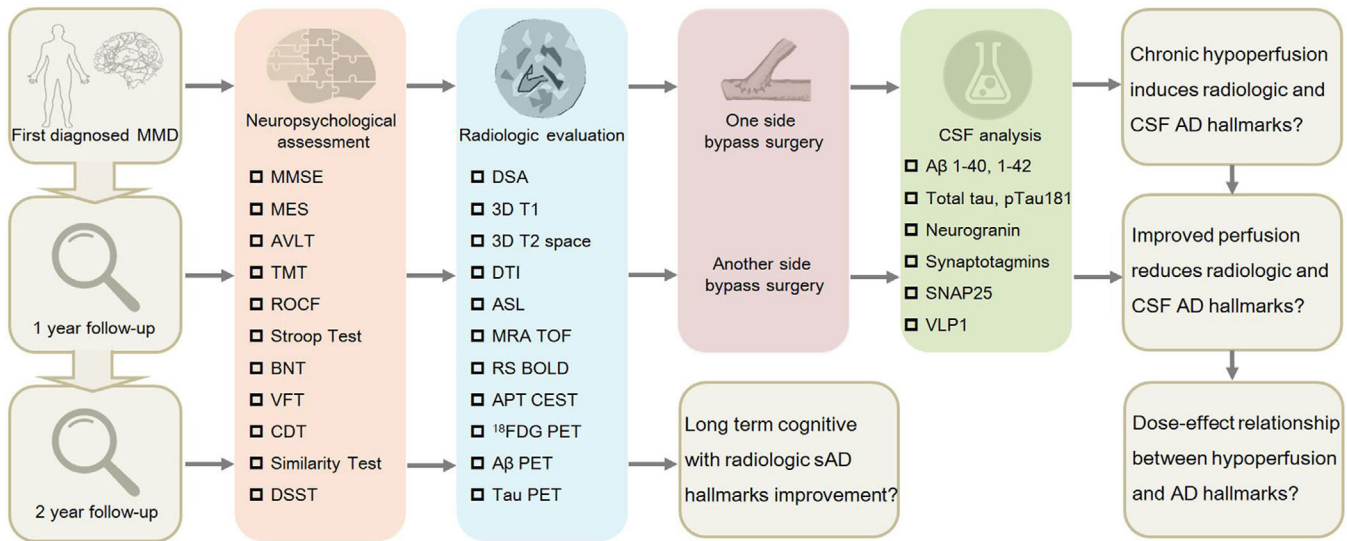
**FIGURE 5** Flow diagram of the MMD cohort. A$\beta$, amyloid beta; AD, Alzheimer's disease; APT-CEST, amide proton transfer-chemical exchange saturation transfer; ASL, arterial spin labelling; AVLT, Auditory Verbal Learning Test; BNT, Boston Naming Test; CDT, Clock Drawing Test; CSF, cerebrospinal fluid; DSA, digital subtraction angiography; DSST, Digit Symbol Substitution Test; DTI, diffusion tensor imaging; [18]FDG: [18]fluorodeoxyglucose, MES, Memory and Executive Screening Test; MMSE, Mini-Mental State Examination; PET, positron emission tomography; ptau, phosphorylate tau; ROCF, Rey-Osterrieth Complex Figures test; RS BOLD, resting-state blood oxygen level-dependent; SNAP25, synaptosome associated protein 25; TMT, Trail Making Test; TOF-MRA, time of flight magnetic resonance angiography; VFT, Verbal Fluency Test; VLP1, neuronal visinin-like protein 1

## 2.4 | Purpose of the study

MMD can be recognized as an ideal chronic hypoperfusion human model that can cause cognitive impairments or even AD. However, in that case, MMD is considered early-stage AD. Based on this verifiable model, we proposed that chronic brain hypoperfusion can independently induce pathological hallmarks of AD such as A$\beta$ and p-tau accumulation. To verify the hypothesis that MMD can be a human hypoperfusion model with pure etiology, for investigating the mechanism of chronic cerebral hypoperfusion in AD and the possibility of revascularization strategy as intervention, we aimed to conduct an MMD cohort to (1) explore if chronic brain hypoperfusion can independently induce the AD pathological hallmarks, confirmed by image and cerebrospinal fluid (CSF) analysis; (2) examine the dose–effect relationship of the AD hallmarks and the ischemic degree; (3) evaluate the efficacy of the timely intervention to reverse brain damage with AD hallmarks and cognition improvement.

