STROKE IN ELDERLY: CURRENT STATUS AND FUTURE DIRECTIONS

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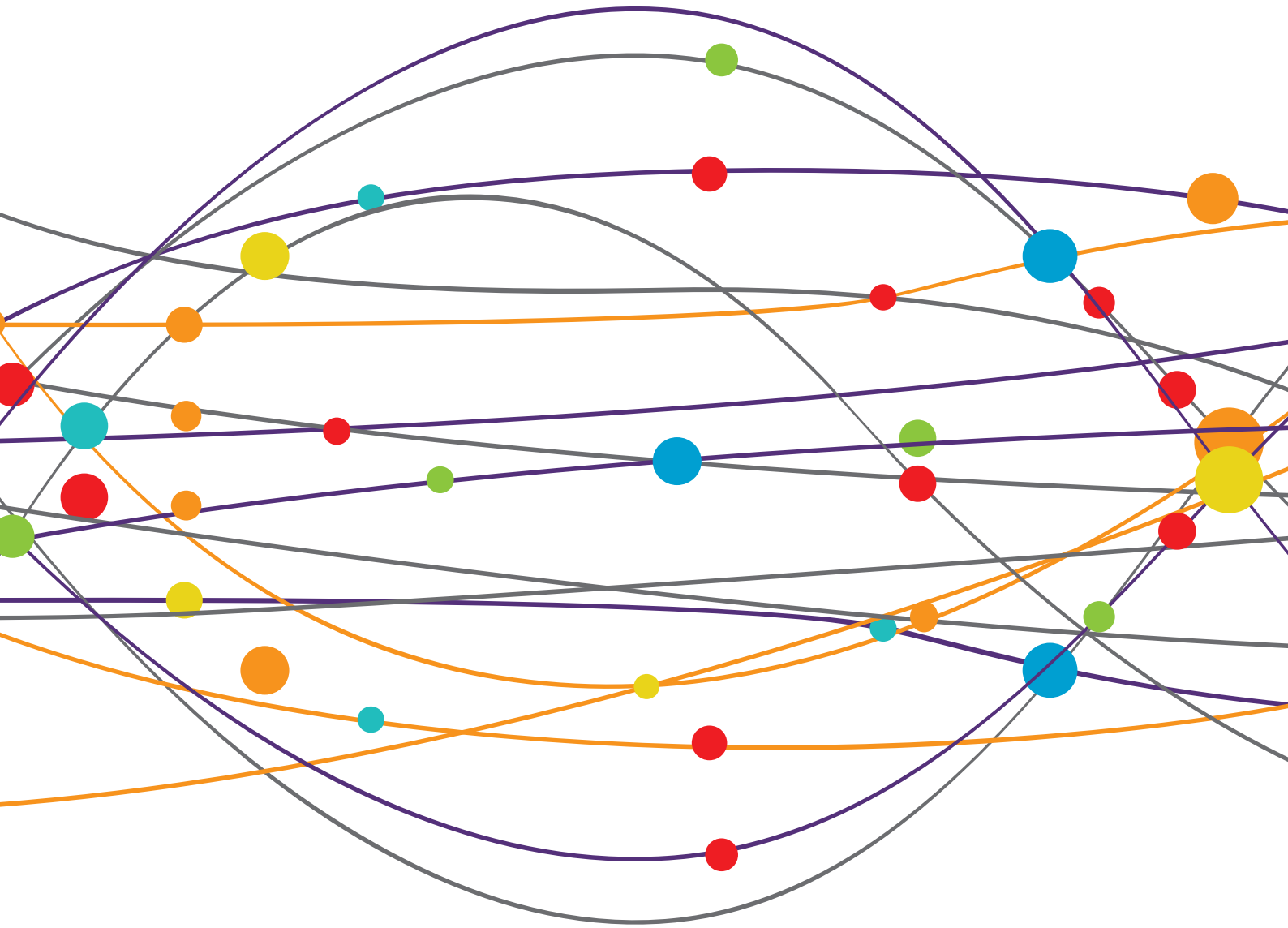

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STROKE IN ELDERLY: CURRENT STATUS AND FUTURE DIRECTIONS

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EDITORIAL
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Editorial: Stroke in Elderly: Current Status and Future Directions

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Keywords: stroke, elderly, stroke recovery, thrombectomy, carotid disease

Editorial on the Research Topic

Stroke in Elderly: Current Status and Future Directions

The worldwide elderly population is rapidly growing[1]. Stroke incidence doubles in octogenarians (1). In the US, the number of people older than 85 years, who currently constitute 2% of the total population, will double by 2060 (2). Therefore, the absolute number of strokes is expected to significantly increase over the course of the next century.

It is therefore important for physicians to understand the etiologies of stroke in this population, minimize risk factors for stroke, manage acute stroke in effective manner, and focus on rehabilitation. In this Research Topic, we focused on research pertaining to elderly stroke.

Prevention: Heo and Bushnell address the topic of carotid disease in the elderly. They highlight the differences in post-procedural stroke and mortality between carotid stenting and carotid endarterectomy among elderly patients. In addition to age, other predictors of outcome include gender, comorbid conditions, and symptomatic status. Wang et al. focus on asymptomatic carotid stenosis. Functional MRI and cognitive testing suggest that carotid stenting for asymptomatic carotid stenosis can improve cognition by increasing perfusion in the left frontal gyrus and connectivity in the posterior cingulate cortex. Cognitive outcomes are an important aspect of care in the elderly and this article provides insight into the role of stenting in improving cognition for the elderly patients.

Blood Pressure: Geng et al. highlight the impact of blood pressure variability in the subacute phase of stroke on long term cognitive outcomes in the elderly. Blood pressure management for the elderly has been a source of debate and this article provides valuable information on how better blood pressure management impacts cognition in the elderly post-stroke patients.

Acute Stroke Treatment: Jayaraman and McTaggart discuss the outcomes of thrombectomy for large vessel occlusion related stroke in the elderly. They provide a detailed review of recent trials in the context of outcomes for elderly undergoing thrombectomy and the need for further studies. Peng et al. evaluate the impact of apolipoprotein E ε4 on imaging and clinical markers in patients with subarachnoid hemorrhage. Patients with the apolipoprotein E ε4 allele were found to have raised intracranial pressure and decreased perfusion in the white matter region after subarachnoid hemorrhage. Apolipoprotein E is a major focus for the elderly and this article ties it to subarachnoid hemorrhage outcomes. Khan et al. evaluate the impact of specific infarct location in distal middle cerebral artery occlusion stroke on outcome. They demonstrate specific infarct locations to be predictive of outcomes with no impact of laterality. Prognostication post stroke in the elderly population is an important aspect of care for the elderly and location of infarct provides valuable insight into prognosis.

Recovery: Xing et al. assess the impact of white matter connectivity on post stroke aphasia utilizing functional magnetic resonance imaging (fMRI). They note a role of temporal lobe pathways in word-level and sentence-level comprehension pertaining to post-stroke aphasia.

[1]https://population.un.org/wpp/Publications/Files/WPP2017_Wallchart.pdf

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Wall et al. also evaluate post stroke aphasia in the context of cognition. They emphasize the need for better strategies to test cognition in patients with aphasia after stroke. Grech et al. tackle a difficult issue of post-stroke spatial neglect. They suggest incorporating Mobility Assessment Course (MAC) testing when evaluating spatial neglect. Marei et al. discuss the use of stem cells for enhancing recovery after stroke and highlight the need for further large clinical trials. The articles provide impact information of recovery pertaining to the elderly which will enable us in prognostication as well as designing better intervention strategies in the post-acute phase.

In summary, elderly stroke patients are a unique group requiring a multifaceted approach incorporating prevention, acute treatment and focus on recovery. In view of the growing elderly population, there is a significant need for further research to improve outcomes for these patients.

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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REVIEW
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Potential of Stem Cell-Based Therapy for Ischemic Stroke

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Ischemic stroke is one of the major health problems worldwide. The only FDA approved anti-thrombotic drug for acute ischemic stroke is the tissue plasminogen activator. Several studies have been devoted to assessing the therapeutic potential of different types of stem cells such as neural stem cells (NSCs), mesenchymal stem cells, embryonic stem cells, and human induced pluripotent stem cell-derived NSCs as treatments for ischemic stroke. The results of these studies are intriguing but many of them have presented conflicting results. Additionally, the mechanism(s) by which engrafted stem/progenitor cells exert their actions are to a large extent unknown. In this review, we will provide a synopsis of different preclinical and clinical studies related to the use of stem cell-based stroke therapy, and explore possible beneficial/detrimental outcomes associated with the use of different types of stem cells. Due to limited/short time window implemented in most of the recorded clinical trials about the use of stem cells as potential therapeutic intervention for stroke, further clinical trials evaluating the efficacy of the intervention in a longer time window after cellular engraftments are still needed.

Keywords: stem cell, mesenchymal stem cell, neural stem cell, induced pluripotent stem cells, ischemic stroke

INTRODUCTION

The number of stroke-related deaths is increasing and stroke remains one of the major causes of deaths and disability worldwide (1, 2). Between 1990 and 2010, the global incidence rate of stroke seemed to be stable, while other parameters such as the incidence of first stroke, prevalence of stroke, disability-adjusted life-years lost due to stroke, and the number of stroke-related deaths increased by 68, 84, 12, and 26%, respectively (1). Differences between rates and numbers might reflect variations in population structure, increase in life expectancy, and the global improvement of health care services.

Two main types of stroke are recognized: ischemic and hemorrhagic stroke. Ischemic stroke accounts for over 80% of the total number of strokes. Thrombolysis and/or thrombectomy is the only validated therapeutic strategy for ischemic stroke (3, 4). Neurorestorative stem cell-based therapy is currently a major priority for stroke research (5, 6). Following ischemic events an inflammatory cascade, is initiated eventually leading to damage of brain tissue.

DIFFERENT CELLULAR SOURCES USED FOR STEM CELL-BASED THERAPY OF STROKE

The drastic damage to brain tissues following ischemic stroke includes not only destruction of a heterogeneous population of brain cell types, but also major disruption of neuronal connections and vascular systems. Several types of stem/progenitor cells such as embryonic stem cells (ESCs), neural stem/precursor cells, mesenchymal stem cells (MSCs), induced pluripotent stem cells (iPSCs), and induced neurons have been assessed as potential cellular-based therapy for stroke. The results of studies of these different cellular types are conflicting. In some studies, the engrafted cells survived, proliferated, differentiated, and restored lost neuronal and vascular elements. Other studies have shown only a limited neurorestorative ability on the part of transplanted cells. In the next section of this review, we elaborate on different stem cell types used for cellular-based therapy of stroke (**Figure 1**).

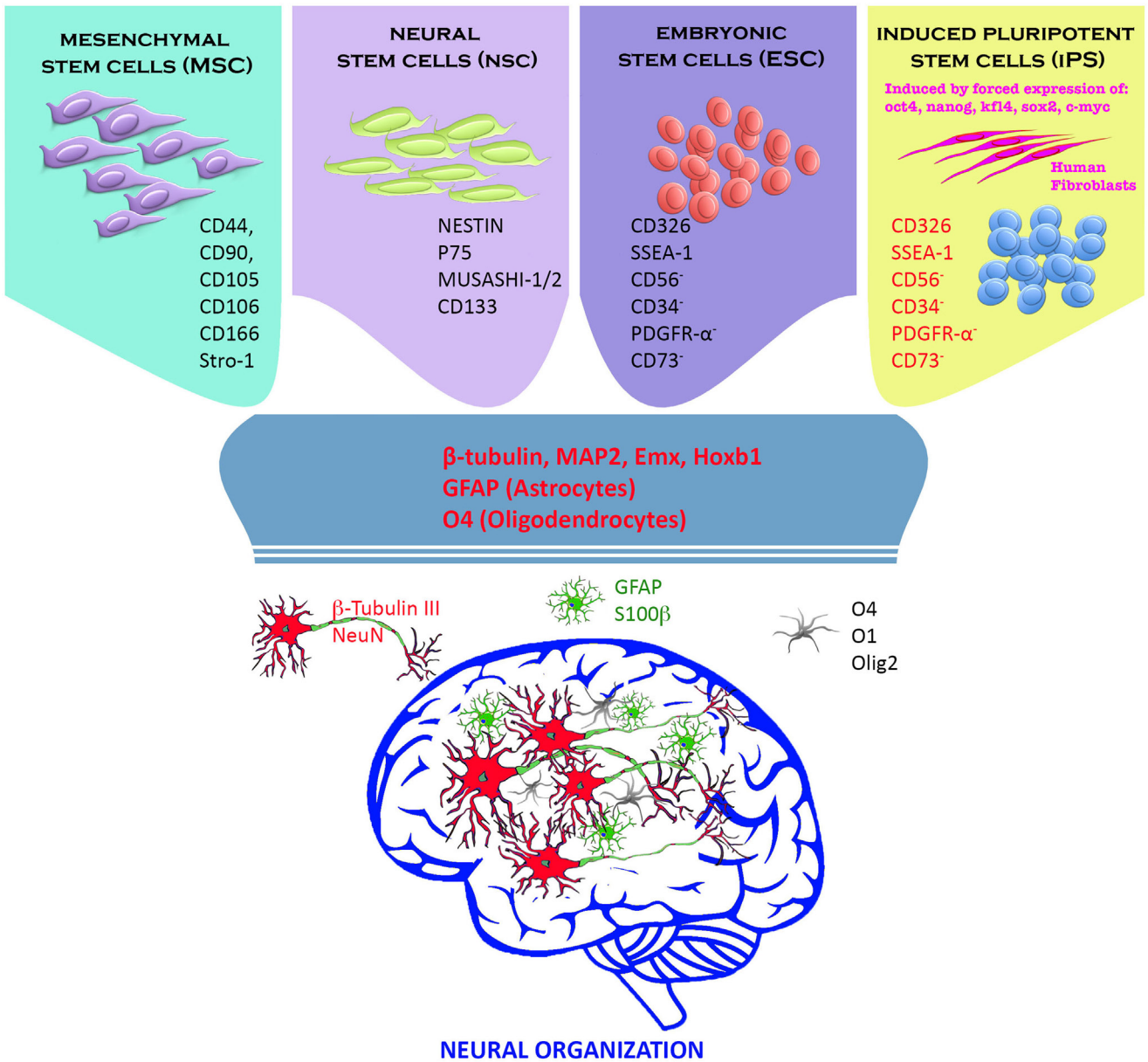

FIGURE 1 | Stem cells and neural progenitor cells have been used to replace neural tissue death following a cerebral insult. Adult (mesenchymal and neural stem cells) and embryonic stem cells (ESCs) exhibited excellent differentiation capacity toward the neural phenotypes (neurons, oligodendrocytes, and astrocytes) *in vitro* and *in vivo*. In our view instead, induced pluripotent stem cells (iPSCs) constitute the greatest prospect for a future cell therapy. iPSCs are derived directly from the patient's connective tissue through a small biopsy and exhibit the same properties of ESCs, overcoming the problems related to immune rejection, and bypassing the need for embryos. They can be generated in a patient-matched manner, implicating that each individual could have their own pluripotent stem cell line. Finally, iPSCs can be used in personalized drug discovery and to understand and deepen the patient-specific basis of disease (7–10).

EMBRYONIC STEM CELLS

Derived from the inner mass of blastocysts, ESCs are pluripotent cells having the ability to differentiate into all other body cells except those of the placenta (11). The regenerative capacity of ESC in stroke is related to their ability to give rise to different neuronal and glial elements forming the brain tissues (i.e., neurons, astrocytes, and oligodendrocytes) (12). Engrafted murine ESCs in cerebral tissue in an ischemic mouse model migrated toward damaged brain areas in the opposite cerebral hemisphere, restored histological and behavioral deficits (13), and repaired damaged synaptic connections associated with stroke lesions (14).

NEURAL STEM/PRECURSOR CELLS

Neural stem cells (NSCs) are multipotent cells residing mainly in the subgranular zone of the dentate gyrus of the hippocampus (15), and in the subventricular zone of the brain's third ventricle (16). The NSCs move from the subventricular zone into the rostral migratory stream and thence to the olfactory bulb where they differentiate into interneurons. Currently, NSCs are a hot research area for neurobiologists. Their ability to differentiate into different neuronal and glial elements that form the CNS make them a promising candidate for restoration of neuronal and behavioral damages associated with different CNS disorders including stroke.

The first attempt to use NSC for cell-based therapy of brain hypoxia was conducted in 1984 when embryonic brain cortex tissue was engrafted in a rat hypoxia model. The transplanted cells proliferated, established connections with host neurons, and improved electrophysiological performance (17, 18).

Embryonic NSCs engrafted into ischemic rat brains survived, migrated to the ischemic lesion, maturing into neurons (19, 20) as well as astrocytes and microglia (21); they restored impaired sensorimotor and spatial learning functions (22). In a macaque stroke model, engrafted NSCs partially differentiated into neurons, and survived up to 105 days (23).

MESENCHYMAL STEM CELLS

Mesenchymal stem cells can be derived from several tissue sources, including bone marrow, placenta, muscle, skin, dental pulp, adipose tissue, umbilical cord, and Wharton's jelly (24, 25). The therapeutic potential of bone marrow MSC (BMSC) for stroke has been extensively assessed both at the preclinical and clinical levels. In an animal stroke model, transplantation of BMSC enhanced sensorimotor function (26), promoted synaptogenesis, stimulated nerve regeneration (27), decreased tissue plasminogen activator-induced brain damage (28), and mediated immunomodulatory effects (29).

At the clinical level, BMSCs appeared to be an attractive alternative that avoided ethical concerns related to the used of fetal cells. Several studies have revealed the feasibility and safety of BMSCs in clinical practice (30–32).

INDUCED PLURIPOTENT STEM CELLS

Reprogramming of somatic cells such as fibroblasts and peripheral blood mononuclear cells through transduction of defined transcriptional factors (Oct3/4, Sox2, Klf4, and c-Myc) is currently becoming a standardized protocol (33, 34). The therapeutic potential of iPSCs in treating various CNS diseases (including stroke) has been addressed in previous studies (35). In comparison with ESCs, iPSCs have the advantage of sparing the damage induced by immune rejection, and avoiding the moral issue associated with the use of embryonic tissues (36). Engraftment of iPSCs in a cerebral ischemia model reduced infarct volume, ameliorated the neurological outcomes, and improved short-term sensorimotor recovery (37). Unfortunately, following engraftment, iPSCs formed teratomas in mouse brains (38, 39). The high propensity of iPSCs for teratoma formation is attributed to the expression of matrix metalloproteinase-9 and phosphorylated vascular endothelial growth factor receptor 2 (40).

One of the promising strategy for the use of iPSC to treat stroke is their ability to differentiate into NSC. Induced pluripotent stem cell-derived neural stem cells (iNSCs) are expected to provide multipotent, autologous cells for stroke cellular-based therapy. In ischemic pig stroke model, implantation of iPSC-derived iNSC was associated with improved recovery. Several mechanisms have been reported to play a role in the observed improvement including cell replacement, and neuroprotection. Others changes have been demonstrated based on the use of longitudinal multiparametric magnetic resonance imaging. These include reduction in the changes of brain metabolism, cerebral blood infusion, and integrity of the white matter. Such tissue recovery in review 8 was primarily attributed to alleviation of negative immune response, activation of neurogenesis, and enhanced neuronal protection. These observation strongly support the importance of iNSCs as a promising cellular source to be used for cell-based therapy of human stroke (41).

TUMOREGINIC POTENTIAL OF PLURIPOTENT CELLS

One of the major concern for the use of pluripotent stem cells (including ESCs and iPSCs) for treatment of ischemic brain injury is their potential to develop a tumor following engraftment. Several studies have reported the tumorigenic transformation of iPSC (38, 40, 42, 43) following their in transplantation. The existence of a small number of undifferentiated iPSCs even after prolonged differentiation of iPSC *in vitro* may trigger the formation of teratoma *in vivo*, and pose a great risk against their clinical application (44). Other factors might also contribute to the tumorigenic potential of iPSC including the transcriptional factors and virus vectors used during iPSC induction (45, 46). The role of the four Yamanaka reprogramming factors (Klf4, c-Myc, Oct4, and Sox2) in induction of teratoma had been suggested by some authors, and they were found to be strongly expressed in iPSC-derived tumors (38). The four factors have been demonstrated to be highly expressed in various cancer types (47–49), and MYC has been demonstrated to be a well-documented oncogene (50, 51). The expression of aforementioned genes has been associated with poor prognosis, and tumor progression

(52). The role of these transcription factors in the tumorigenic potential of iPSC has been indirectly demonstrated where inhibition of the tumor suppressors in the p53 pathway was found to increase the reprogramming ability of Oct4, Klf4, and Sox2 (53). Elimination of the "unsafe" undifferentiated residual cells has been suggested to guard against the development of iPSC-associated teratoma. Toward this aim, several strategies such as magnetic-activated cell sorting and fluorescence-activated cell sorting (54) have been used. Other strategies to mitigate potential tumorigenic potential of engrafted pluripotent cells include the use of cytotoxic antibodies such as mAb 84 (55), use of virus-free iPSCs, and encapsulation of pluripotent stem cell-derived grafts (56) were also effective.