## 2.5 | Study design

The sample size in this cohort was designed to be 300. Inclusion criteria of participants include patients first diagnosed as MMD by digital subtraction angiography (DSA, the gold standard), and who are: (1) aged 16 to 65 years; (2) Han Chinese; (3) able to walk, communicate, participate in physical examinations, and provide informed consent; (4) without MRI and PET contraindications; (5) without image-confirmed stroke history; (6) without another chronic disease, cancer, psychiatric disorders, and family history of dementia; (7) eligible for bypass surgery.

After inclusion in the cohort, patients will receive detailed neuropsychological assessments and radiologic evaluation as described below. After that, all patients in this cohort will receive bypass surgery in one hemisphere (generally the more severe ischemic side). During the surgery, local cortex subarachnoid CSF will be obtained for biomarker analysis. Based on those results, we will verify the role of chronic hypoperfusion. At 1-year follow-up, patients will be admitted to our institution for neuropsychological and radiologic examination. After admission, patients will receive bypass surgery on their other hemisphere. Intraoperative local cortex subarachnoid CSF will be obtained and analyzed again. Because the cortex subarachnoid CSF is related to the glymphatic pathway, it will reflect the AD hallmarks level in local brain parenchyma more closely.[73] The results of neuropsychological, radiologic, and CSF examinations will be correlated to assess any improvement in cognition and AD hallmarks. After another year of follow-up, patients will receive neuropsychological and radiologic assessments to verify the long-term gains (Figure 5).

## 3 | DETAILED METHODS AND RESULTS

### 3.1 | Neuropsychological assessment

A battery of neuropsychological tests will be used to evaluate the cognitive function of each participant. The battery will comprise the Mini-Mental State Examination (MMSE), Memory and Executive Screening Test (MES), AVLT, TMT, Rey-Osterrieth Complex Figure test (ROCF), Stroop Test, BNT, VFT, Clock Drawing Test (CDT), Similarity Test, and DSST. These tests will be translated, adapted, and validated from

**TABLE 1** Parameters of sequences used in 7T and 3T MRI scan

| | MRI sequence | Voxel size (mm) | FOV (mm) | TR (ms) | TE (ms) | Flip angle (°) |
|---|---|---|---|---|---|---|
| 7T | 3D-T1 MP2rage | 0.7 × 0.7 × 0.7 | 192 × 100% | 3800 | 2.29 | 7 |
| | 3D-T2-space | 0.7 × 0.7 × 0.7 | 150 × 142% | 4000 | 118 | Vertigo |
| | MRA-TOF | 0.2 × 0.2 × 0.5 | 200 × 81.9% | 20 | 4.34 | 18 |
| | GRE APT-CEST | 1.6 × 1.6 × 3.0 | 230 × 100% | 3.5 | 1.64 | 6 |
| 3T | ASL (PRISMA) | 1.5 × 1.5 × 3.0 | 192 × 100% | 4600 | 16.18 | 180 |
| | DCE | 1.5 × 1.5 × 3.6 | 240 × 100% | 4.9 | 1.9 | 12 |

Abbreviations: APT, amide proton transfer; ASL, arterial spin labeling; CEST, chemical exchange saturation transfer; DCE, dynamic contrast enhanced; FOV, field of view; GRE, gradient echo; MP2RAGE, magnetization prepared 2 rapid acquisition gradient echoes; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; TOF, time of flight; MRI, magnetic resonance imaging; TE, echo time; TR, repetition time.

Western countries; harmonized to Chinese culture, covering global cognition, executive function, spatial construction function, memory, language, and attention. The battery will be administered in Chinese by certified study psychometrists within 90 minutes.

## 3.2 | Neuroimaging assessment

Following a predetermined protocol, all participants will undergo a baseline multi-modality brain MRI on the same 7-Tesla scanner (MAGNETOM terra), including 3D T1, T2, diffusion tensor imaging (DTI), ASL, dynamic contrast enhanced (DCE),[74,75] magnetic resonance angiography-time of flight (MRA-TOF), resting-state blood oxygen level-dependent (BOLD), and APT-CEST. The specific parameters of each sequence at baseline are listed in Table 1. In addition, the patients will also receive $^{18}$FDG/A$\beta$/tau-PET CT scans.

## 3.3 | Cerebrospinal fluid biomarkers

During bypass surgery, CSF will be collected near the cortex. After craniotomy and dura incision, the arachnoid surface will be cleaned by smooth suction. Then a tiny incision will be made on arachnoid above sulcus, and a small soft syringe will be put in to collect CSF sample for 1-2 mL. Therefore, besides the traditional A$\beta$1-42, A$\beta$1-40, phosphorylated tau 181, and total tau,[76-78] axonal damage and synaptic dysfunction markers like neurogranin, synaptotagmins, synaptosome associated protein 25 (SNAP25), and the neuronalvisinin-like protein-1 (VLP-1) will also be analyzed.[79-82]

## CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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