IMMUNOGENICITY OF STEM CELL-BASED THERAPY FOR STROKE

The potential of allogeneic stem cells in the treatment of stroke has been highlighted before. Savitz et al. (57) have tested the potential of fetal porcine in transplantation in patients with basal ganglia infarcts and stable neurological deficits. In a trial to suppress the immunorejection of the transplanted cells, patients were pretreated with anti-MHC1 antibodies with no immunosuppressive drugs. No adverse effects have been observed, while the fourth patient exhibited a deterioration in motor functions deficits 3 weeks after transplantation. Other side effects that might indicate rejection of engrafted cells were shown in the fifth patients who have developed seizures 1 week after transplantation. The study was terminated by the FDA after the inclusion of five patients. This study was the first that pointed out to the potential use of non-tumor cells in ischemic stroke patients.

MECHANISM OF ACTION OF STEM CELL-BASED THERAPY FOR STROKE

The potential mechanism(s) by which different types of engrafted stem cells help to restore lost neuronal function after stroke are still a matter of dispute. Several mechanisms have been demonstrated including cell replacement, trophic influences, immunomodulation, and enhancement of endogenous repair processes.

The mechanism by which the engrafted BMSCs exerts their beneficial actions is still under investigation. Whether or not the improvement occurred following transplantation of BMSCs is a primary concern, but their ability to replace dead or damaged neuronal and glial elements still needs further confirmation.

Release of soluble trophic factors and cytokines is suggested as one major mechanism by which NSC bring about improvement in post-stroke neurological function (58). A wide array of trophic and growth factors has been reported to be released from endogenous cells such as astrocytes and endothelial cells (59). These include VEGF/Flk1 and Ang-1/Tie2 (60), BDNF, nerve growth factor, VEGF, IGF-1, hepatocyte growth factor, and GDNF. These factors promote angiogenesis, stabilize vasculature, enhance cell survival proliferation and differentiation, promote neurogenesis, effect endogenous cell repair, trigger neuroblast proliferation, and trigger migration from SVZ and decreased apoptosis (61).

CELL REPLACEMENT

Cell replacement involves the ability of engrafted cells to migrate, survive, proliferate, and finally differentiate into the various types of cells forming nervous tissue histo-architecture. These include neurons of different classes, oligodendrocytes (the myelin forming cells), and astrocytes. Following stroke or other neurological insults/disorders several neurodegenerative and inflammatory pathways are activated creating an inhospitable environment for engrafted cells. Astrocytes usually respond by extensive proliferation and formation of a glial scar (62) which renders the damaged area unsuitable for engrafted exogenous cells.

Based on the initial number of cells engrafted and the route of administration, the necessary first step in restoring damaged cellular elements following stroke is the migration of transplanted cells to damaged brain regions. This is usually achieved through the ability of engrafted stem/progenitors cells to target damaged regions (63) in response to different chemotactic signals of specific cytokines, such as the vascular cell adhesion molecule 1, stromal-derived factor 1, monocyte chemotactic protein-1, chemokine (C–C motif) ligand 2 (21).

CLINICAL TRIALS

In a recent meta-analysis of stem cell therapies for patients with brain ischemia, Chen et al. (64) concluded that stem cell therapy significantly enhanced neurological functions and quality of life, but more investigation is required to provide more evidence to support clinical application of stem cell transplantation (64, 65).

In a very recent clinical trial, the safety and efficacy of autologous bone marrow mononuclear cells transplantation in stroke patients were assessed. The study suggests that a higher dose of BM-MNC (3×10^6 or more) provided a better outcome in stroke patients (66).

In another recent clinical trial, improved neurological function with no tumor formation or adverse events was demonstrated following engraftment of an immortalized human neural stem-cell line (67).

A double-blind randomized placebo-controlled Phase III confirmatory clinical trial of intravenous infusion of autologous NSC derived from bone marrow of stroke patients resulting from cerebral infarction is currently under way (68).

To evaluate the safety and clinical outcomes of surgical transplantation of modified bone marrow-derived MSCs, cells were engrafted in 18 patients with stable, chronic stroke. This therapeutic paradigm was proven to be safe, and was associated with improvement in clinical outcome end points after 12 months (69). Nagpal et al. (70) investigated the use of autologous stem cell therapy for stroke survivors with chronic disability. The primary outcomes to be measured are safety and feasibility of intracranial administration of autologous human adult DPSC in patients with chronic stroke; as well as determination of the maximum tolerable dose in humans. Secondary outcomes to be assessed include estimation of the measures of effectiveness required to design a future Phase 2/3 clinical trial (70).

In summary, the conclusions of several preclinical studies have encouraged the translation of stem cell-based therapies

at the clinical level. Several clinical studies related to the use of different types of stem cells for cell-based therapy of stroke have been conducted since 2005 using MSCs (30), MNC (32, 71), and NSCs (57, 72).

ONGOING CLINICAL TRIALS

To the best of our knowledge, there are currently more than 53 clinical trials on the use of stem cell-based therapy for stroke. Most of them use MSCs isolated from different body tissues: umbilical cord, endometrial polyps, menstrual blood, adipose tissue, and bone marrow (73). Although use of autologous MSCs is the method of choice to guard against immune rejection, the long time frame needed to obtain sufficient numbers of MSCs from the patient's own tissue (i.e., bone marrow), makes the use of "off-the-shelf" allogeneic MSC therapy more convenient. Manipulation of MScs to overexpress genes with potentially beneficial properties and the ability to rapidly release different trophic factors was found to enhance their therapeutic potential and effects (74). Administration of multipotent adult progenitor cells was safe and well tolerated in patients with acute ischemic stroke. Although no significant improvement was observed at 90 days in neurological outcomes with multipotent adult progenitor cells treatment, further clinical trials evaluating the efficacy of the intervention in an earlier time window after stroke (<36 h) are planned (75).

Different routes of administration have been used to deliver stem cells into the stroke patients, namely intra-arterial, intravenous, and intraparenchymal routs. An early subacute delivery of cells to reduce acute tissue injury and modify the tissue environment in a direction favorable to reparative processes (for example, by being anti-inflammatory, anti-apoptotic, and encouraging endogenous stem cell mobilization); the other exploring later delivery of cells during the recovery phase after stroke to modulate the local environment in favor of angiogenesis and neurogenesis. The former approach has generally investigated intravenous or intra-arterial delivery of cells with an expected paracrine mode of action and no expected engraftment within the brain. The latter has explored direct intracerebral implantation adjacent to the infarct. Several relevant trials have been conducted, including two controlled trials of intravenously delivered bone marrow-derived cells in the early subacute stage, and two small single-arm phase 1 trials of intracerebrally implanted cells (76).

FUTURE PERSPECTIVES AND CONCLUSION

Stem-based therapy for ischemic stroke is still in its infancy. Several alternative approaches including the use of ESCs, MSCs, NSC, and iPSCs have been tried in hopes of improving the drastic neuronal and functional impairment that usually follows a stroke insult. The outcomes of various preclinical studies have been encouraging, with (in most cases) engrafted stem cells succeeding in bringing about neurofunctional improvements. The mechanism(s) by which different types of stem cells induce improvement are still under investigation. Cell replacement, bystander effects, neurotrophic influence, immune and inflammatory modulation are all among the suggested mechanisms. At the clinical level, most of the clinical trials have used MSCs or NSCs (whether wild-type, genetically modified to overexpress certain neurotrophic genes, or preconditioned with the intent to promote cell survival and differentiation following transplantation) engrafted into an ischemic brain region. Autologous cells (mostly bone marrow-derived MSCs) are used in most of the ongoing clinical trials, although there is a current trend that favors the use of "off-the-shelf" allogeneic MSC as a way to overcome the long time frame needed to obtain sufficient numbers of cells for transplant. Most current clinical trials aim to measure the safety and feasibility of intravascular and/or intracranial administration of autologous/allogeneic human adult stem cells in patients with chronic stroke and to determine the maximum tolerable dose. Secondary outcomes include estimation of the measures of effectiveness required to design a future Phase 2/3 clinical trial.

ETHICAL STATEMENT

This article does not contain any studies with human participants or animals performed by any of the authors.

AUTHOR CONTRIBUTIONS

ME: study concept and design. HA, AA, and AN: analysis and interpretation. RR: acquisition of data. CC and TC: critical revision of the manuscript for important intellectual content. AS: study supervision.

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REVIEW
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Endovascular Treatment of Anterior Circulation Large Vessel Occlusion in the Elderly

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Endovascular treatment of anterior circulation large vessel occlusion in the elderly population presents special challenges and opportunities. In this review, we discuss the published literature regarding thrombectomy in elderly patients and also discuss specific issues related to treatment in this patient population. In summary, while the overall outcomes following thrombectomy in elderly patients are worse than following thrombectomy in younger patients, there appears to be a similar benefit as in young patients. While there are challenges with successfully delivering thrombectomy in older patients, age alone should not be an independent exclusion from thrombectomy.

Keywords: stroke, large vessel occlusion, thrombectomy, elderly, intervention

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INTRODUCTION

Acute ischemic stroke caused by large vessel occlusion (LVO) in the anterior circulation is the leading cause of adult disability in the developed world. Until recently, the only therapy proven to improve outcomes for all ischemic stroke patients was the intravenous (IV) administration of tissue plasminogen activator (tPA), which can be administered up to 4.5 h from the onset of symptoms or when the patient was last known normal. Unfortunately, those strokes caused by occlusion of the large intracranial vessels, such as the internal carotid artery (ICA) and proximal middle cerebral artery (MCA), had low rates of response to IV tPA, and subsequently, poor outcomes (1).

The next revolution in stroke began in 2015, when five randomized trials all showed that rapid mechanical thrombectomy, primarily using stent-retriever devices, significantly improves outcomes in anterior circulation (ICA and MCA) LVO stroke patients (2–7). Even more striking was the absolute magnitude of benefit, with a number needed to treat as low as 2.5 to have one patient be less disabled (8, 9). Few, if any, therapies in medicine can approach that level of benefit. Recently, the benefit of thrombectomy has been shown to extend out to 24 h, in patients with a favorable imaging profile (10).

The application of this highly effective therapy to the older population presents unique challenges, however. The incidence of stroke is higher in the older population (11), and it is likely that we will encounter this issue with increasing frequency in daily clinical practice. In this review, we will highlight these issues in the aging population. We will focus on LVO in the anterior circulation, predominantly in the ICA or MCA.

CURRENT LITERATURE—IS THERE A BENEFIT FOR THE ELDERLY?

Single Armed Trials of Treatment

Several single and multicenter case series have been published examining the question of whether there is a benefit of treatment in the elderly (12–16). Sallustio and colleagues compared the outcomes between patients younger than 80 and those 80 and older, in a series of 239 patients. They found no significant differences in clinical outcomes at 90 days with 34.3% of young patients achieving independence (modified Rankin score 0–2) compared with 30.6% of the older group (14). While overall mortality was higher in the older cohort (40.3 vs. 29.2%), the neurologic related mortality was lower in the older group (14.5 vs. 21%), suggesting a larger number of preexisting comorbidities. By contrast, in the multicenter NASA registry, only 27.3% of patients 80 or older achieved independence at 90 days, compared with 45.4% for the younger group (17), suggesting worse outcomes in the older group.

Singer evaluated 362 patients in the multicenter ENDOSTROKE registry and showed a significant dependence of age on outcomes. Only 17% of patients in the oldest quartile (77–94 years old) achieved independence at 90 days, compared with 37% in those 69–67 years old, 47% in the 57- to 68-year-old group, and 60% in those younger than 57. In addition, there was an increasing rate of poor outcome despite recanalization with age, reaching 53% in the oldest age group. They suggested that medical comorbidities, procedural issues such as tortuous anatomy, the use of general anesthesia, and impaired collaterals all played a role in these observed poor outcomes (18). Shi also showed that in a pooled analysis of the MERCI, TREVO, and TREVO 2 trials, increasing age was a strong predictor of poor outcome (19).

Khan and colleagues examined the impact of treatment on nonagenarians, compared with the younger cohort (12). They did show a much lower rate of good outcome in the nonagenarians, with only 11.1% mRs 0–2 at 90 days vs. 48% in the younger cohort, but they acknowledge a higher baseline level of disability in the older group and suggest that there may be a role for therapy in nonagenarians with good prestroke functional status. Recently, Imahori et al. examined the benefit of complete recanalization (TICI 3) vs. incomplete recanalization (TICI 0–2b) in a series of 80 patients, dichotomized by age ≥80 vs. <80 years (15). They found that independence at 90 days (mRs 0–2) was 65% in the older cohort and 68% in the younger cohort, when TICI 3 recanalization was achieved, and 21 vs. 45% for TICI 0–2b in the older and younger cohorts, respectively. This would suggest that perhaps, with complete recanalization, older patients can achieve similar rates of functional independence.

A meta-analysis by Duffis examined this specific issue and found higher rates of symptomatic intracranial hemorrhage and lower rates of good functional outcome in patients older than 80 (20). However, while they included a total of 8 studies with 2,279 patients, there was extreme heterogeneity in the endovascular treatment methods, and most patients were not treated with modern stent-retriever or aspiration devices.

In summary, most single armed trials of thrombectomy in anterior circulation stroke show worse outcomes with older age as compared with younger cohorts.

Randomized Trials of Thrombectomy

However, all of the aforementioned series were reporting outcomes of patients treated with thrombectomy. What about randomization compared with medical therapy alone? Among the current generation of randomized thrombectomy trials, prespecified analysis based on an age threshold shows significant benefit in older subgroups in the ESCAPE and MR CLEAN trials (divided as 80 years or older vs. younger) and in the SWIFT-PRIME (divided as 70 years or older vs. younger) trial, with no heterogeneity of benefit. In the REVASCAT trial, there was not a difference between medical and endovascular therapy in the older subgroup, but this difference was not statistically significant. These results are summarized in **Table 1**. The sample size in EXTEND-IA was too small to allow for such an analysis. In HERMES, the pooled, patient level meta-analysis of these five trials, there was no difference in the benefit of thrombectomy across the entire age spectrum using a mixed methods linear regression (8). That is to say, the older patients did worse than the younger patients regardless of treatment modality, but the same degree of benefit of endovascular therapy was present throughout the age spectrum. In addition, when divided into subgroups, the adjusted common odds ratio was not significantly different among the age 50–59, 60–69, 70–79, and 80+ groups, with 218, 333, 371, and 198 patients in those groups, respectively. Similarly, even in the 6–24 h time window, the DAWN trial showed similar benefit to those less than 80 vs. 80 and older, with odds ratios of 1.9 and 2.3, respectively, for benefit with thrombectomy (10).

In summary, while older patients may have worse outcomes overall, there is no heterogeneity of treatment effect seen by age. Thrombectomy is just as effective in elderly patients as

TABLE 1 | Summary of outcomes in older patients in seven randomized trials of modern endovascular stroke thrombectomy (primarily using stent-retriever devices).

Trial	Patients	Odds ratio for favorable outcomes with thrombectomy	Independence at 90 days (mRs 0–2) in older and younger groups; endovascular vs. control
MR CLEAN (6)	500	Age <80 years: 1.6 Age ≥80 years: 3.2	Not reported
ESCAPE (4)	316	Age ≤80 years: 3.0 Age >80 years: 2.7	Age ≤80 years: 59.3 vs. 33.4% Age >80 years: 37 vs. 18%
REVASCAT (3)	206	Age ≤70 years: 2.5 Age >70 years: 0.9	Age ≤70 years: 52.5 vs. 23.3% Age >70 years: 30.9 vs. 34.9%
SWIFT-PRIME (2)	191	Age <70 years: 1.67 Age ≥70 years: 1.78	Age <70 years: 65 vs. 40% Age ≥70 years: 54 vs. 31%
THRACE (7)	402	Age <70 years: 1.6 Age ≥70 years: 1.5	Not reported
DAWN (10)	206	Age <80 years: 1.9 Age ≥80 years: 2.3	Age <80 years: 54 vs. 17% Age ≥80 years: 32 vs. 4%

it is in younger ones. In addition, the outcomes with medical therapy alone are dismal in older patients, and rapid, successful thrombectomy may by the best chance the older patients have at a favorable outcome.

Preprocedure: Making the Treatment Decision

Ultimately, deciding to take the patient to the angiography suite for thrombectomy means that the treating team feels the procedure is likely to improve the patient's chance of meaningful neurologic recovery. In the preprocedure time period, this is dependent on the patient's baseline functional status, as well as the status of the brain tissue, as assessed by brain imaging.

Almost all the patients in the recent randomized trials of thrombectomy were required to be functionally independent for enrollment, typically defined as modified Rankin scale score of 0 or 1. As such, in patients with preexisting disability, randomized data comparing the outcomes with thrombectomy vs. best medical therapy is lacking. Elderly patients may have a higher rate of preexisting disability, which can make the treatment decision more difficult. Pohjasvaara examined the level of pre- and poststroke disability in a cohort of 486 patients in Helsinki. They found higher levels of prestroke disability in the group aged 71–85 as compared with those aged 55–70 (21). In addition, the older group was more disabled after stroke than the younger group. Another study, compared patients older or younger than 75 and found that indeed the older group had higher prestroke levels of disability, and overall higher mortality after stroke (22). In series of IV thrombolysis in patients with preexisting disability, it has been shown that while the overall mortality is higher, the likelihood of good outcome was not influenced by previous dependency (23). Those authors suggested withholding thrombolysis in patients with preexisting disability might not be justified. Similarly, Leker and colleagues showed that while the overall outcomes following anterior circulation thrombectomy are worse in those with preexisting disability, there were some who were able to maintain their prestroke level of disability, and as such, those with moderate disability should not be excluded from thrombectomy (24). Treatment guidelines from the American Heart Association consider treatment of patients with preexisting disability as "may be reasonable," but suggest additional data would be helpful (25).

There can be additional difficulties in establishing a functional baseline in patients who come from a non-home living situation. Patients may be in assisted living facilities requiring varying amounts of assistance with activities of daily living. However, in the time critical period between hospital arrival and treatment decision, it may be difficult to elucidate how functional the patient was prestroke, especially when family is not available to provide additional history. These additional items should not delay thrombectomy, but may be difficult to obtain in a timely fashion. It is also possible that patient age may play a role in determining if a patient should be transferred from a non-thrombectomy capable center to one where they can be treated, although data are lacking in this regard.

In summary, preexisting disability is more common in elderly patients and would have excluded them from most randomized trials of thrombectomy. While preexisting disability is not an absolute contraindication to treatment, the team evaluating the patient should do their best to assess prestroke functional status and make an individualized decision in elderly patients with preexisting disability.

Preprocedure: Imaging Issues

Baseline brain parenchymal imaging (with non-contrast CT) and vessel imaging [with CT angiography (CTA)] should be the minimum standard on all stroke patients, regardless of severity (26). The degree of completed infarction (infarct core) on NCCT is often measured using the Alberta Stroke program early CT score. Core infarct estimation can also be made with assessment of the degree of collateral filling beyond the occlusion on CTA (CTA-Collateral Score), using dynamic CT perfusion, or using diffusion-weighted imaging (DWI) sequences on MRI. With respect to vascular imaging, older patients may have diminished cardiac output, which may result in suboptimal bolus acquisition on CTA. The use of multiphase CTA, with two additional scans through the brain, may ameliorate some of those issues by allowing for additional imaging in those patients with poor cardiac output (27).

Preexisting leukoaraiosis, typically more prevalent in an older patient, has been associated with worse outcomes after thrombectomy as well (28). In addition, leukoaraiosis may lead to overestimation of infarct core in the white matter on CT perfusion using relative cerebral blood flow thresholds (29). Agarwal and colleagues showed in a small series of patients undergoing whole brain CT perfusion that age was negatively correlated with normalized lesion and penumbral volume, but not core volume (30). These changes occurred despite an increased collateral response in older patients and suggest future study is warranted into this age-dependent response to ischemia.

Some series have suggested an age-dependent threshold may be accurate for the degree of baseline infarct beyond which endovascular thrombectomy is unlikely to help the patient (31). A recent series trichotomized patients into age groups, with the oldest group being older than 75 (32). Not surprisingly, the elderly patients had favorable outcomes in 50% of cases with minimal baseline infarction (DWI lesion volume <5 mL), as compared with 80 and 91% of patients with similar lesion volumes in the age 66–75 and age less than 66 cohorts, respectively. More profound, however, was the difference in clinical outcomes when baseline DWI lesion was more than 5 mL, where only 19% of elderly patients achieved independence, compared with 44 and 56%, respectively. This would indeed suggest an age-dependent relationship between baseline infarct and likelihood of a good outcome. The DAWN study also used this concept, with an age-dependent infract core threshold, excluding patients older than 80 if they had a core infarct on CT perfusion or DWI of larger than 21 mL, but allowing infarct cores up to a volume of 50 mL in younger patients.

In summary, when evaluating pretreatment imaging one may need to take patient age into account, especially as it

pertains to the evaluation of core infarct volume, regardless of modality.

STARTING THE PROCEDURE: ANESTHESIA AND PATIENT COOPERATION

In the HERMES dataset, it was beneficial to use conscious sedation or local anesthesia as opposed to general anesthesia. This effect may be more so in the elderly population, as there are additional risks from anesthesia. Some recent studies, however, have suggested no difference in outcomes between sedation and general anesthesia (33, 34). However, the vast majority of the patients in AnStroke and SIESTA were younger. There can be greater blood pressure decreases in patients under general anesthesia (35), which can be detrimental to collateral flow. Patient cooperation, if the patient is being treated with sedation or local anesthesia, may also be an issue, especially if the patients have some level of preexisting cognitive dysfunction. The use of benzodiazepines, typically diazepam or midazolam is common during procedural sedation. Scholer showed an inverse correlation between age and the dose of both diazepam and midazolam needed to successfully perform endoscopy (36). Interestingly, they showed an even steeper decline in the dose of midazolam needed as compared with diazepam as patients aged.

When using propofol for procedural sedation during endoscopy, Heuss showed that while elderly patients (age >70 years) had slightly higher rates of short periods of oxygen desaturation below 90%, and an overall decrease in oxygen saturation below 5%, especially in those above the age of 85, but they felt that overall, propofol is safe for sedation in the elderly (37).

To summarize, while no study has demonstrated a benefit to using general anesthesia over conscious sedation, nor are there substantial data evaluating the relationship of mode of anesthesia with outcomes in older patients undergoing endovascular stroke thrombectomy, it may be preferable in patients of all ages to use conscious sedation whenever possible.

Intraprocedure

Intraprocedurally, elderly patients pose anatomic challenges, primarily due to greater tortuosity of their vasculature. Placement of the large bore guiding catheters, including balloon guide catheters, can be more difficult in the elderly population. In extreme cases, direct carotid puncture can be performed, but also likely introduces additional risk. In the NASA registry, procedure times were slightly longer in the elderly cohort, which may be on the basis of the arterial anatomy (17). Imahori also showed longer revascularization times in older patients (45 vs. 31 min) in their single center series (15). In contradistinction, Sallustio showed slightly shorter recanalization times in older patients (60 vs. 78.5 min) (14).

Postprocedural Care

Post revascularization, critical issues include the need to closely follow the patient's neurologic exam as well as hemodynamic parameters to potentially minimize the likelihood of intracranial hemorrhage. In elderly patients treated under general anesthesia, postoperative delirium may be common and can cloud the neurologic examination (38).

Patients with higher baseline systolic blood pressure have higher rates of symptomatic intracranial hemorrhage after systemic thrombolysis. As such, current recommendations are to maintain blood pressure below 185 systolic and 110 diastolic following systemic thrombolysis (39, 40). While the optimal target blood pressures after thrombectomy are unknown, a recent retrospective analysis showed that after TICI 2b or greater recanalization, patients in whom the systolic blood pressure was kept below 160 mmHg had better clinical outcomes than those with higher blood pressures (41).

FUTURE DIRECTIONS AND UNANSWERED QUESTIONS

Among the main unanswered questions, regarding thrombectomy is whether our systems of care are sufficiently well enough organized to provide access to this therapy. Should patients be routed in the field to endovascular capable centers, bypassing closer, non-endovascular capable centers? (42, 43). If so, would there be a bias on the part of EMS to preferentially divert younger patients and not older ones? If such diversion is to occur, is there a differential accuracy of field severity screening tools in younger vs. older patients? One recent study suggests in patients with leukoariosis, severity scores may be less accurate for detection of LVO (44). In addition, a newer trial (NCT02930018) is examining whether a novel neuroprotective agent can improve outcomes in patients undergoing thrombectomy for ICA or M1 occlusions. Will this (or other agents), if shown to be beneficial, have the same effectiveness in older patients?

SUMMARY

In summary, while the overall benefit of thrombectomy is similar in older and younger patients, elderly patients are less likely to achieve functional independence. This may be on the basis of slightly higher levels of prestroke disability, decreased functional reserve, and diminished tolerance to larger core infarcts before recanalization. Age alone should not exclude patients from thrombectomy, but the treating team should be aware of and prepared for factors, which make treatment in this group potentially more challenging.

AUTHOR CONTRIBUTIONS

Both authors contributed to literature review, manuscript revision, and final review.

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The Mobility Assessment Course for the Diagnosis of Spatial Neglect: Taking a Step Forward?

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Spatial neglect after stroke can be a challenging syndrome to diagnose under standard neuropsychological assessment. There is now sufficient evidence that those affected might demonstrate neglect behavior in everyday settings despite showing no signs of neglect during common neglect tasks. This discrepancy is attributed to the simplified and unrealistic nature of common pen and paper based tasks that do not match the demanding, novel, and complex environment of everyday life. As such, increasing task demands under more ecologically valid scenarios has become an important method of increasing test sensitivity. The main aim of the current study was to evaluate the diagnostic utility of the Mobility Assessment Course (MAC), an ecological task, for the assessment of neglect. If neglect becomes more apparent under more challenging task demands the MAC could prove to be more diagnostically accurate at detecting neglect than conventional methods, particularly as the time from initial brain damage increases. Data collected by Guide Dogs of SA/NT were retrospectively analyzed. The Receiver Operating Characteristic (ROC) curve, a measure of sensitivity and specificity, was used to investigate the diagnostic utility of the MAC and a series of paper and pencil tests in 67 right hemisphere stroke survivors. While the MAC proved to be a more sensitive neglect test (74.2%) when compared to the Star Cancellation (43.3%) and Line Bisection (35.7%) tests, this was at the expense of relatively low specificity. As a result, the ROC curve analysis showed no statistically discernable differences between tasks ($p > 0.12$), or between subacute and chronic groups for individual tasks ($p > 0.45$). It is concluded that, while the MAC is an ecologically valid alternative for assessing neglect, regarding its diagnostic accuracy, there is currently not enough evidence to suggest that it is a big step forward in comparison to the accuracy of conventional tests.

Keywords: assessment of neglect, mobility, vision, clinical utility, ecological validity, sensitivity, specificity

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INTRODUCTION

The impact of stroke is devastating. Presently, stroke remains one of the top causes of disability-adjusted life years lost globally (1). A common disability of stroke is spatial neglect, the hallmark symptom being a failure to report or respond to stimuli presented in the contralesional space (2). Importantly, neglect is not attributed to primary sensory or motor defects and is commonly considered to be an attention-related disorder (2). Neglect after stroke affects up to 82% of right hemisphere

damaged persons but may also occur after left hemisphere damage (3). The prevalence of neglect is thought to decrease with time, with most recovery happening within the first 12–14 weeks post-stroke before a plateau is reached (4, 5).

The presence of neglect is associated with extended hospital stays (6), and poor functional outcomes and higher requirements for assisted care when likened to stroke victims without the condition (7, 8). While many people recover rapidly, the more persistent symptoms of neglect make it difficult to live independently and safely (9). Neglect increases the person's risk of accident and injury when crossing roads and having to navigate potentially dangerous objects in the environment (10). Accordingly, the increased need for assistance with daily routines places a significant burden on the families of those affected (11).

To mitigate the harmful consequences of neglect, reliable and accurate symptom detection is key. The most commonly employed clinical tests use paper-and-pencil methods requiring the individual to cancel out static targets (12), to indicate the middle of a line (13), or to copy an object (14). More functional neglect tests assess presence and severity of neglect in daily activities, such as dressing, eating, navigating, and locating familiar items (15–17). However, of the countless neglect tests that are now available, many report low sensitivity (18). Moreover, there is now sufficient evidence that those affected may exhibit neglect behavior despite showing no signs of neglect in common paper-and-pencil tasks (19–32).

An important reason for the relatively low sensitivity of paper-and pencil tasks is their failure to capture everyday demands. Neuropsychological assessments are designed to elicit an optimal performance, whereby distractors, task demands, and task length is controlled and kept to a minimum (33). Such controlled testing situations, however, do not represent everyday life in which patients continuously face novel, dynamic, and complex situations. Indeed, task complexity is a well-established modulator of neglect, and several studies have shown that neglect behavior becomes more apparent with increasing task demands (30, 32, 34).

Failure to detect neglect has important clinical implications. First, undetected neglect may prevent proper access to rehabilitation services. Demonstrating the presence of neglect is a prerequisite of initiating interventions that reduce symptoms and increase independence. Second, a significant number of those affected by neglect may return to their premorbid activities where they put themselves and others at risk in activities of daily living such as driving, road crossing, and the use of dangerous objects/devices (30). Finally, upon assessing the effectiveness of the intervention, there is a risk that the marked improvement in paper-and-pencil task performance might not necessarily translate to everyday life (35). Previous research highlights that a lack of ecologically valid tasks to judge the usefulness of treatments to improve ordinary skills in persons with neglect is a fundamental weakness of *many* clinical neglect trials (35, 36).

In light of the aforementioned issues, a number of alternatives have been proposed. One of these alternatives is the observation of how persons affected by neglect scan the environment while walking a designated course. That is, the individual is asked to walk a standardized Mobility Assessment Course (MAC) and to detect targets located on the corridor walls. The increased task demands and added complexity of walking under multitask conditions have been shown to increase neglect behavior (34). The simplicity of this alternative with high face validity is very appealing as it is easily carried out in a variety of settings, including hospital wards and rehabilitation facilities. Surprisingly, the alternative has not drawn a lot of research interest as of today, nor has there been a thorough investigation of the MACs diagnostic utility as a suitable neglect measure.

The studies that investigated the effectiveness of the MAC as a tool for measuring neglect report encouraging results (37, 38). Both studies demonstrated that neglect participants missed significantly more left-sided targets than controls and that this neglect is also associated with the performance in common neglect tasks. For example, targets missed on the left correlate with performance in the Behavioral Inattention Test (BIT) (37) and the Catherine Bergego Scale (38). The expected correlations provide significant support for the construct validity of the MAC. Moreover, both studies judged the MAC to be an ecologically valid test that is quick to administer and relatively straight forward to implement in clinical settings. Albeit, a complete standardization across different testing times and settings appears less achievable since corridor design and traffic flow are likely to differ in various institutions (38).

The aim of the current study was to expand on the findings of Ten Brink and colleagues by evaluating the diagnostic utility of the MAC paralleled to paper-and-pencil tasks during different stages of stroke recovery (subacute <1 month; chronic > 1 month). The Receiver Operating Characteristic (ROC), was used to evaluate the diagnostic utility of the tasks. Rather than comparing sensitivities of different scores, the ROC-based analysis combines sensitivity and specificity into a single variable, to quantify how accurately a task can discriminate between two states (neglecting and non-neglecting participants). If neglect becomes more apparent under more challenging task demands (31), the MAC could prove to be more efficient at detecting neglect than conventional methods, particularly as the time from initial brain damage increases (28, 29, 39). Moreover, with the MACs improved accuracy, it could offer a more time effective alternative to using large testing batteries since multiple neglect measures will be less necessary.

A secondary aim was to investigate the relationship between basic visual functions and MAC performance. Many stroke survivors report impaired visual abilities (40, 41). While these impairments may be unrelated to neglect, it is conceivable that they could adversely impact the detection of targets in the MAC.

MATERIALS AND METHODS

The current study retrospectively analyzed data collected by Guide Dogs SA/NT as a part of the standardized vision assessment of their referred clients. Moreover, 50 healthy participants were prospectively recruited to obtain control data for the MAC. The University of South Australia's Human Research Ethics Committee approved the study, with all participants signing an agreement to use the results of their vision assessment for the evaluation of Guide Dogs SA/NT assessment procedures.

Participants

Stroke Participants

Clients referred for a vision assessment at Guide Dogs SA/NT between January 1, 2013 and August 31, 2016 were assessed for eligibility. Participants were eligible if they (a) were over the age of 18, (b) were clinically diagnosed with a right-sided cerebrovascular accident (confirmed by medical referral letters), (c) completed a vision assessment on site at Guide Dogs SA/NT by the same expert Orientation and Mobility Instructor (OMI), (d) had satisfactory ability to produce and understand language (assessed by OMI), and (e) were physically able to participate (walking aids and self-propelling wheelchairs permitted).

Controls

Fifty healthy age-matched controls came from a convenience sample consisting of volunteer groups associated with Guide Dogs SA/NT.

Procedure and Tasks

All stroke participants completed a battery of tasks relating to visual function, paper-and-pencil neglect assessments and the MAC.

Visual Function Assessment

The visual function assessment comprised visual field testing using the Neuro Vision Technology (NVT) System and confrontation testing. The NVT system consists of the NVT scanning device (a light bar consisting of two rows of 10 colored lights, displayed on a horizontal panel placed at eye level approximately 30 cm from the client, and extending approximately 80 cm either side of central fixation) and computer software utilizing a standardized presentation of lights to determine the presence and degree of field loss (37). A secondary confrontation visual field test (Donders' test) was used to provide additional information regarding the presence of gross field loss. Visual reading acuity was measured using Dr. Alan Johnston's logMAR chart and low contrast reading chart. For overall contrast sensitivity, the Mars Letter Contrast Sensitivity Test (log contrast sensitivity) was employed.

Paper-and-Pencil Neglect Assessments

Two paper-and-pencil tasks were previously administered to the participants during their vision assessment. These included the Star Cancellation and the Line Bisection, both of which are subtests of the BIT (42). All tasks are on an A4 piece of paper, centered to the participant. Participants were instructed to avoid leaning to one side and to avoid adjusting the position of the paper during the assessment. However, there was no restriction of head and eye movements. Time pressure was, also, not imposed.

The Star Cancellation (43) consists of 56 small stars (the targets), 52 larger stars, 12 letters, and 10 short words in pseudo random order. Firstly, the administrator demonstrates by crossing out two of the small stars located in the middle of the page. The participant is then instructed to locate all remaining small stars (27 on the left and 27 on the right). The maximum score is 54. Previous research suggests neglect is evident in scores ranging from 44 to 51 (44–46). In the current study, we compared both cutoffs for star score (51 and 44) by computing the sensitivities and specificities for each cutoff with reference to the other neglect tasks. To assess the presence of a lateralizing deficit the star ratio, dividing the number of stars canceled in the left column by the number of stars canceled in the right, was computed. Values close to 0.50 indicate a symmetrical performance. Scores that range between 0 and 0.46 indicated neglect (44, 47).

In the Line Bisection, the participant is presented with three horizontal 8 inches (204 mm) lines offset in a staircase fashion (42). The extent of each line is pointed out to the participant who is then instructed to estimate the middle of each line. Deviations from the midpoint drawn by the participant to the actual midpoint for each line are measured. Scores ranging between 0 and 3 for each line were derived using the BIT template. A smaller score indicates that a mark is placed further from the midline. The maximum score is 9. Scores less than 6.5 indicate the probability of neglect (42).

Mobility Assessment Course

The MAC, located at Guide Dogs SA/NT and based on Verlander, Hayes (37), is a standardized route spanning 43 m in length (**Figure 1**). There is one sharp turn in the middle of the course indicated by an arrow at the wall. Pedestrian traffic is hardly present. However, the corridor is readily accessible to all Guide Dogs SA/NT staff. Along the corridor, 40 targets (20 on each side) are located on the walls at varying heights, ranging in size (10–20 cm), shape (squares, rectangles, circles, and stars), and color (yellow, blue, orange, pink, silver, and gold). Consistent scanning was required as targets were occasionally obstructed from view (Inside windowsills and behind fire hydrants) until the participant reached the target.

An example of the targets is shown to each participant at the beginning of the course. The instruction was to move through the course at a leisurely pace and to find all targets, so as to represent a dual-task (walking and visual search). The OMI followed, so as not to hinder the participant's mobility, while the participant pointed to each target as it became visible. The following outcomes were recorded: the total percentage of targets found and the asymmetry score, indicated by the difference between the number of targets found on the left and the right sides. A lower total score indicates a poorer performance. A higher asymmetry score, indicating more targets located on the right than left sides, reflects a poorer performance.

Statistical Analyses

Participants were grouped based on a 2-h vision assessment run by an experienced OMI. There is a lack of a reliable gold standard for the diagnosis of neglect (48), thus, as in Rengachary et al. (39), the clinical diagnosis of left neglect was the criterion standard used in defining the presence of neglect. A single OMI with 15 years' experience in vision and neglect assessments made the diagnosis. Participants who were deemed to have neglected based on this evaluation formed the neglect group. Participants without a neglect diagnosis were referred to the non-neglect group. The groups were then further subdivided into subacute (<1 month) and chronic (>1 month) stages of stroke recovery.

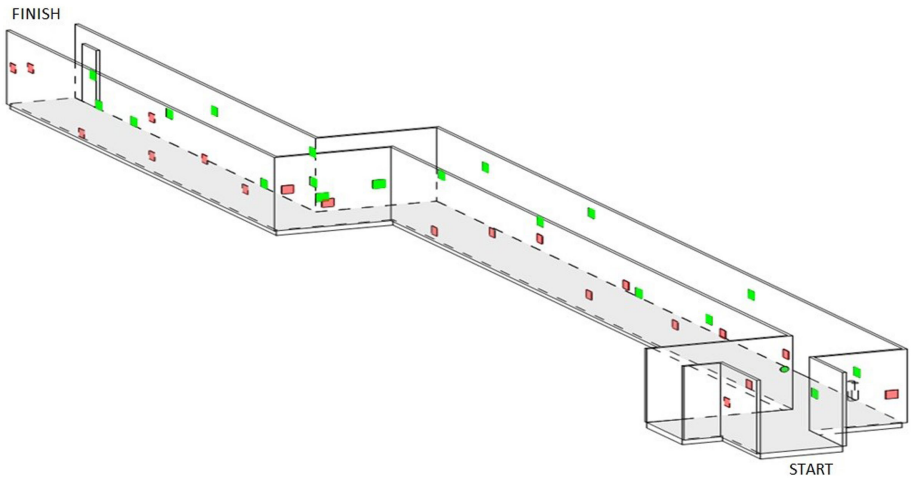

FIGURE 1 | A schematic 3D model of the Mobility Assessment Course situated at Guide Dogs of SA/NT. Red targets are corresponding to the left wall. Green targets are corresponding to the right wall.

The diagnostic utility of each task was evaluated using the Receiver Operating Characteristic (ROC) curve (49, 50). Often, specificity is neglected when assessing the diagnostic accuracy of neglect assessments. The ROC analysis combines both sensitivity and specificity to quantify how accurately a test can separate the tested groups into neglecters and non-neglecters. The sensitivity of a clinical test refers to the ability of the test to identify the participants with neglect correctly. A test with 100% sensitivity/100% specificity, suggests that the test identified all participants with neglect (sensitivity) and without neglect (specificity) correctly (51).

The ROC-based analysis (52) trade-offs between sensitivity (true positives) and specificity (false positives). In the ROC curve, the true positive rate is plotted against the false negative rate for different cutoff points. Each point on the ROC curve represents a single cut-off for the plotted pair (sensitivity, 1-specificity) corresponding to a chosen threshold. The area under the ROC curve (AUC) represents a measure of the test's discriminatory power. The higher the score, the greater discriminatory ability of the test [i.e., the true positive rate is high and the false positive (1-Specificity) rate is low]. The AUC can range from 0.0 to 1.0. Interpretation of AUC values are such that a value of 1.0 suggests perfect discriminatory abilities, that is all participants with neglect, and without neglect, are classified accordingly, 0.9–0.99 has outstanding discriminatory abilities, 0.8–0.89 has excellent discriminatory abilities, 0.7–0.80 has acceptable discriminatory abilities, 0.51–0.69 has poor discriminatory abilities, and a value of 0.5 suggests that the test is "no better than chance" at discriminating neglect participants from non-neglect participants (53).

To compare the diagnostic accuracy of the AUC at different levels, we used the methods of DeLong et al. (54) and Hanley and McNeil (51). For independent sample analyses, such as the comparisons between subacute and chronic groups, any significant differences were evaluated using the methods of Hanley and McNeil (51). For differences in same sample comparisons between tasks, DeLong et al.'s (54) methodology was employed. For all multiple comparisons, the chosen adjusted alpha level was 0.01. Statistical analyses were performed using MedCalc software for Windows, version 9.3.2.0 (MedCalc Software bvba, Mariakerke, Belgium) and IBM SPSS Statistics for Windows, version 20.0 (IBM Corp., Armonk, New York, NY, USA).

The same threshold for neglect as in Azouvi et al. (21) was applied for the MAC, such that any participant scoring poorer than the fifth percentile of the control group was considered to be affected by neglect.

We investigated the relationships between performance at the MAC, paper-and-pencil tasks, and the visual function measures with a series of Spearman correlations. The statistical significance was set at 0.05. An r of 0.1 was considered a small, 0.3 a medium, and 0.5 a large correlation (55).

RESULTS

Overall, this study included 67 stroke survivors and 50 healthy control participants (**Table 1**). There were no significant differences between the right hemisphere damage and control groups in relation to age, $t = 0.782$, $p = 0.436$. The 50 healthy controls completed the course providing participant cutoffs for indicating the presence of neglect. Control participants found on average 84.70% (SD 7.31) of the targets located on the MAC with an asymmetry score of −2.15 targets (SD 4.68). Applying a fifth percentile cutoff criterion for neglect (21) the threshold for neglect was an asymmetry score of >+6.13% and a total target score of <71.30%.

As shown in **Table 2**, the MAC identified more neglect cases than any other paper-and-pencil task. The total number of targets found was a better predictor of neglect than asymmetry scores. The total and asymmetry scores on the MAC exposed a considerable amount of false positives compared to both paper-and-pencil tasks, misclassifying more individuals as affected by neglect when the clinical diagnosis suggested otherwise. Importantly, while the paper-and-pencil tasks showed remarkable specificity values, the

TABLE 1 | Group demographics divided by subacute and chronic stages of recovery for neglecters and non-neglecting right hemisphere damage participants.

	Subacute (<1 month)		Chronic (>1 month)		
	Neglecters, *N* = 11	**Non-neglecters, *N* = 17**	**Neglecters, *N* = 20**	**Non-neglecters, *N* = 19**	**Controls (*n* = 50)**
Gender (Male/Female)	8/3	11/6	15/5	13/6	16/34
Age in years, M (SD)	73.82 (7.20)	64.88 (14.54)	67.90 (12.29)	58.37 (18.33)	63.40 (11.95)
Days since stroke, M (SD)	20.91 (8.23)	21.53 (6.92)	178.10 (301.12)	399.89 (1140.25)	–
Visual field defect (yes/no)	10/1	11/6	16/4	14/5	–
Mobility					
Independent no aids	8	17	18	18	50
Independent (walking cane)	3	0	0	1	
Wheelchair	0	0	2	0	

TABLE 2 | Number of true/false negative/positive calculations for the Star Cancellation using the star ratio and two laterality indexes (<44, <51), the Line Bisection—deviation score, and the MAC total score and asymmetry cutoffs derived from the control data.

	N	Cutoff point	Mean (SD)	% beyond cutoff point	True positives (sensitivity)	False positives	True negatives (specificity)	False negatives
Star cancellation								
Total	66	<51	50.95 (5.84)	22.4	13 (43.3%)	2 (5.6%)	34 (94.4%)	**17 (56.7%)**
		<44	50.95 (5.84)	10.4	6 (20%)	1 (2.8%)	35 (97.2%)	24 (80%)
Star ratio	66	<0.46	0.48 (0.06)	12.1	8 (26.7%)	0 (0%)	36 (100%)	21 (73.3%)
Line Bisection, deviation score	59	<6.5	7.95 (2.15)	14.9	10 (35.7%)	0 (0%)	31 (100%)	18 (64.3%)
MAC								
Total	67	<71.3%	73.95 (15.00)	**50.7**	**23 (74.2%)**	11(30.6%)	25 (69.4%)	8 (25.8%)
Asymmetry (R minus L total)	67	>+6.13%	2.40 (10.71)	31.3	12 (38.7%)	9 (25%)	27 (75%)	19 (61.3%)

The number of participants completing each task differs as the availability of test data varied.

low sensitivity meant a high number of positive neglect cases were overlooked.

Figure 2 displays the AUC as a measure of the diagnostic utility of each task. To investigate the performance as a function of time post stroke, the AUC was computed at two stages of stroke recovery, subacute (<1 month) and chronic (>1 month). The AUC values indicated that no single test was considered to have outstanding accuracy in distinguishing a neglecting participant from a non-neglecting participant. When considering the tests discriminative abilities, the majority of the AUC values fell in the "poor" to "acceptable" range. As per *post hoc* tests, no significant differences existed between tests at subacute or chronic stages of recovery ($p > 0.12$), or between subacute and chronic groups for individual tasks ($p > 0.45$).

All MAC measures were significantly related to the Star Cancellation ratio (**Table 3**). Similarly, all measures on the MAC, except for asymmetry, showed moderate to large correlations with the Line Bisection deviation score.

DISCUSSION

The main aim of the current study was to evaluate the diagnostic utility of the MAC compared to a series of paper-and-pencil neglect tests during different stages of stroke recovery. The hypotheses that the MAC measure with greater task demands, relevancy, and transparency could improve detection of neglect, compared to the conventional tests, particularly at more chronic stages of recovery, were not supported. The 95% confidence intervals of the AUC values overlapped across the different test scores and recovery stages. There were no statistically discernable differences between tasks at subacute or chronic stages or, between subacute and chronic groups for individual tasks. These results suggest, irrespective of time since brain damage, the MAC is just as accurate at detecting neglect as the tasks under question here.

Our results are in contrast to the abundance of literature suggesting a superiority of functional and more demanding tasks over conventional paper-and-pencil neglect tasks (21, 26, 27, 31, 56, 57). An explanation for the discrepancy is that the current study investigated test accuracy by combining the task's sensitivity and specificity into one measure. Indeed, if we only assess the sensitivity of the test, i.e., their ability to detect neglect (true positives), the MAC showed the highest sensitivity values (74.2%). The symptom detection skills of the Star Cancellation (43.3%) and Line Bisection tests (35.7%) are less comparable. However, the MAC's high sensitivity is at the expense of a low specificity, as such, the MAC (based on total targets located) falsely implicated 30.6% of our participants without neglect as affected by neglect. In comparison, the Star Cancellation falsely diagnosed only 2.8% of the sample as affected by neglect.

The different sensitivity and specificity values of the MAC and the conventional tests are, therefore, a likely reason that the combined inspection of these two values in a ROC curve does not reveal statistically significant differences between the tests. Thus, at the very least our results highlight the importance of taking into account sensitivity and specificity when evaluating the diagnostic utility of a test. It is noteworthy that the large body of literature on neglect assessments focuses on sensitivity testing, and thereby neglects specificity (58–61), as such, crucial information is missing that adequately judges the true diagnostic accuracy of these tests.

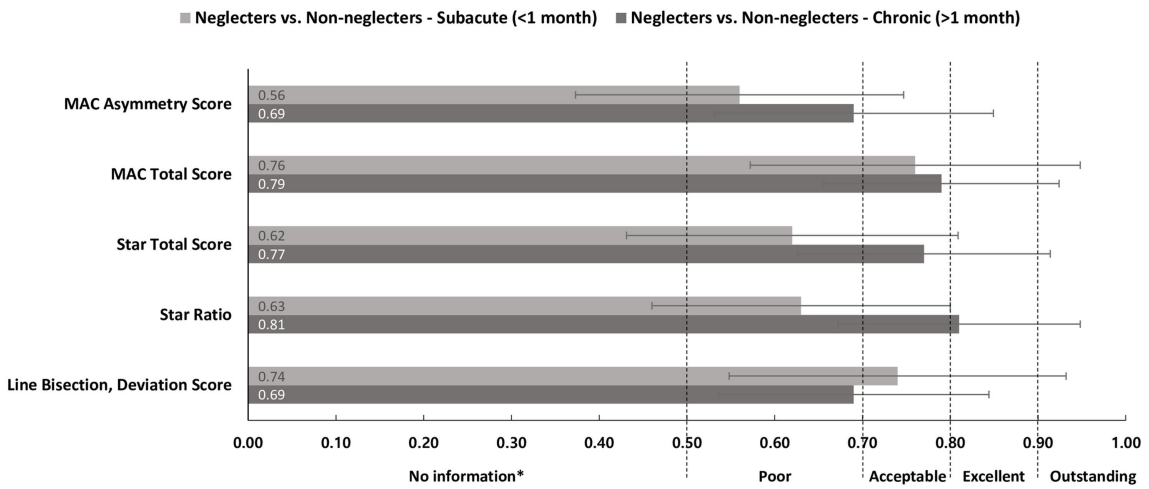

FIGURE 2 | Area under the ROC curve (*x*-axis) and neglect measures (*y*-axis) for participants in subacute (<1 month) and chronic (>1 month) recovery stages. Classification terms (poor, acceptable, excellent, and outstanding) refer to the discriminative abilities of each outcome. Error bars represent 95% confidence intervals. Abbreviations: R, right; L, left; MAC, Mobility Assessment Course. *Test provides no useful information.

TABLE 3 | Spearman correlations between MAC, Star Cancellation, Line Bisection, contrast sensitivity, and visual acuity.

		MAC targets found		
Outcome	***N***	**Total**	**Contralesional**	**Asymmetry**
Star Cancellation, star ratio	66	0.40**	−0.42**	−0.27*
Line Bisection, deviation	60	0.58**	0.48**	−0.07
Visual acuity	66	−0.11	−0.14	0.08
Contrast sensitivity	66	0.13	0.05	−0.07

The number of participants completing each task differs as the availability of test data varied.
**Correlation is significant at the 0.05 level.*
***Correlation is significant at the 0.001 level (two tailed).*
MAC, Mobility Assessment Course.

From a clinician's point of view, it might be more acceptable for an assessment tool to be less specific, than less sensitive, since the main purpose of the clinical assessment is to uncover symptoms. The high sensitivity of the MAC has an apparent advantage in circumstances in which significant remaining impairments are monitored safely. For example, the discovery of a contralesional deficit in attention which would affect driving ability and subsequently avoid crashes. What is significantly riskier is a missed diagnosis that denies the person access to vital assisted care or rehabilitation. As a result, the risk of accidents and injuries increases, particularly if a suspended license is reinstated or the individual returns to work.

The AUC values indicate that no single test score has outstanding accuracy in distinguishing a non-neglecting participant from a neglecting participant. The majority of the measures fell into the "poor" to "acceptable" range. Just like the standard practice in current neglect assessments, the implications of the tests suboptimal diagnostic accuracies are clear cut; to guarantee the correct diagnosis of all persons affected by neglect, the administration of a battery of neglect tests is necessary. In other words, the idea that the MAC could potentially justify the reduction of tests required for a neglect diagnosis was not supported. It is important to keep in mind that neglect is a heterogeneous syndrome manifesting in many different ways (62). It is, therefore, unlikely that we will capture neglect in its many forms with just one task. Nevertheless, a quick assessment of neglect (i.e., fewer tasks) would be advantageous since it makes room for further neurological testing while reducing the risk of exhaustion in the participant.

The MAC measures (total and contralesional targets found) were significantly related to performances in the conventional neglect tests. The observed medium to large effect sizes is similar in size to previously reported relationships between the performances in the MAC and standard neglect tests (37, 38). The finding of these relationships across three different studies each with different MAC settings and designs points to the MACs high construct validity and may help to further establish the MAC as an ecologically valid alternative for assessing neglect.

An important novel aspect of this study was the assessment of the effects of basic visual functions on the performance in the MAC. We found no relationship between the patients (corrected) visual acuity, contrast sensitivity, and their ability to spot targets during the MAC. These results need further confirmation with larger and more diverse samples, but low vision impairments commonly found in stroke survivors may not significantly affect the diagnostic properties of the MAC. If this holds true, then this further adds to the validity of the MAC.

An interesting, yet still unanswered question, is whether test accuracy is modulated by the presence or absence of visual

field defects. Only a small proportion of participants (15%) were without a visual field defect in this study; we, therefore, were unable to assess its effects on the MAC reliably. Buxbaum et al. (59) found that a virtual reality program (VRLAT) was equally as likely to categorize those with and without visual field defects as being affected by neglect. The VRLAT has many similarities with the MAC. Therefore, the MACs abilities to differentiate between those with and without field defects are promising. Future research is essential to evaluate this likelihood further.

In sum, validating previous studies (37, 38), we conclude that the MAC is an ecologically valid alternative for assessing neglect. Regarding its diagnostic accuracy, there is currently not enough evidence to suggest that it is a big step forward in contrast to the accuracy of more commonly used tasks. However, the high sensitivity of the MAC has an apparent advantage when screening neglect and positive results can be further investigated due to the tests relatively low specificity. Moreover, the MAC is likely to be an insightful exercise for people affected by neglect. The participant can repeat the course allowing the clinician to make visible neglected targets and to provide feedback on performance characteristics, such as walking speed or visual scanning behavior. The MAC does highlight self-awareness in contralesional deficits in a more practical sense and, therefore, is considered here to be a step in the right direction.

ETHICS STATEMENT

The University of South Australia's Human Research Ethics Committee granted approval for the study, with all participants signing an agreement to use the results of their vision assessment for the evaluation of Guide Dogs SA/NT assessment procedures.

AUTHOR CONTRIBUTIONS

TL, MG, LW, and TS conceived and designed the study. MG and TS collected data. TL and MG analyzed the data. All authors were involved in the interpretation of the data, writing and drafting of the manuscript, and overlooked the final manuscript before submission.

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The Impact of Carotid Artery Stenting on Cerebral Perfusion, Functional Connectivity, and Cognition in Severe Asymptomatic Carotid Stenosis Patients

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Background and purpose: Asymptomatic carotid artery stenosis can lead to not only stroke but also cognition impairment. Although it has been proven that carotid artery stenting (CAS) can reduce the risk of future strokes, the effect of CAS on cognition is conflicting. In recent years, pulsed arterial spin labeling (pASL) MRI and resting-state functional MRI (R-fMRI) have been employed in cognitive impairment studies. For the present study, cognition is evaluated in severe asymptomatic carotid artery stenosis patients undergoing CAS, and the mechanisms underlying the cognitive change are explored by pASL MRI and R-fMRI.

Materials and methods: We prospectively enrolled 24 asymptomatic, severe (≥70%), unilateral internal carotid artery stenosis patients, who were expecting the intervention of CAS. Cognition assessment (including the Montreal Cognitive Assessment Beijing Version, the Minimum Mental State Examination, the Digit Symbol Test, the Rey Auditory Verbal Learning Test, and the Verbal Memory Test) and an integrated MRI program (pASL MRI, and R-fMRI) were administered 7 days before and 3 months after CAS.

Results: 16 subjects completed the follow-up study. After stenting, significant improvement in the scores of the MMSE, the Verbal Memory test, and the delayed recall was found. No significant difference was found in the scores of the Montreal Cognitive Assessment Beijing Version, the Digit Symbol Test, and the immediate recall. After CAS treatment, asymptomatic carotid artery stenosis patients showed increased perfusion in the left frontal gyrus, increased amplitude of low-frequency fluctuation (ALFF) in the right precentral gyrus, and increased connectivity to the posterior cingulate cortex (PCC) in the right supra frontal gyrus. However, no significant correlations were found between these imaging changes and cognition assessments.

Conclusion: Successful CAS can partly improve cognition in asymptomatic carotid artery stenosis patients. The cognition improvement may be partly attributed to the increased perfusion in the left frontal gyrus, increased ALFF in the right precentral gyrus, and increased connectivity to the PCC in the right supra frontal gyrus.

Keywords: carotid artery stenting, asymptomatic carotid artery stenosis, cognition, pulsed arterial spin labeling, resting-state functional MRI, default mode network

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INTRODUCTION

Carotid artery stenosis without transient ischemic attack (TIA) and stroke is considered as "asymptomatic" (1, 2). However, a number of studies have demonstrated that asymptomatic carotid artery stenosis patients had significantly poorer performance in executive function and memory, indicating that "asymptomatic" carotid stenosis might not be truly asymptomatic (3–7). Carotid endarterectomy (CEA) had been traditionally performed to prevent stroke in patients with high-grade carotid stenosis (8). However, carotid artery stenting (CAS) is now being investigated as an alternative to CEA (9). Although both CEA and CAS have been proven to reduce future strokes, the effect of CEA and CAS on cognition still remained conflicting (9–11).

In past few years, several imaging techniques, such as pulsed arterial spin labeling (pASL) MRI and resting-state functional MRI (R-fMRI), had been increasingly used to study cognitive impairment in humans. In this study, we evaluated the cognition performance in severe asymptomatic carotid artery stenosis patients undergoing CAS and explored the mechanisms underlying the cognition changes by the integrated MRI techniques including pASL MRI and R-fMRI.

PARTICIPANTS, INCLUSION AND EXCLUSION CRITERIA

From January 2015 to June 2016, successful CAS was performed in 24 asymptomatic carotid artery stenosis patients, and the follow-up study was completed for 16 patients. No vascular complications occurred in these 16 subjects. The inclusion criteria were as follows: (1) age between 55 years and 80 years; (2) unilateral internal carotid artery stenotic degree $\geq$ 70%; (3) right-hand-dominant; (4) free of stroke, TIA, dementia, and depression; (5) modified Rankin Scale: 0 or 1; (6) no major medical conditions; and (7) obtained written informed consent. The exclusion criteria were as follows: (1) contralateral internal carotid artery stenosis $\geq$ 50%; (2) posterior circulation diseases; (3) MMSE $<$ 26, which is a cutoff value for mild cognitive impairment; (4) functional disability (modified Rankin Scale $\geq$ 2); (5) severe systemic diseases and neuropsychiatric diseases (such as congestive heart failure and history of stroke); (6) any contraindications for MRI scan (e.g., metal implants); (7) low education level ($<$6 years); (8) evidence of carotid dissection; (9) intracranial aneurysm or arteriovenous malformation; and (10) allergy to heparin, aspirin, or clopidogrel. All procedures involved in this study were approved by Zhongnan Hospital Review Board.

CAS PROCEDURE AND CLINICAL FOLLOW-UP

After stenting, all final residual diameter stenosis was $\leq$20%. Systolic blood pressure was carefully maintained between 100 and 140 mmHg, and no complications were found. Aspirin and clopidogrel were continued for at least 3 months after successful intervention.

NEUROCOGNITIVE ASSESSMENT

Cognition assessments were completed within 1 week after MRI scan. The MMSE and MoCA Beijing Version were used to assess the global cognition. In the Digit Symbol Test, subjects were required to translate numbers to symbols in a given time and correct translations within 90 s were recorded. The Rey Auditory Verbal Learning Test was used to evaluate the memory and verbal learning ability. In this test, participants had to recall all the words remembered, and this procedure was repeated five times. These were recorded so that the total number of words was immediately recalled during the first five repeats and the delayed recall of the first list. In the Digit Span Test, participants were required to repeat the orally presented lists of numbers, beginning with a two-number sequence, and each correct performance was followed by one additional number. In the forward span, participants were asked to retell the span in forward order, and in the backward span, the participant was asked to retell the span in reverse order.

BRAIN IMAGING ACQUISITION

MRI images were acquired using a 3.0 T Siemens scanner in Zhongnan Hospital. T1 images were collected using MP-RAGE sequence. Scan parameters were as follows: flip angle = 9°, TR = 2,250 ms, TE = 2.26 ms, slice thickness = 1.0 mm, inversion time = 900 ms, number of slices = 176, data matrix = 215 × 256, and FOV = 256 mm × 224 mm. pASL perfusion images were collected using Q2TIPS II technique. Scan parameters were as follows: TR = 2,500 ms, TE = 11 ms, FOV = 240 mm × 240 mm, matrix = 64 × 64, FA = 90°, and slice thickness = 6 mm. R-fMRI was acquired using EPI sequence: repetition time = 2,000 ms, echo time = 30 ms, flip angle = 90°, number of slices = 33, slice thickness = 3.8 mm, gap = 1 mm, data matrix = 64 × 64, and field of view = 240 mm × 240 mm.

IMAGE PROCESSING

Pulsed arterial spin labeling

relCBF maps were automatically generated by Siemens workstation, and the relCBF correct map of each participant was normalized to EPI template provided by Statistical Parametric Mapping 8 (SPM8). The final voxel size was 3 mm× 3 mm× 3 mm. Each subject's relCBF map was transformed into standard MNI space using these transformation parameters. The normalized relCBF maps were smoothed for comparisons with 8-mm FWHM isotropic Gaussian kernel. These individual maps were then entered into SPM8 to identify significant different regions between two groups.

R-fMRI Preprocessing

Resting-state functional MRI preprocessing was performed with Data Processing Assistant for Resting-State fMRI (DPABI 2.1). The first 10 volumes of each time series were abandoned. Then, the images were corrected for slice timing and realigned. Afterward, images were normalized into standard MNI space and smoothed with 8-mm FWHM isotropic Gaussian kernel.

Amplitude of Low-Frequency Fluctuation (ALFF)

Amplitude of low-frequency fluctuation calculation was performed with Resting-State fMRI Data Analysis Toolkit (REST 1.8). One-sample *t*-test was performed using SPM8 in each group to detect the regions with higher-than-mean ALFF. Two-sample *t*-test was performed to determine differences between these mALFF images. Significantly different regions were shown on MNI templates. The two-sample *t*-test results were restricted within the mask made from the results of one-sample *t*-tests performed for two groups.

Functional Connectivity

All images were filtered with a 0.01–0.08 Hz band-pass filter to reduce the noise before FC analysis. The ROI was located in the bilateral posterior cingulate cortex (PCC). The mean ROI signal was counted by average all voxels in bilateral PCC. The ROI time course was used for correlation analysis with all other voxels in the brain. To normalize the correlation coefficients, Fisher *z*-transform was then applied. One-sample *t*-test was performed using SPM8 in each group to detect the regions with significant connectivity to the PCC. Then, two-sample *t*-test was performed to determine differences between these *z*-FC image groups. Significant different regions were shown on MNI templates. The two-sample *t*-test results were restricted within the mask made from the results of one-sample *t*-tests performed for two groups.

Statistical Analysis

We used IBM SPSS 20.0 and SPM8 to perform statistical analyses. Paired Student's *t*-test was used to detect significant differences, and significance was set at 0.05. Age and education were used as covariates in all tests involving cognition. After analyzing pASL, ALFF, and FC, regions with significant differences were extracted as ROIs, and Spearman correlation was then performed to detect the relationship between imaging differences and cognition scores.

RESULTS

Part 1: **Table 1** shows the demographic information and cognitive test scores at baseline and 3 months after CAS. Significant improvements in the MMSE, Verbal Memory test, and delayed recall were observed. There is no decline in any individual scores (**Table 1**).

Part 2: Difference in CBF between baseline and 3 months after performance. Compared with baseline, the asymptomatic carotid artery stenosis patients showed the increased CBF mainly in the left frontal gyrus, anterior cingulate, left occipital gyrus, and left cerebellum (**Table 2**; **Figure 1**).

Part 3: Differences in ALFF between baseline and 3 months after treatment. After treatment, the asymptomatic carotid artery stenosis patients showed significantly increased ALFF predominantly in the right precentral gyrus. The asymptomatic carotid artery stenosis patients also showed decreased ALFF mainly in the left and right cerebellum anterior lobe (**Table 3**; **Figure 2**).

TABLE 1 | Demographic information and neuropsychological test scores at baseline and 3 months after CAS.

Characteristics	Baseline	3 months after stenting	*P*-value
Age (years)	66.8 ± 5.8		
Male:female	12:4		
Education (years)	9.9 ± 3.0		
Hypertension	15		
Diabetes mellitus	4		
Hypercholesterolemia	7		
Stenotic side			
Left	5		
Right	11		
MMSE	27.0	28.0	0.01*
MoCA	23.5	24.0	0.05
Verbal Memory Test			
Forward digit span	6.0	6.0	0.04*
Backward digit span	4.0	5.0	0.04*
Rey Auditory Verbal Learning Test			
Immediate recall	29.5	34.5	0.19
Delayed recall	4.0	6.5	0.03*
Digit Symbol Test	26.5	30.5	0.14

**Statistically significant difference.*
CAS, carotid artery stenting.

TABLE 2 | Significant CBF difference between baseline and 3 months after CAS with their location.

	Number of voxels	Peak MNI coordinate			Peak MNI coordinate region	Peak *T* value
		X	*Y*	*Z*		
1	1956	−12	−81	−36	Left occipital gyrus, left cerebellum	5.98
2	1212	−3	15	12	Left frontal gyrus, anterior cingulate	3.97

CAS, carotid artery stenting.

Part 4: Differences in FC to PCC between baseline and 3 months after intervention. After intervention, the asymptomatic carotid artery stenosis patients showed the increased connectivity to the PCC mainly in the right supra frontal gyrus. There was no region showing decreased connectivity to the PCC (**Table 4**; **Figure 3**).

Part 5: Relationship between imaging changes and cognition scores. No significant correlation was found between imaging differences and cognition scores ($P > 0.05$ for all).

DISCUSSION

In this study, we found that CAS could improve global cognition (assessed by MMSE) and memory (assessed by Verbal Memory test and delayed recall test) in asymptomatic carotid artery stenosis patients, which is agreed with previous reports (12, 13). Since cognitive impairment could also predict mortality, it may be misleading that using stroke as the only outcome marker in CEA and CAS (14).

Silent infarction and cerebral hypoperfusion are the main mechanisms in the development of cognitive decline in asymptomatic carotid artery stenosis patients, indicating that cognition may be improved by reducing silent infarction and restoring CBF.

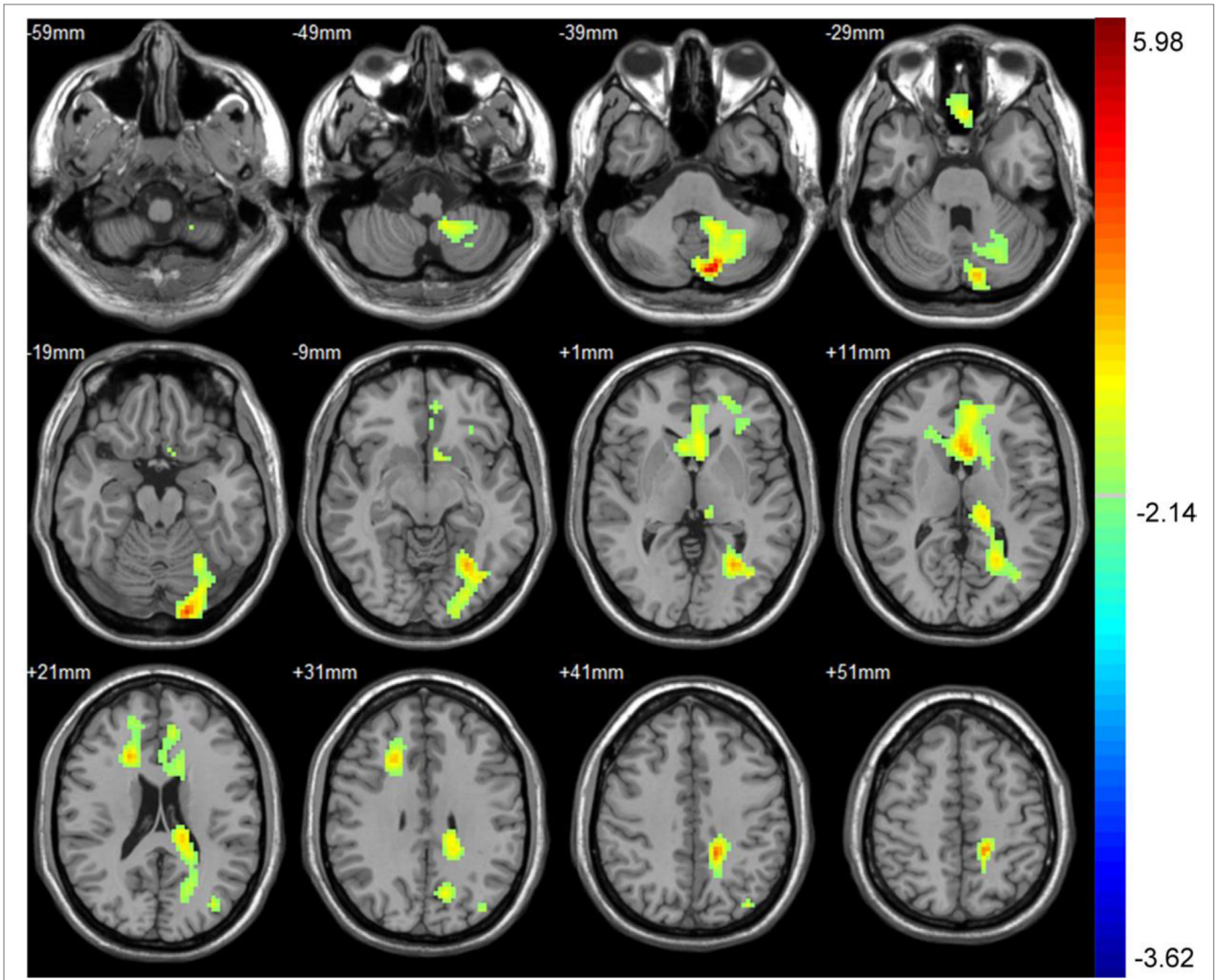

FIGURE 1 | The CBF was significantly increased in the left frontal gyrus, anterior cingulate, left occipital gyrus, and left cerebellum 3 months after carotid artery stenting. The result was corrected using the AlphaSim program, which was set at $P < 0.01$ and number of voxels > 611, which was corresponded to a corrected $P < 0.05$. The left part of the figure represented the patient's right side.

TABLE 3 | Significant ALFF difference between baseline and 3 months after treatment with their location.

	Number of voxels	Peak MNI coordinate			Peak MNI coordinate region	Peak *T* value
		X	*Y*	*Z*		
1	267	24	−12	60	Right precentral gyrus	5.24
2	550	6	−57	−27	Left and right cerebellum anterior lobe	−6.92

T > 0 indicated increased ALFF 3 months after treatment. T < 0 indicated decreased ALFF 3 months after treatment.
ALFF, amplitude of low-frequency fluctuation.

Our results showed the increased regional CBF mainly in the left frontal gyrus, anterior cingulate, left occipital gyrus, and left cerebellum after CAS. The increased CBF found in the occipital gyrus and cerebellum could be explained by the presence of functional circle of Willis. Since frontal gyrus and anterior cingulate consisted of regions that mediated memory and executive function, increased CBF in these regions may contribute to the cognitive improvement after CAS.

In recent years, more and more studies had demonstrated that cognition output was not dependent on the individual brain region, but dependent on network regions (15). A number of studies had already demonstrated this opinion in patients with neurodegenerative diseases (16, 17). The default mode network (DMN) was one of them (18). By functional MRI and PET studies, the most common DMN components are the PCC, the medial prefrontal cortex, the anterior cingulate cortex, the inferior parietal lobule, and other regions (19, 20). The DMN was suggested to play important role in cognition, such as reviewing past knowledge and processing memory (18, 21–23). Another reason

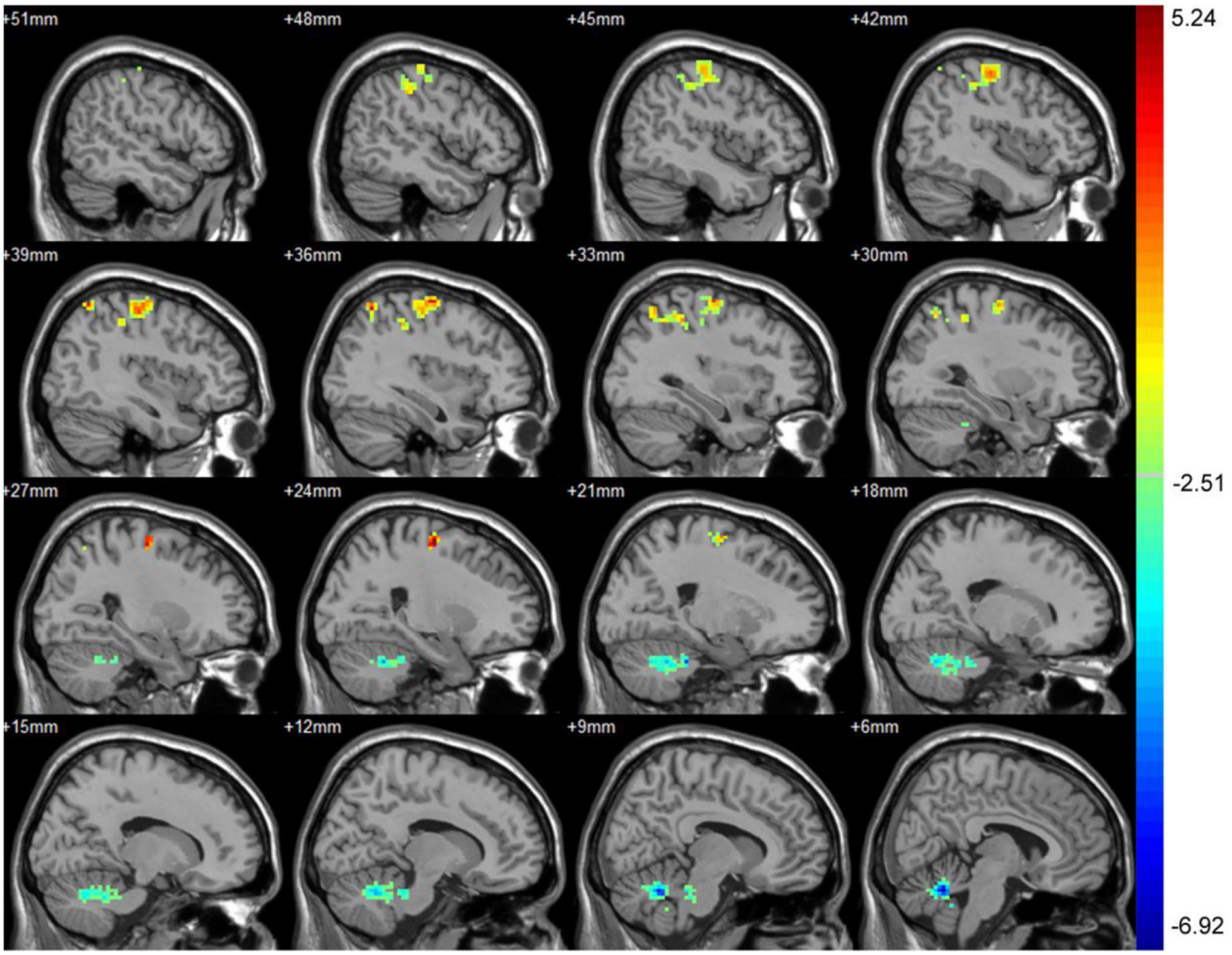

FIGURE 2 | Significant difference in amplitude of low-frequency fluctuation (ALFF) between baseline and 3 months after treatment. After treatment, the asymptomatic carotid artery stenosis patients showed significantly increased ALFF predominantly in the right precentral gyrus. The asymptomatic carotid artery stenosis patients also showed decreased ALFF mainly in the left and right cerebellum anterior lobe. Red indicates 3 months after treatment > baseline and blue indicates 3 months after treatment < baseline. The result was corrected using the AlphaSim program, which was set at $P < 0.01$ and number of voxels > 175, which was corresponded to a corrected $P < 0.025$.

TABLE 4 | Significant connectivity difference to the posterior cingulate cortex between baseline and 3 months after intervention with their location.

	Number of voxels	Peak MNI coordinate			Peak MNI coordinate region	Peak *T* value
		X	*Y*	*Z*		
1	186	24	57	3	Right supra frontal gyrus	3.49

selecting DMN for analysis was that previous study had demonstrated that DMN was especially easily affected by hypoperfusion (24). The PCC, supplied by the precuneal artery from its origins at the ICA, had been shown to be a key point in DMN and involved in cognitive decline (19).

Among the indexes utilized in R-fMRI, ALFF was a useful index to reflect spontaneous neuronal activities (25–28). We noted that the asymptomatic carotid artery stenosis patients showed increased ALFF mainly in the right precentral gyrus after CAS, which belonged to the DMN. Thus, cognitive improvement after CAS could also be partially attributed to the increased activities in these regions. Since previous studies had indicated that the cerebellum not only regulated motor control but also involved in cognition tasks (29, 30). The decreased ALFF in the cerebellum anterior lobe may further illustrate the cognition role of cerebellum, but the mechanisms had not been illustrated exactly and needed further more studies.

We compared the FC to the PCC before and after CAS treatment and found that the asymptomatic carotid artery stenosis patients showed increased connectivity to the PCC mainly in the right supra frontal gyrus after CAS. There was no region showing decreased connectivity to the PCC. The increased regions were also overlapped with the anterior part of the DMN. Since the anterior part of the DMN was specially associated with executive function and memory, the cognitive improvement

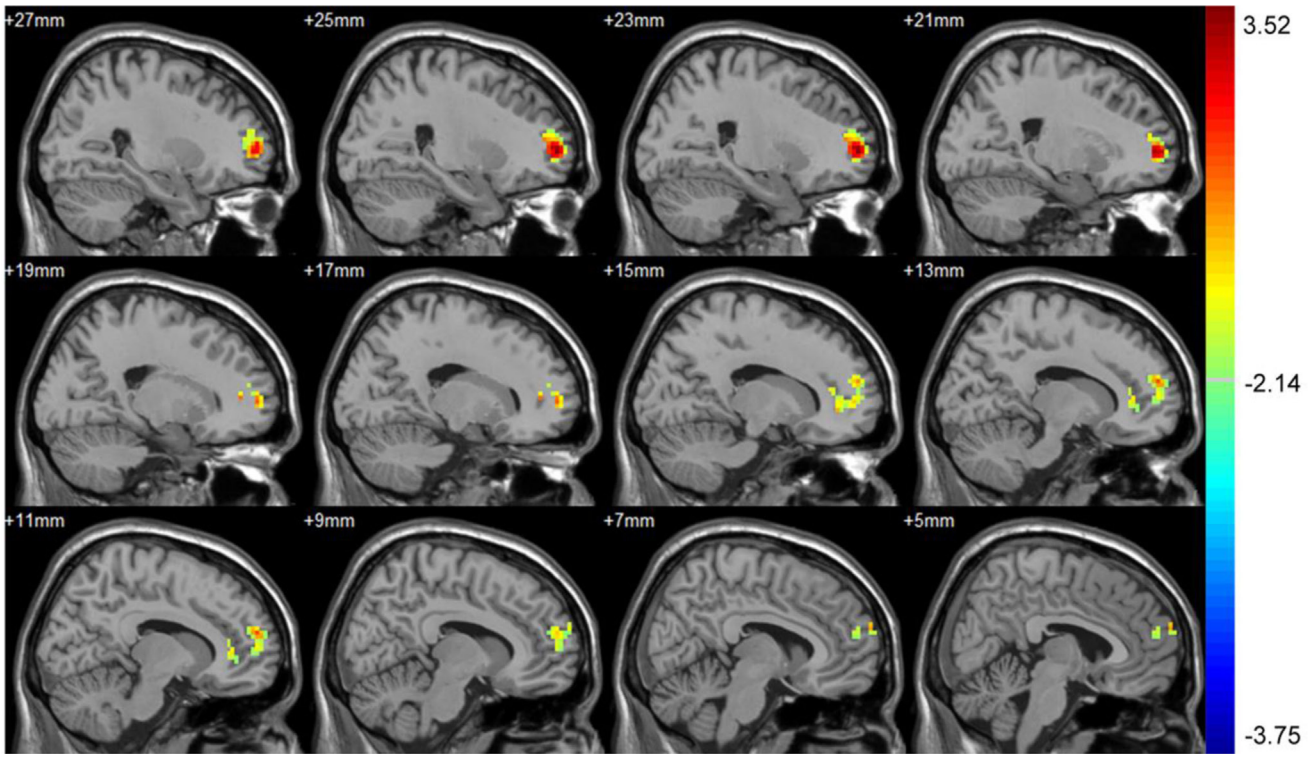

FIGURE 3 | Significant connectivity difference to the posterior cingulate cortex (PCC) between baseline and 3 months after intervention. After treatment, the asymptomatic carotid artery stenosis patients showed the increased connectivity to the PCC mainly in the right supra frontal gyrus. The result was corrected using the AlphaSim program, by setting at $P < 0.01$ and number of voxels > 142, which corresponded to a corrected $P < 0.05$.

could also be partially attributed to the increased FC to the PCC in the anterior part of DMN, but no significant correlation was found (31, 32).

Nevertheless, several limitations in this study should be discussed. First, the sample size was not big enough. Second, it was extremely difficult to define the stenosis timing. Longer occlusion duration may potentially affect the cognition reversibility. Third, the follow-up interval was relatively short. Fourth, no control group was included.

In summary, this prospective study demonstrated that successful CAS could partly improve cognition dysfunction in asymptomatic carotid artery stenosis patients. By the integrated MRI techniques including pASL MRI and R-fMRI, we also found increased perfusion in the left frontal gyrus and anterior cingulate, increased ALFF in the right precentral gyrus, and enhanced connectivity to the PCC in the right supra frontal gyrus after CAS. Since these regions are overlapped with DMN, the cognition improvement by CAS in asymptomatic carotid artery stenosis patients may be partly attributed to these changes.

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of "Zhongnan Hospital Review Board" with written informed consent from all subjects. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the "Zhongnan Hospital Review Board."

AUTHOR CONTRIBUTIONS

TW: analysis and interpretation of data. DS, YL, BM, HL, and SZ: acquisition of data. JZ: study concept and design.

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Midterm Blood Pressure Variability Is Associated with Poststroke Cognitive Impairment: A Prospective Cohort Study

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Objective: The aim of this study was to investigate the relationship between blood pressure variability (BPV) and poststroke cognitive impairment (PSCI).

Methods: Seven-hundred ninety-six patients with acute ischemic stroke were included in this study. Midterm BPV was evaluated by calculating the SD and coefficient of variation (CV, 100 × SD/mean) of systolic blood pressure (SBP) and diastolic blood pressure during the 7 days after stroke onset. Cognitive function was assessed using the Montreal Cognitive Assessment (MoCA) at admission and at all follow-up visits. Patients with MoCA scores <26 were considered to have PSCI.

Results: The incidence of PSCI reached its peak (72%) 3 months after stroke onset and decreased to 30.3% at 12 months poststroke. After adjusting for covariables, the increase in the prevalence of PSCI at 3 months was independently associated with increases in the CV of blood pressure during the 7 days after stroke [odds ratios and 95% CI for patients in the second to fifth quintiles of SBP CV were 2.28 (1.18, 4.39), 2.33 (1.18, 4.62), 2.69 (1.31, 5.53), and 4.76 (1.95, 11.67), respectively]. Sub-analysis of the MoCA scores revealed that the patients had impairments in visuoperceptual abilities and executive functions, as well as in naming and delayed recall ($p < 0.05$).

Conclusion: Midterm BPV during the early phase of acute ischemic stroke is independently associated with PSCI, especially in the visuoperceptual, executive, and delayed recall domains.

Clinical Trial Registration: http://www.chictr.org.cn, identifier ChiCTR-TRC-14004804.

Keywords: stroke, cognitive impairment, Montreal Cognitive Assessment, blood pressure variability, subfactors

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INTRODUCTION

Poststroke cognitive impairment (PSCI) involves deficits in memory, comprehension, perception, language, and executive function (1). In the past 10 years, PSCI has been the subject of much attention, as it leads to poor life quality, slow functional recovery, and higher mortality. Current evidence suggests that PSCI occurs is about two-thirds of patients during the acute phase of

ischemic stroke (2), and that 20–30% of patients with PSCI will develop dementia (3).

Multiple factors have been found to lead to progression of cognitive impairment and dementia after stroke. These include older age, family history, genetic variations, poor educational status, vascular comorbidities, and depression (4). Recently, a cohort study of 6,506 elderly individuals who were followed up for 8 years indicated that an increase of 1 SD in the coefficient of variability of systolic blood pressure (SBP) or diastolic blood pressure (DBP) is associated with an increase of about 10% in the risk of dementia (5). Higher visit-to-visit blood pressure variability (BPV) has also been proved to be associated with cognitive function impairment in the elderly (6). BPV has also been shown to be associated with neurological impairment (7), progression of brain white matter lesions (8), hemorrhagic transformation after ischemic stroke (9), and poor long-term prognosis (10). However, it is still unclear whether higher BPV is a cause or consequence of PSCI.

Poststroke cognitive impairment is not a unitary disease, but involves deficits in multiple domains. However, prospective follow-up studies regarding long-term domain-specific cognitive impairments are rare (11). The aim of this study was to investigate the relationship between BPV and PSCI and the prevalence of domain-specific cognitive impairment.

MATERIALS AND METHODS

Study Design and Participants

We carried out a single-center, prospective, observational study. The protocol of this study was registered with Chinese Clinical Trial Registry (ChiCTR-TRC-14004804; http://www.chictr.org.cn/index.aspx) and derived from the expanded content of "stroke risk assessment form" and "follow-up table" determined by "stroke risk factors screening and intervention project," People's Republic of China Health Committee. Acute stroke was defined as the sudden attack of neurological deficit of cerebrovascular cause for more than 24 h. Computed tomography (CT) and magnetic resonance imaging (MRI) were used to diagnose stroke, to distinguish hemorrhage and ischemia, and to divide up the infarcts into the anterior and posterior depending on the location and area. The infarct volume was calculated by the Pullicino formula (12). From January 2013 to June 2014, 986 consecutive patients with acute ischemic stroke were registered in the Stroke Registry database. The study was approved by the ethic committee of the First People's Hospital of Lianyungang (No. Lianyungang-2012-06) and written informed consent was obtained from each patient or his/her proxy.

Inclusion and Exclusion Criteria

Patients meeting all of the following criteria were eligible to participate in our study: acute ischemic stroke within 24 h of onset, identified signs of focal neurological dysfunction, the National Institutes of Health Stroke Scale (NIHSS) scores ≥4, and the total scores ≥2 of the fifth motor arm and the sixth motor leg on NIHSS, ages between 40 and 75 years and SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg.

Patients meeting any of the following criteria were excluded from the study: severe disturbance of consciousness identified by a level of consciousness score >1 on the NIHSS (21 patients); modified Rankin Scale score >1 before stroke onset (no patients); severe mental disorder or dementia (7 patients); serious systemic diseases or expected life span <90 days (24 patients); alanine transaminase or aspartate aminotransferase >2.0, which is at the upper limit of normal, or severe liver disease (23 patients); estimated glomerular filtration rate <30 ml/min/1.73 m^2 or sever kidney disease (13 patients); aphasia ($n = 36$), inability to complete the Montreal Cognitive Assessment (MoCA) ($n = 41$); or being considered inappropriate (living or working non-local and have a lower degree of integrity) for the study ($n = 25$) (Figure S1 in Supplementary Material).

Management and Measurement of Blood Pressure

Patients with acute ischemic stroke were treated according to the 2010 Chinese Guidelines for the diagnosis and treatment of acute ischemic stroke. The antihypertensive strategies were in accordance with the 2010 Chinese Guidelines for Prevention and Treatment of Hypertension (13, 14). During the first 24 h of hospitalization, SBP and DBP were controlled to between 140 and 159 mmHg, and 90 and 99 mmHg, respectively. Patients with SBP ≥ 180 mmHg and DBP ≥ 120 mmHg were given nitroglycerine or sodium nitroprusside intravenous pump. The rate of blood pressure reduction was controlled at ≤5 mmHg/h by adjusting the dose of the medication. For patients with SBPs of 160–180 mmHg and/or DBPs of 100–120 mmHg, single or combined antihypertensive drugs were administered. For patients with SBP < 160 mmHg and/or DBP < 100 mmHg at admission, no antihypertensive drugs were given. After the first 24 h of hospitalization, patients with SBP ≥ 140 mmHg and DBP ≥ 90 mmHg were given reasonable antihypertensive drugs.

Supine BP was measured by trained nurses using a standard mercury sphygmomanometer on the non-paralyzed arm on admission and every 4 h on days 1–7. In the stroke unit, BP was measured using a non-invasive BP monitoring system (Philips SureSigns VM6 monitor; Royal Dutch Philips Electronics Ltd., Amsterdam, Netherlands). Midterm BPV was evaluated by calculating the SD and coefficient of variation (CV, 100 × SD/mean) of SBP and DBP during the 7 days after stroke onset (15).

Clinical Assessment

Ischemic stroke was defined as stroke identified by radiographic diagnosis (CT or MRI) and clinical diagnosis (16). The acute phase of ischemic stroke was defined as the 7 days following symptom onset (17). The infarct volume on CT/MRI (diffusion-weighted imaging/fluid attenuated inversion recovery) images was calculated using the Pullicino equation (net infarct volume = $L \times W \times H/2$; L, W, and H refer to the length, width, and height of the infarct lesion, respectively) (12). Thrombolytic therapy was defined as intravenous administration of recombinant tissue-type plasminogen activator (rt-PA) within 4.5 h of symptom onset or catheter-directed thrombolysis using rt-PA within 12 h of symptom onset.

Judgment of Outcomes and Follow-up

All participants were followed up 14 days, 3 months, 6 months, and 12 months after onset by trained neurologists. In this study, cognitive function was assessed using the MoCA. Patients with MoCA scores ≤25 and education levels <12 years or those with MoCA scores ≤26 and education levels >12 years were considered cognitively impaired (18). A study by Nasreddine and his colleagues demonstrated that the MoCA has a sensitivity of 90% and a specificity of 87% when a cutoff score of 26 is used (19). It is also reported that the MoCA is an effective and brief tool for detecting cognitive impairment in the elderly (20) and is more in line with the criteria for mild cognitive impairment than the Mini-Mental State Examination in populations older than 60 years (21).

At the 1-year follow-up, 62 patients had died and 124 patients were lost (Figure S1 in Supplementary Material). The patient deaths were due to pulmonary infection, recurrence of cerebral infarction, cerebral hemorrhage, myocardial infarction, gastrointestinal bleeding, liver and kidney failure, or other complications. Loss to follow-up was due to the patients not agreeing to repeat the MoCA, or loss of contact due to changes in residence. Six-hundred ten patients were left at the 12-month follow-up.

Sample Size Estimation

According to the sample size calculation formula for cohort studies:

$$n = \frac{(u_{\alpha/2}\sqrt{2pq} + u_{\beta}\sqrt{p_0q_0 + p_1q_1})^2}{(p_1 - p_0)^2}$$

in which p_0 is the estimated prevalence of cognitive impairment, p_1 is the estimated prevalence of PSCI, $q_0 = 1 - p_0$, $q_1 = 1 - p_1$, $p = (p_0 + p_1)/2$, $q = 1 - p$. u_α and u_β are the significance testing statistic, $\alpha = 0.05$, $\beta = 0.10$. The calculated sample size required for the study was 115, based on those estimations that the prevalence of cognitive impairment and PSCI were 12.7 and 30% (22, 23).

Statistical Analysis

Normally distributed continuous variables are presented as means ± SDs and were compared using Student's *t*-tests. Not normally distributed variables were presented as median (interquartile range) and were compared between groups using Mann–Whitney *U* test. Categorical variables are expressed as frequency and percentage and were compared using χ^2 tests. To evaluate the association between midterm BPV and cognitive function, patients were divided into quintiles (Q1–Q5) according to the CVs of SBP and DBP during the 7 days after stroke onset. The odds ratios (ORs) and 95% confidence intervals (CIs) were calculated by logistic regression and the following confounders was adjusted age, gender, education degree (less than 12 years), hypertension, SBP and DBP on admission, CIV, location of infarction (cortex, cortex-subcortical, subcortical, brain stem, and cerebellum), HAMD, and thrombolytic therapy. *p* Values <0.05 were considered statistically significant. Data were analyzed using SPSS.v19.0.1 software package.

RESULTS

Clinical Characteristics

The clinical characteristics of the 708 patients are presented according to the presence of cognitive impairment 3 months after stroke onset, the patients who had died and those lost to follow-up are excluded from the data (**Table 1**). The average age of these patients was 63.1 ± 10.0. Three-hundred eighty-three of the patients (54.1%) were men and 561 (79.2%) had less than 12 years of education. Compared to patients with no cognitive impairment, those with cognitive impairment were more likely to be older and have lower education levels and higher blood pressure on admission. They were also more likely to have a history of hypertension and lower NIHSS scores and to have received thrombolysis (**Table 1**). Patients with cognitive impairment also had higher CVs of blood pressure, cortical and subcortical infarction, large artery atherosclerosis, and small-artery occlusion, as classified by the guidelines of Trial of Org 10172 in Acute Stroke Treatment (TOAST) (Table S1 in Supplementary Material).

MoCA Score and Incidence of PSCI

The incidence of PSCI began to rise at 14 days after onset (31.6%) and peaked 3 months after the stroke (72.6%). Six months after stroke onset, the incidence of PSCI began to decrease (66.5%). It reached the baseline level 12 months after the stroke (34.7%) ($p < 0.05$). A reciprocal trend for MoCA scores is shown in **Figure 1**.

Cognitive Impairment and BPV

Simple comparisons between patients with no cognitive impairment and those with cognitive impairment indicated that the two groups had differences in age, education level (more vs. less than 12 years), hypertension, systolic and DBP at admission, TOAST classification, location of infarction, NIHSS score at admission, and the use of thrombolysis (all $p < 0.05$) (**Table 1**; Table S1 in Supplementary Material). Logistic analysis indicated that the CV of SBP had a significant association with PSCI, and that this relationship still existed after multi-parameter adjustments. When compared to patients in Q1, the adjusted ORs and 95% CIs of those in Q2-Q5 were 2.28 (1.18, 4.39), 2.33 (1.18, 4.62), 2.69 (1.31, 5.53), and 4.76 (1.95, 11.67) (**Table 2**). The risk factors for PSCI are shown in Table S2 in Supplementary Material. Men were more likely to have cognitive impairment than women (OR = 1.08, 95% CI = 1.06, 1.10), and lower education levels (less than 12 years) (OR = 7.72, 95% CI = 4.73, 12.61). These factors are both associated with an increased likelihood of cognitive impairment. Hypertension (OR = 2.07, 95% CI = 1.15, 3.72) and higher NIHSS scores at admission (OR = 1.33, 95% CI = 1.24, 1.44) were also more likely to increase the incidence of PSCI (Table S2 in Supplementary Material).

MoCA Score in Each Cognitive Domain 3 Months after Stroke Onset and CV during the 7 days after Stroke Onset

Table 3 shows the relationship between MoCA scores in each cognitive domain 3 months after stroke onset and the CV of SBP

TABLE 1 | Comparison of baseline characteristics between patients with and without cognitive impairment 3 months after onset.

Variable	Total (n = 708)	No cognitive impairment (n = 198)	Cognitive impairment (n = 510)	t value, U value χ^2	p-Value
Age (mean ± SD, years)	63.1 ± 10.0	58 ± 11.6	65.1 ± 8.5	−8.972	<0.001
Males (n, %)	383 (54.1)	115 (58.1)	268 (52.6)	1.758	0.185
Body mass index (mean ± SD, kg/m^2)	25.7 ± 2.8	25.6 ± 2.9	25.8 ± 2.8	−0.740	0.460
Less than 12 years of education (n, %)	561 (79.2)	115 (58.1)	446 (87.5)	74.783	<0.001
Hypertension (n, %)	624 (88.1)	160 (80.8)	464 (91.0)	14.114	<0.001
Hyperlipidemia (n, %)	397 (56.1)	112 (56.6)	285 (55.9)	0.027	0.869
Diabetes mellitus (n, %)	161 (22.7)	47 (23.7)	114 (22.4)	0.156	0.693
Coronary heart disease (n, %)	96 (13.6)	26 (13.1)	70 (13.7)	0.043	0.836
Atrial fibrillation (n, %)	139 (19.6)	46 (23.2)	93 (18.2)	2.257	0.133
History of TIA (n, %)	114 (16.1)	32 (16.2)	82 (16.1)	0.001	0.978
Current smoking (n, %)	211 (29.8)	63 (31.8)	148 (29.0)	0.534	0.465
Current drinking (n, %)	152 (21.5)	40 (20.2)	112 (22.0)	0.262	0.609
Systolic blood pressure (mean ± SD, mmHg)	168 ± 25.0	165 ± 24.8	169.1 ± 25.0	−2.002	0.046
Diastolic blood pressure (mean ± SD, mmHg)	107.9 ± 16.4	105.7 ± 16.5	108.7 ± 16.3	−2.148	0.032
Homocysteine (mean ± SD, μmol/l)	14.1 ± 1.7	14 ± 1.7	14.2 ± 1.7	−1.459	0.145
eGFR (mean ± SD, ml/min/1.73 m^2)	95.6 ± 10.5	96.6 ± 10.6	95.2 ± 10.4	1.574	0.116
National Institutes of Health Stroke Scale on admission (median, interquartile range)	11.0 (4.0)	9.0 (3.0)	12.0 (4.0)	28,736.5	<0.001
Modified Rankin Scale on admission (median, interquartile range)	3.0 (0)	3.0 (0)	3.0 (0)	48,476.5	0.301
HAMD (mean ± SD, points)	3.5 ± 2.1	3.7 ± 2.1	3.4 ± 2.0	1.892	0.059
CIV (mean ± SD, cm^3)	10.1 ± 2.1	10.1 ± 2.1	10.1 ± 2.1	0.273	0.785
Thrombolysis (n, %)	51 (7.2)	23 (11.6)	28 (5.5)	8.007	0.005

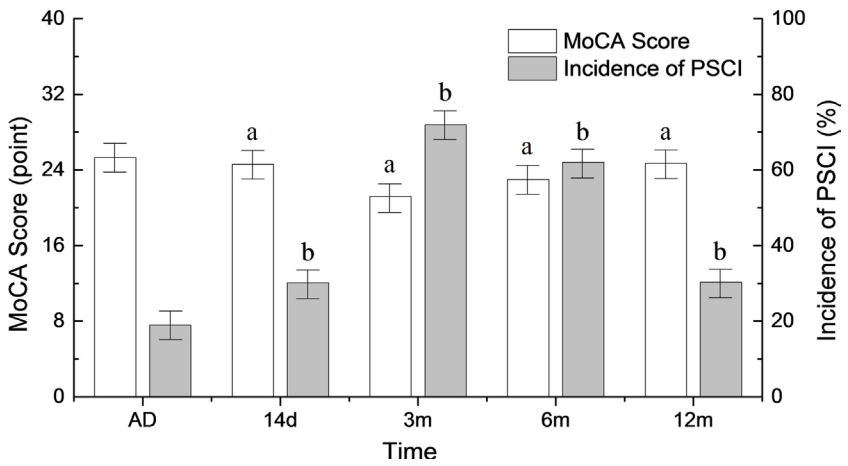

FIGURE 1 | Changes in the incidence of poststroke cognitive impairment (PSCI) and MoCA scores during the follow-up period. AD, at admission. [a]$p < 0.05$ compared to MoCA score at admission. [b]$p < 0.05$ compared to PSCI at admission.

during the 7 days after stroke onset. Score in the visuoperceptual/executive and delayed recall domains were significantly different between patients with different SBPs. In addition, MoCA scores had an inverse relationship with the CV of SBP (all $p < 0.05$). Patients in Q4 and Q5 had lower scores in the naming domain than those in Q2 and Q3 ($p < 0.05$). Score on the abstraction domain were lower in patients in Q2 than in those in Q1 ($p < 0.05$). Patients in Q5 had lower scores in the orientation domain than those in Q1and Q2 ($p < 0.05$). Patients in Q4 had lower scores in the language domain than those in Q5 ($p < 0.05$). There were no significant differences in the cognitive domains of attention between the groups (all $p > 0.05$) (**Table 3**).

Cognitive Impairment and Site of Cerebral Infarction

After adjusting for covariables, Cortical–subcortical and subcortical infarctions were more likely to lead to PSCI than cortical infarctions [ORs and 95% CIs were 2.03 (1.12, 3.65) and 2.86 (1.54, 5.33), respectively] (**Figure 2**).

DISCUSSION

Our findings suggest that high midterm BPV within 7 days of stroke onset is independently associated with an increased

TABLE 2 | Logistic regression analyses of CV during the 7 days following onset and cognitive impairment 3 months after onset.

Variables	E/R, *n* (%)	Unadjusted		Model I		Model II		Model III	
		OR (95% CI)	*p*-Value	OR (95% CI)	*p*-Value	OR (95% CI)	*p*-Value	OR (95% CI)	*p*-Value
CV of systolic blood pressure									
Q1 (4.5–7.7)	85/143 (59.4)	Ref	–	Ref	–	Ref	–	Ref	–
Q2 (7.8–8.1)	99/136 (72.8)	1.90 (1.11, 3.25)	0.019	1.95 (1.10, 3.43)	0.021	1.87 (1.01, 3.47)	0.047	2.28 (1.18, 4.39)	0.014
Q3 (8.2–8.5)	106/142 (74.6)	2.21 (1.26, 3.89)	0.006	2.23 (1.22, 4.08)	0.009	2.12 (1.11, 4.04)	0.022	2.33 (1.18, 4.62)	0.015
Q4 (8.6–9.2)	107/143 (74.8)	2.39 (1.33, 4.27)	0.003	2.40 (1.29, 4.48)	0.006	2.44 (1.24, 4.8)	0.010	2.69 (1.31, 5.53)	0.007
Q5 (9.3–15.1)	113/144 (78.5)	3.31 (1.61, 6.84)	0.001	3.29 (1.53, 7.08)	0.002	4.08 (1.75, 9.5)	0.001	4.76 (1.95, 11.67)	0.001
CV of DBP									
Q1 (3.7–6.9)	90/136 (66.2)	Ref	–	Ref	–	Ref	–	Ref	–
Q2 (7.0–7.5)	100/142 (70.4)	0.89 (0.51, 1.54)	0.675	0.83 (0.46, 1.49)	0.534	0.67 (0.35, 1.28)	0.225	0.57 (0.28, 1.15)	0.116
Q3 (7.5–8.2)	114/146 (78.1)	1.24 (0.69, 2.21)	0.474	1.14 (0.61, 2.10)	0.685	0.86 (0.43, 1.69)	0.655	0.98 (0.48, 2.01)	0.954
Q4 (8.2–8.8)	97/140 (69.3)	0.66 (0.36, 1.21)	0.178	0.60 (0.31, 1.13)	0.113	0.41 (0.2, 0.85)	0.017	0.31 (0.14, 0.68)	0.004
Q5 (8.8–14.6)	109/144 (75.7)	0.72 (0.35, 1.48)	0.369	0.63 (0.29, 1.36)	0.244	0.33 (0.13, 0.86)	0.024	0.27 (0.1, 0.74)	0.011

Model I was adjusted for age and gender; Model II was based Model I plus education degree (less than 12 years), hypertension, SBP and DBP on admission, CIV and location of infarction (cortex, cortex–subcortical, subcortical, brain stem, and cerebellum); Model III was Model II plus National Institutes of Health Stroke Scale and thrombolytic therapy. E/R, event/risk.

TABLE 3 | The relationship of MoCA score in each cognitive domain at 3 months and CV of systolic blood pressure within 7 days of stroke onset.

	Q1 (*n* = 143)	Q2 (*n* = 136)	Q3 (*n* = 142)	Q4 (*n* = 143)	Q5 (*n* = 144)	*F* value	*p*-Value
Total scores	23.6 ± 3.4	22.1 ± 3.3	21.1 ± 3.6	20.3 ± 3.9	19.0 ± 3.9	32.874	<0.001
Visuoperceptual/executive	3.3 ± 1.3	2.7 ± 1.4	2.1 ± 1.5	1.5 ± 1.5	1.0 ± 1.3	64.339	<0.001
Naming	2.5 ± 0.7	2.4 ± 0.9	2.4 ± 1	2.6 ± 0.8	2.7 ± 0.6	3.333	0.010
Abstraction	1.8 ± 0.4	1.7 ± 0.6	1.7 ± 0.6	1.7 ± 0.5	1.8 ± 0.4	1.418	0.226
Orientation	5.1 ± 1.3	5 ± 1.3	5.2 ± 1.3	5.2 ± 1.1	5.4 ± 1.1	2.037	0.087
Attention	4.8 ± 1.5	4.7 ± 1.6	4.7 ± 1.6	4.7 ± 1.5	4.5 ± 1.6	0.461	0.764
Language	2.5 ± 0.8	2.5 ± 0.9	2.5 ± 0.9	2.6 ± 0.9	2.4 ± 0.8	1.211	0.305
Delayed recall	3.5 ± 1.6	3.1 ± 1.6	2.5 ± 1.6	1.9 ± 1.7	1.2 ± 1.7	43.874	<0.001

Values are presented as mean ± SD.

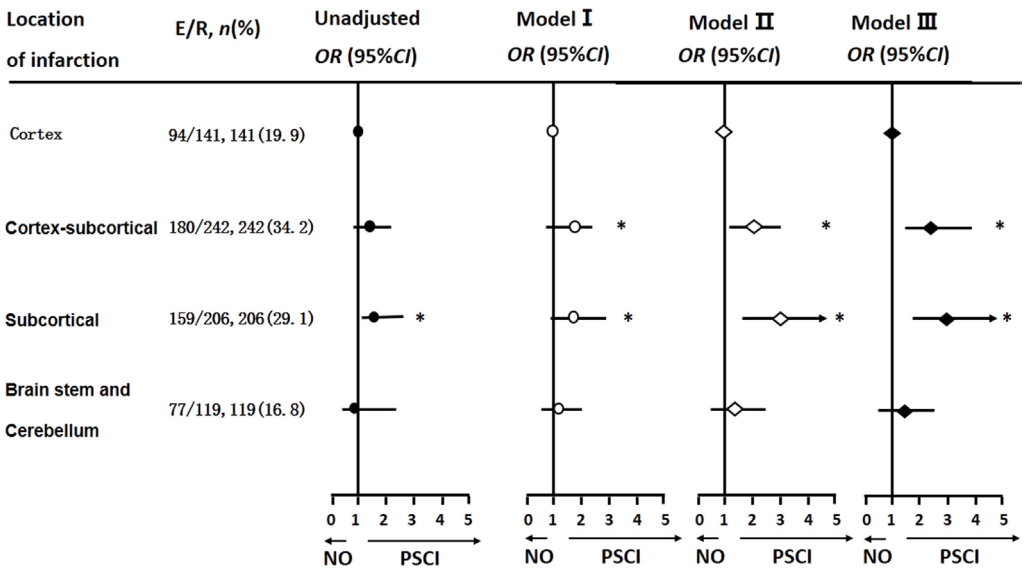

FIGURE 2 | Logistic regression analyses of location of infarction and cognitive impairment 3 months after stroke onset. The multi-parameter model used is the same as that used in **Table 2**.

risk for PSCI 3 months after the stroke. Our findings also indicate that male sex, low education levels, high NIHSS scores, cortical–subcortical infarction, and subcortical infarction are risk factor for PSCI. In contrast, cardioembolism of TOAST classification has no effects on cognitive impairment after stroke.

Blood pressure variability is a complex phenomenon that includes short-term fluctuations occurring within a 24-h period, midterm fluctuations over different days, and blood pressure changes over weeks, months, and even years (24). These variations in BP are thought to be the result of complex interactions between extrinsic environmental and behavioral factors and intrinsic cardiovascular regulatory mechanisms (central neural, reflexive neural, and humoral influences) that are not yet completely understood (15). Most importantly, high short-term BPV is a predictor of target organ damage and future cardiovascular events (25, 26). High midterm SBP variability in daytime was a predictor of cardiovascular and all-cause mortality (27). In addition, a recent study has reported that higher midterm BPV was associated with progression of brain white matter lesions and lower cognitive function (28). The authors of the above study suggest that higher BPV is a risk factor for lower hippocampal volume and cerebral mircobleeds independent of average systolic and DBPs. In some analyses, therefore, the predictive value of BPV is even greater than that of average BP during treatment.

A recently study reported an increase in the incidence of stroke in China (29), which may result in an increased prevalence of PSCI. In our study, the incidence of PSCI reached its peak 3 months after ischemic stroke onset. Changes in the incidence of PSCI have an inverse relationship with MoCA scores. Consistent with our findings, the incidence of cognitive impairment 3 months after ischemic stroke was reported to be 71% in a study of 409 middle age and elderly patients with cerebral infarction (10). However, in the hospital-based cohort studies of Ihle-Hansen et al. (30) and Kandiah et al. (31), the incidence of PSCI was 37.5% 1 year after stroke and 37.32% 6 months after stroke. The broad range of reported PSCI incidence may be mainly attributed to differences in race, age, education level, location of stroke, and evaluation methods. We found that the prevalence of PSCI reaches its peak 3 months after stroke and decreases thereafter. It is, however, still unclear whether this trend is a consequence of transient cerebral function disorders and the recovery of stress injury.

The relationship between variability in blood pressure during the acute phase of ischemic stroke and lower cognitive performance 3 months after stroke onset was assessed using multiple parameter logistic regression analysis in our study. Independently of the confounding factors, SBP variability, but not DBP variability, was found to significantly predict the occurrence of cognitive decline. Consistent with our results, a recent epidemiological study (32) reported that day-to-day variability in SBP is significantly related to cognitive impairment (OR, 1.51; $p = 0.02$). In a study of 353 people, McDonald et al. (33) found that daytime variability in blood pressure is independently associated with greater decreases in total Cambridge Cognitive Examination and Mini-Mental State Examination scores after 5 years of fellow-up. Qin et al. (34) have suggested that higher visit-to-visit variability in systolic BP, but not mean systolic BP, is a predictor of cognitive decline. This stronger relationship can be explained by the fact that more information is provided by measuring the variability of BP than mean BP (35). In addition, the white-coat effect can be eliminated (36) and more target organ damage can be revealed than when using conventional BP measurements (37). However, Kilander et al. (38) suggested 24-h SBP was not associated with cognition. Other study of community-living adults also found no association between SBP and cognitive function (39). It may be explain from it, community-living adults were better able to automatically adjust the effect of systemic SBP on cerebral blood perfusion, which keep them with better baseline perfusion. Some studies have found higher DBP variability was related to poorer cognitive function (40), whereas in other studies no associated between variability in DBP and cognitive function was found (41). However, in our study, higher variability in DBP did not seem to be protective for cognitive decline.

Nevertheless, the potential mechanism for the relationship between high BPV and cognitive impairment is still unclear. Recently, a study demonstrated that higher variability in BP, especially in SBP, can predict the progress of arteriosclerosis (42), lead to subcortical lesions (43), and contribute to the pathogenesis of cerebral vascular disease (44). All of the above factors may have negative impacts on cognitive function. Most importantly, hypertension and further decreases in blood pressure may reduce the coupling efficiency of the neurovasculature and impair dynamic cerebral autoregulation, which would then result in cerebral hypoperfusion. This may then lead to neurological impairment (45) and lead to progressive neurodegeneration (46). Considering energy requirements and blood supply, result in a neuronal energy crisis and cerebral hypometabolism, which may in turn lead to Alzheimer's disease-related pathology (47).

Sub-analysis of the MoCA scale scores indicated that scores in the visuoperceptual and executive functions domains, as well as those for delayed recall, were decreased in individuals with high BPV. This suggests that visuoperceptual abilities, executive function, and delayed recall are more vulnerable than other domains of cognition. Consistent with our findings, a recent study showed that basal ganglionic lacunar infarcts and cerebral small vessel injuries are related to dysfunctions in delayed memory (48, 49). In addition, periventricular white matter hyperintensities have significant associations with executive function deficits (50). Using the same cohort as that used here, we have previously reported that patients with large artery atherosclerosis based on TOAST classification have lower scores in the visuoperceptual ability and executive function, and delayed recall and attention domains after correction for covariables (51). The potential mechanisms underlying poststroke cognitive decline are still unclear, although the cerebral cortex and hippocampus are sensitive to cerebral ischemia and anoxia (52), which may be a potential mechanism for impairment of visuoperceptual abilities, executive function, and delayed recall after stroke.

We also observed that cortical–subcortical and subcortical infarctions are more likely to lead to PSCI. Our results are in agreement with those of Hilal et al., who, in a study of 550 patients, reported that subcortical gray matter atrophy, such as that indicated by lacunes and white matter lesions, is not only observed in dementia but is also found in the preclinical stages of cognitive impairment (53). Rocque et al. reported that patients with large carotid plaques are more likely to have

cognitive impairment (54). Pathophysiologically, multi-vessel, extracranial atherosclerotic disease may cause chronic diffuse brain hypoperfusion, which may be associated with cognitive impairment (55).

Our study has some limitations. First, only ages between 40 and 75 years were included in our study and other inclusion and exclusion criteria operated will influence BP variability and could weaken the external validity of results. Second, the use of different antihypertensive agents and other medications may have affected the variability in blood pressure and the relationship between BPV and poststroke cognition. What's more, the study also had selection bias, as only hospitalized patients were enrolled, although this was inevitable. Another limitation of this study is that obstructive sleep apnea, which is associated with both BPV and cognitive dysfunction, could not be measured.

CONCLUSION

Higher midterm SBP variability during the acute stage of cerebral infarction was found to be associated prospectively and independently with increased risk of PSCI, especially in the domains of executive function, naming, and delayed recall. This highlights the need for neurologists to pay more attention to the variability of blood pressure in patients with acute ischemic stroke. Population-based prospective studies are required to confirm our conclusions.

ETHICS STATEMENT

Study on optimizing control strategy of blood pressure for the prevention of stroke in rural community. Ethical Review and Approval Documents. Our hospital is to carry out "Study on optimizing control strategy of blood pressure for the prevention of stroke in rural community," the ethics committee of our hospital has a review of relative medical ethics issue of the project.

AUTHOR CONTRIBUTIONS

Conceptualization: SG, NL, PM, NJ, and MH. Data curation: SG and MH. Formal analysis: SG and MH. Investigation: YS, YX, BX, ZL, XN, YZ, CX, and XZ. Methodology: SG, NL, PM, and MH. Project administration: SG, NL, PM, NJ, and MH. Resources: SG, NL, PM, NJ, YS, YX, GZ, XH, ZC, BW, BX, ZL, XN, YZ, CX, and XZ. Software: SG and NL. Supervision: SG and MH. Validation: GS, NL, PM, NJ, MH, YS, YX, GZ, XH, and ZC. Visualization: SG and NL. Writing—original draft: SG. Writing—review and editing: SG and MH.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at http://journal.frontiersin.org/article/10.3389/fneur.2017.00365/full#supplementary-material.

SUPPORTING INFORMATION

Shan Geng et al., study investigators. Midterm BPV Is Associated with poststroke cognitive impairment.

Data Definition

Body mass index was estimated from the equation: height $(m)^2$/weight (kg). Hypertension was defined as systolic blood pressure of ≥140 mmHg and/or diastolic blood pressure of ≥90 mmHg or taking antihypertensive drugs. Low density lipoprotein cholesterol of ≥4.14 mmol/l, and/or high-density lipoprotein cholesterol of <1.04 mmol/l, triglyceride of ≥2.26 mmol/l or taking lipid-lowering drugs were defined as dyslipidemia. Diabetes mellitus was defined as fasting plasma glucose of ≥7.0 mmol/l, HbA1c of ≥6.5%, or treatment with oral antidiabetic drugs or insulin. Diagnosis of atrial fibrillation was confirmed by electrocardiography. Current smoking was defined as smoking cigarettes continuously or accumulates for 6 months and smoking in 30 days before the survey. Current drinking was determined as drinking more than 20 g each time and more than once a week.

FIGURE S1 | The flow chart of the study.

FIGURE S2 | Curves of cumulative survival.

TABLE S1 | Comparison of baseline characteristics of patients with and without cognitive impairment 3 months after onset.

TABLE S2 | Logistic regression analyses of CV during the 7 days following onset and cognitive impairment 3 months after onset. Model I was adjusted for age and gender; Model II was based Model I plus education degree (less than 12 years), hypertension, systolic blood pressure and DBP on admission, CIV and location of infarction (cortex, cortex–subcortical, subcortical, brain stem, and cerebellum); Model III was Model II plus National Institutes of Health Stroke Scale and thrombolytic therapy. E/R, event/risk.

TABLE S3 | Comparison of baseline characteristics of patients with and without cognitive impairment 12 months after onset.

TABLE S4 | Logistic regression analyses of CV during the 7 days following onset and cognitive impairment 12 months after onset. Model I was adjusted for age and gender; Model II was based Model I plus education degree (less than 12 years), hypertension, systolic blood pressure and DBP on admission, CIV and location of infarction (cortex, cortex–subcortical, subcortical, brain stem, and cerebellum); Model III was Model II plus TOAST classification, TIA, NHISS, and modified Rankin Scale score. E/R, event/risk.

TABLE S5 | The relationship of the loss at different time points and CV of BP within 7 days of stroke onset.

DATASHEET S1 | Continued Table 1.

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REVIEW
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Factors Influencing Decision Making for Carotid Endarterectomy versus Stenting in the Very Elderly

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As the population ages worldwide, the number of elderly patients with carotid stenosis is also increasing. There have been many large clinical trials comparing carotid endarterectomy (CAE) versus stenting, but the inclusion criteria (i.e., symptomatic or asymptomatic), stenting methods (i.e., protection device), and primary end point (i.e., the definition of myocardial infarction and follow-up period) were different between trials. Therefore, the interpretation of those results is difficult and requires attention. When it comes to age, the patients older than 80 years were excluded or stratified to a high risk group in previous landmark trials. However, a recent guideline recommended that endarterectomy may be associated with lower stroke risk compared with carotid artery stenting in patients older than 70 years with symptomatic carotid disease. The annual risk of stroke in individuals with asymptomatic carotid stenosis is about 1–3% but the risk is about 4–12% with symptomatic stenosis without carotid intervention. Although the outcome of CAE is better than that of carotid stenting in patients older than 70 years, the perioperative risk is higher in older patients. Therefore, it is important to classify high risk patients and consider underlying disability and life expectancy of very elderly patients before deciding whether to undergo a carotid intervention. In addition, we should also consider that the stroke rate with intensive medical treatment is unknown and is currently being investigated in randomized controlled trials. Intensive medical treatment includes high intensity statins, diabetes and blood pressure control, and aggressive antiplatelet treatment. The aim of this review is to report the factors that may be responsible for the variability in the treatment of carotid stenosis, particularly in the elderly population. This will allow the readers to integrate the current available evidence to individualize the treatment of carotid stenosis in this challenging population.

Keywords: carotid stenosis, carotid endarterectomy, carotid stenting, stroke, elderly

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INTRODUCTION

Atherosclerosis is a chronic inflammatory disease of the arterial wall that slowly progresses pathologically causing arterial stenosis, resulting in cerebrovascular or coronary artery diseases (1, 2). It usually arises at the bifurcation of blood vessels having a disruption of laminar flow, and the carotid bulb or sinus is the region where most atherosclerotic plaques are found. Stroke caused by carotid stenosis is more severe in neurological deficits and has a high risk of recurrence (3).

The basic treatment of carotid atherosclerosis is management of risk factors such as hypertension, dyslipidemia, diabetes, and smoking with lifestyle modification, and antiplatelet medications. However, current guidelines recommend carotid revascularization procedures such as carotid endarterectomy (CEA) or carotid artery stenting (CAS) depending on the presence of symptoms and the degree of stenosis (4, 5). Various other conditions such as age and patient factors, features of atherosclerotic lesions, anatomical characteristics of cerebral and extracerebral vessels, and medical comorbidity should also be considered. In the past, either because of the concern of excessive risk or decreased post-procedure life expectancy, elderly patients (usually >80 years) have been excluded from randomized trials (6–10). However, recent trials showed more favorable outcomes after CEA versus CAS in elderly patients, so the guideline changed the recommendation for symptomatic older patients (i.e., older than ≈70 years) to undergo CEA rather than CAS (4, 11–13).

In western countries, there has been a remarkable increase in the population of those over 80 years. In non-western countries, one study predicts there is more than a 50% probability that by 2030, national female life expectancy will break the 90 year barrier in South Korea, a level that was deemed unattainable by some at the turn of the twenty-first century (14). Stroke is the fifth leading cause of death in the United States and is a major cause of serious disability for the elderly (15). Extracranial carotid artery disease is responsible for up to 20% of these strokes and accounts for a higher proportion in elderly patients (16, 17). The numbers of elderly patients with carotid stenosis will increase exponentially, and the results of medical treatment and CAS are getting better. Therefore, the selection of treatment method for carotid stenosis in elderly patients will be more complex.

In this review article, our aim is to describe the selection criteria for the appropriate treatment methods in elderly patients and the considering factors that affect it, based on current literature.

SHORT-TERM AND LONG-TERM OUTCOMES AFTER CAROTID REVASCULARIZATION IN SYMPTOMATIC AND ASYMPTOMATIC PATIENTS

Treatment of Asymptomatic Carotid Stenosis

Asymptomatic carotid artery stenosis is a very important health issue, as out of the 135,701 carotid revascularizations performed in the US in 2005, 122,986 (92%) were for asymptomatic carotid artery stenosis (18). Since the results of large clinical trials comparing CEA with drug therapy in the treatment of asymptomatic carotid stenosis was published in 1990s, CAS, optimal medical treatment, and variations of surgical approaches to CEA have been also developed (8, 19). In the Asymptomatic Carotid Atherosclerosis Stenosis (ACAS) and Asymptomatic Carotid Surgery (ACST) trials, the 5-year risk of stroke or procedural morbidity was estimated to be 6.5% for CEA patients and 11.0% for patients treated medically among asymptomatic patients with carotid artery stenosis of greater than 60% (8, 20). The meta-analysis of the Veterans Administration Cooperative Study (VA), ACAS, and ACST trials shows that in patients with asymptomatic carotid stenosis, despite about a 3% perioperative stroke or death rate, CEA reduces the risk of ipsilateral stroke and any stroke, by approximately 30% over 3 years (21). In the case of asymptomatic stenosis, CEA is beneficial if the incidence of surgical complication is less than 3% in patients with stenosis of 60% or more, but some researchers claim that the complication rate should be lower than 3% because of improved drug treatment results. In recent studies, the annual rate of stroke in medically treated patients with an asymptomatic carotid artery stenosis has fallen to ≤1% (22, 23).

The National Institute of Neurological disorders and Stroke-sponsored Carotid Revascularization Endarterectomy versus Stenting Trial (CREST) included symptomatic patients only at baseline, but expanded inclusion criteria for asymptomatic patients (final proportion of asymptomatic patients was 47.2% of the total) (12). In the analysis among patients with asymptomatic carotid stenosis, there was no difference in the primary outcome between CAS and CEA [5.6 versus 4.9%; hazard ratio (HR) 1.17, 95% confidence interval (CI) 0.69–1.98, $p = 0.56$]. All stroke cases within 30 days and the occurrence of ipsilateral stroke between 30 days and 4 years were 4.5% in CAS group and 2.7% in CEA group so there was no statistical difference (HR 1.86; 95% CI 0.95–3.66, $p = 0.07$). The incidence of ipsilateral stroke between 30 days and 4 years (i.e., durability of the intervention) was similar, with 2.0% in the CAS group and 2.4% in the CEA group. The durability was favorable in long-term follow-up for both groups (12). The Asymptomatic Carotid Trial (ACT)-1, which compared the outcomes of CEA versus CAS in patients with asymptomatic severe carotid artery stenosis who were at standard risk for surgical complications, revealed that CAS was non-inferior to CEA with regard to the primary composite end point (3.8 and 3.4%, respectively; $p = 0.01$ for non-inferiority), but this study excluded patients who were 80 years of age or older (24).

ACST-1 was a 10-year follow-up study that investigated the long-term prognosis after the ACST trial (25). The incidence of stroke or death within 30 days of CEA was 3.0% (95% CI 2.4–3.9) in all patients undergoing CEA. Excluding perioperative events and non-stroke mortality, stroke risks (immediate versus deferred CEA) were 4.1 versus 10.0% at 5 years (gain 5.9%, 95% CI 4.0–7.8) and 10.8 versus 16.9% at 10 years (gain 6.1%, 2.7–9.4); ratio of stroke incidence rates 0.54, 95% CI 0.43–0.68, $p < 0.0001$. Combining perioperative events and strokes, net risks were 6.9 versus 10.9% at 5 years (gain 4.1%, 2.0–6.2) and 13.4 versus 17.9% at 10 years (gain 4.6%, 1.2–7.9). In spite of stroke or death associated with surgery, the surgical outcome was excellent. In addition, more than half of the patients with stroke (166/287) died of or were disabled by stroke, and the proportional reduction in disabling or fatal stroke seemed to be similar to that for any stroke.

Treatment for Symptomatic Carotid Stenosis

In the North American Symptomatic Carotid Endarterectomy Trial (NASCET), CEA reduced the two-year risk of ipsilateral stroke from 26% in the medical arm to 9% in the surgical group,

yielding an absolute risk reduction of 17% (6). This result was similar to other randomized clinical trials comparing CEA with medical treatment such as the European Carotid Surgery Trial (ECST) and the Veterans Affairs Cooperative Study (VACS) (7, 26). Pooled analysis of the VACS, NASCET, and ECST found a 30-day stroke and death rate of 7.1% in the CEA arm in patients with transient ischemic attack (TIA) or stroke within 6 months, and CEA was highly beneficial in those with 70–99% stenosis (27). The role of CEA is less clear in the symptomatic patients with moderate stenosis (50–69%). In NASCET patients with a stenosis of 50–69%, the 5-year rate of any ipsilateral stroke was 15.7% in CEA arm compared with 22.2% in medical arm ($p = 0.045$).

Comparative studies between CEA and CAS such as the Stent-Protected Angioplasty of the Carotid Artery versus Endarterectomy (SPACE), the Endarterectomy Versus Angioplasty in patients with Symptomatic Severe carotid Stenosis trial (EVA-3S), and the International Carotid Stenting Study (ICSS) showed better periprocedural outcomes in CEA rather than CAS, especially in older patients (11, 13, 28, 29). Meta-analysis from these trials revealed any stroke or death occurred significantly more often in the CAS group (8.9%) than in the CEA group (5.8%) in the first 120 days after randomization [risk ratio 1.53 (95% CI 1.20–1.95), $p = 0.0006$] (11). Subgroup analysis from ICSS trial using MRI showed the presence of at least one new ischemic brain lesion on diffusion weighted imaging 1–3 days after treatment was more common in CAS group than CEA group (50 versus 17%; $p < 0.0001$) (30).

However, because CAS was potentially favorable in the Carotid And Vertebral Artery Transluminal Angioplasty Study (CAVATAS) and the Stenting and Angioplasty with Protection in Patients at High Risk of Endarterectomy (SAPPHIRE) trials, CREST was designed to compare the efficacy of CAS with that of CEA (31, 32). In this non-inferiority trial, 2,502 symptomatic and asymptomatic patients with carotid stenosis were enrolled and randomized to CAS or CEA. There was no significant difference in the composite primary outcome [30-day rate of stroke, death, and myocardial infarction (MI) and 4-year ipsilateral stroke] in patients treated with CAS versus CEA (7.2 versus 6.8%; HR for stenting, 1.1; 95% CI 0.81–1.51; $p = 0.51$). In symptomatic patients, the 4-year rate of the primary end point was 8.6% with CAS versus 8.4% with CEA (HR, 1.08; 95% CI 0.74–1.59; $p = 0.69$) (12, 33). Periprocedural rates of individual components of the end points differed between the CAS group and CEA group: for death (0.7 versus 0.3%, $p = 0.18$), for stroke (4.1 versus 2.3%, $p = 0.01$), for MI (1.1 versus 2.3%, $p = 0.03$), and for cranial nerve palsies (0.3 versus 4.7%; $p = 0.0001$).

In most studies evaluating long-term outcome after CEA versus CAS, there was no difference in major vascular outcomes between the treatment methods after the periprocedural period (34–39). In the SPACE trial, the rate of ipsilateral ischemic strokes up to 2 years including any periprocedural strokes or deaths after procedure was similar for CEA and CAS groups (9.5 and 8.8%; HR 1.10 (0.75–1.61); log rank $p = 0.62$). In addition, the rate of ipsilateral ischemic stroke within 31 days and 2 years was not different between CAS (2.2%) and CEA (1.9%) (35). In the 4-year follow-up of EVA-3S trial, the risk of ipsilateral stroke was low and similar in both treatment groups after the periprocedural period (37). In the ICSS trial, the cumulative 5-year risk of fatal or disabling stroke did not differ significantly between CAS and CEA groups (6.4 versus 6.5%; HR 1.06, 95% CI 0.72–1.57) (34). Over 10 years of follow-up in the CREST trial, there was no significant difference in the rate of the primary end point between CAS group (11.8%) and CEA group (9.9%) (HR 1.10; 95% CI 0.83–1.44) (38).

Overall, there have been more periprocedural vascular events in CAS compared with CEA, but there was no significant difference in long-term results of randomized controlled trials. It is possible that the inclusion of asymptomatic patients could have offset the risk of high periprocedural events from symptomatic patients in the trials that enrolled both symptomatic and asymptomatic patients. In addition, we should consider the possibility that the difference in treatment effect was diminished by death from other causes in patients with higher atherosclerotic burden and comorbidity at the long-term follow-up. However, long-term prognosis and complications were not different in studies that followed patients for more than 2 years. Therefore, CAS seems to have the similar effect to CEA in the long-term period. We summarized the main randomized clinical trials comparing CEA and CAS in **Tables 1** and **2**. We did not include the CAVATAS study because only 25 patients (10%) actually underwent CAS among the endovascular group ($n = 251$) (31).

In conclusion, CEA is recommended in patients with symptomatic carotid artery stenosis (>50%), especially in elderly patients when periprocedural complications are considered. CAS is indicated as an alternative to CEA for those who are asymptomatic, younger, and have higher operative risk. These trials have also shown that the efficacy of CAS was influenced by the patient's age, medication, and the experience of the interventionists, and was similar to that of CEA in long-term follow-up.

AGE ISSUES FOR SELECTING A CAROTID REVASCULARIZATION METHOD

The current guidelines, based on the results of previous clinical trials, emphasize that the presence of symptoms and the degree of stenosis are most important factors that impact the treatment of carotid stenosis (4, 5). Some review articles stated that patients aged 80 years or more are high risk for both CEA and CAS (**Table 3**) (40, 41). However, previous randomized clinical trials excluded patients over 80 years old, so the exact benefits and risks of CEA versus CAS in the very elderly are not well known. In subgroup analysis of NASCET and ECST, the risk of stroke and death in patients ≥75 years was higher in the medical treatment group than the CEA group and it suggested indirect favorable effects of CEA in the very elderly (42). In elderly patients, life expectancy is shorter than that of younger patients, so concerns about operative risk and vascular outcome are critical. However, patients in the medical arm had a higher risk of recurrent stroke, so the limitation of medical treatment used at the time of the trial also exists. Recent clinical trials comparing CEA with CAS included a substantial proportion of elderly patients. The rate of periprocedural and long-term vascular events was more prevalent in CAS group rather than

TABLE 1 | Major carotid revascularization trials comparing carotid endarterectomy with stenting.

Trial	Sample size, *n* (CEA/CAS)	Old age, *n* (%)	Symptomatic (%)	Protection device (%)	30-Day total stroke (%)	30-Day composite outcome (%)	Follow-up period (years)	Long-term outcome; all stroke (%)	Long-term outcome; periprocedural stroke or death plus ipsilateral stroke postprocedural ipsilateral stroke or (%)
SAPPHIRE (32, 39)	167/167	19.5[a]	29	100	3.1/3.6	9.8/4.8[f]	3	10.7/10.1	10.2/9.0[j]
SPACE (28, 35)	584/599	21.6[b]	100	27	6.2/7.5	6.5/7.7[g]	2	10.1/10.9	8.8/9.5
EVA-3S (29, 37)	259/261	36.3[c]	100	92	2.7/8.7	3.9/9.6[g]	4	7.3/12.8	5.3/10.9
ICSS (13, 34)	858/855	53.3[d]	100	72	4.1/7.7[e]	5.2/8.5[e]	5	9.4/15.2	7.2/11.8
CREST (12, 33, 38)	1,240/1,262	9.6[a]	53	96	2.3/4.1	2.3/4.4[g]	4	7.9/10.2	4.7/6.4
CREST-S	653/668		100		3.2/5.5	3.2/6.0[g]	4	6.4/7.6	6.4/8.0
CREST-A	587/594		0		1.4/2.5	1.4/2.5[g]	4	2.7/4.5	2.7/4.5
ACT-1 (24)	364/1,089	0	0	100	1.4/2.8	2.6/3.3	1	2.2/3.3[h]	3.3/3.8[j]

[a]*The cutoff age for old age group is more than 80 years old.*
[b]*The cutoff age for old age group is more than 75 years old.*
[c]*The cutoff age for old age group is 75 or more years old.*
[d]*The cutoff age for old age group is 70 or more years old.*
[e]*A composite of stroke, death, or myocardial infarction within 120 days.*
[f]*A composite of death, stroke, or myocardial infarction within 30 days.*
[g]*A composite of death or stroke within 30 days.*
[h]*A composite of all stroke within 30 days plus ipsilateral stroke within 31 days to 1 year.*
[i]*A composite of stroke or death at 30 days plus ipsilateral stroke or death from neurological causes within 31 days to 3 years.*
[j]*A composite of death, stroke, or myocardial infarction within 30 days plus ipsilateral stroke within 31 days to 1 year.*
SAPPHIRE, the Stenting and Angioplasty with Protection in Patients at High RIsk for Endarterectomy; SPACE, Stent-Supported Angioplasty of the Carotid Artery versus Endarterectomy; EVA-3S, Endarterectomy versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis; ICSS, International Carotid Stenting Study; CREST, the Carotid Revascularization Endarterectomy versus Stenting Trial; CREST-S, CREST symptomatic carotid stenosis group; CREST-A, CREST-asymptomatic carotid stenosis group; ACT-1, Asymptomatic Carotid Trial 1.

TABLE 2 | Primary end point and definition of myocardial infarction in major carotid revascularization trials.

Trial	Primary outcome	Definition of myocardial infarction for primary end point
SAPPHIRE (32)	A composite of death, stroke, or myocardial infarction within 30 days after the intervention or death or ipsilateral stroke between 31 days and 1 year	A CK level higher than two times the upper limit of normal with a positive MB fraction
SPACE (28)	Ipsilateral ischemic stroke or death from time of randomization to 30 days after the procedure	
EVA-3S (29)	The incidence of any stroke or death within 30 days after treatment	
ICSS (13)	The 3-year rate of fatal or disabling stroke in any territory	
CREST (12)	Stroke, myocardial infarction, or death from any cause during the periprocedural period or any ipsilateral stroke within 4 years after randomization	A CK-MB or troponin level that was twice the upper limit of the normal range or higher according to the center's laboratory, in addition to either chest pain or symptoms consistent with ischemia or ECG evidence of ischemia, including new ST segment depression or elevation of more than 1 mm in two or more contiguous leads according to the core laboratory
ACT-1 (24)	The composite of death, stroke (ipsilateral or contralateral, major or minor), or myocardial infarction during the 30 days after the procedure or ipsilateral stroke within 1 year	Q-wave myocardial infarction—the development of new pathological Q waves in two or more contiguous leads with post-procedure CK or CK-MB levels elevated above normal Non Q-wave myocardial infarction—elevation of CK levels to greater than two times the upper limit of normal in the presence of elevated CK-MB and in the absence of new pathological Q waves. (WHO definition)

SAPPHIRE, the Stenting and Angioplasty with Protection in Patients at High RIsk for Endarterectomy; SPACE, Stent-Supported Angioplasty of the Carotid Artery versus Endarterectomy; EVA-3S, Endarterectomy versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis; ICSS, International Carotid Stenting Study; CREST, the Carotid Revascularization Endarterectomy versus Stenting Trial; ACT-1, Asymptomatic Carotid Trial; CK, creatine kinase; ECG, electrocardiography; WHO, World Health Organization.

CEA group, likely because of the vascular tortuosity and severe vascular calcification in the very elderly patients (**Table 1**) (43).

The age definition of "elderly" was different between studies. In meta-analysis, comparing early outcomes of CEA or CAS in old and young age groups was published in 2013 (44). Among 54 studies included, 38 studies used age 80 years as the cutoff for elderly, 13 studies used age 75 years, 2 studies used age 70 years, and another study used age 65 years. Of note, NASCET and CREST were the only RCTs included in the analysis, whereas the rest were observational studies. CAS was associated with increased incidence of stroke in elderly patients compared with younger patients [odds ratio (OR), 1.56; 95% CI 1.40–1.75], whereas CEA had equivalent cerebrovascular outcomes in old and young age groups (OR, 0.94; 95% CI 0.88–0.99). CAS had

TABLE 3 | High risk condition or contraindication for carotid intervention of very elderly patients (40, 41).

	CEA	CAS
Anatomic	Prior CEA Prior neck surgery Prior neck irradiation Symptomatic ICA lesion High ICA lesion Low CCA lesion Neck immobility Tracheostomy Contralateral laryngeal nerve palsy Contralateral ICA occlusion Intraluminal thrombus Long subtotal ICA occlusion (string sign)	Symptomatic ICA lesion Steep aortic arch, tortuous CCA, tortous distal ICA Long subtotal ICA occlusion (string sign) Poor femoral access Extensive intracranial microvascular disease Circumferential ICA calcification Intraluminal thrombus Chronic ICA occlusion Intracranial aneurysm or AVM requiring treatment
Medical factors	Age > 80 Class III or IV heart failure Non-revascularized left main or multivessel coronary disease Class III or IV angina Myocardial infarction within 30 days Severe renal insufficiency Severe pulmonary disease Female sex Concomitant cardiac surgery Recent implantation of a coronary drug eluting stent	Age > 80 Severe renal insufficiency Major stroke within 4–6 weeks Intolerance to aspirin and/or clopidogrel

CEA, carotid endarterectomy; CCA, common carotid artery; ICA, internal carotid artery; AVM, arteriovenous malformation.

similar peri-interventional mortality risks in old and young patients (OR, 0.86; 95% CI 0.72–1.03), whereas CEA was associated with heightened mortality in elderly patients (OR, 1.62; 95% CI 1.47–1.77).

A pooled analysis of EVA-3S, SPACE, and ICSS showed that age was the only factor which significantly altered the relative risk of stroke or death between CAS and CEA in the short term (45). Whereas risk estimates were similar with both treatments among patients <70 years old, a twofold increase in risk with CAS over CEA was observed in the older age group. Age also significantly modified the effect of treatment on disabling stroke or death. The exploratory analysis of relative treatment risks across six age levels was consistent with the assumption of a linear increase in risk of periprocedural stroke risk associated with CAS. In CREST, there was an interaction between age and treatment efficacy ($p = 0.02$) (46). For the primary outcome, the hazard for CAS compared with CEA rose from 0.6 (95% CI 0.31–1.18) for patients aged under 65 to 1.08 (95% CI 0.65–1.78) for patients 65–74 years old to 1.63 (95% CI 0.99–2.69) for patients aged ≥75 years. The effect of age appeared primarily in the stroke risk, which increased with age more in the CAS group than in the CEA group. The age at which the HR was 1.0 was 70 years old for the primary outcomes and 65 years old for stroke.

In asymptomatic patients, the elderly (especially those over 80 years old) is a group in which the benefit of revascularization is controversial because in both the ACAS and ACST, the benefit from revascularization was seen after five-year follow-up (8, 20). ACAS did not enroll subjects greater than 80 years of age, and there was no benefit seen in those over 75 years in ACST. A report from the national cardiovascular data registry related to CEA showed elderly patients > 85 years of age were at increased risk for death or perioperative complications of stroke, death, and MI after CEA compared with those who were relatively younger. Among asymptomatic elderly patients, mortality rate was significantly higher in those older than 75 years (47). However, age cannot be an absolute contraindication with increasing life expectancy, because excellent outcomes after both CEA and CAS have been demonstrated in prudently selected patients (48, 49).

Therefore, if other conditions are similar, it is likely that CEA is more recommended than CAS for symptomatic patients older than 65–70 years old and it is difficult to determine which is better for asymptomatic patients in comparison with medical treatment. Meta-regression analysis investigating potential effects of publication time of each study on perioperative adverse events after CEA revealed no significant relationship. However, a significant effect of publication time on peri-interventional stroke and mortality in the patients who underwent CAS was reported (44). We need to consider comorbid medical conditions of the individual patients and wait for the results of research in progress.

RISKS AND SPECIFIC CONSIDERATIONS FOR CAROTID REVASCULARIZATION OF VERY ELDERLY PATIENTS

In elderly patients, it is necessary to know and confirm various situations that improve the outcomes after carotid revascularization. We reviewed specific considerations in very elderly patients undergoing CEA or CAS. However, we do not mention anatomic or medical conditions which is well known to be more appropriate for CAS or CEA in general population. We describe the conditions associated with an increased procedural risk and contraindications for CEA and CAS in **Table 3** (40, 41).

Sex

The effect of sex on carotid revascularization has been controversial. Previous studies such as NASCET and ECST showed a higher benefit in men than in women on perioperative stroke and death from CEA (42). Another study suggested that women were more likely to have less favorable outcomes, including surgical mortality, neurological morbidity, and recurrent carotid stenosis after CEA (50).

In general, surgical risk was higher in women than in men, whereas risk of CAS was virtually unaffected by sex (4, 51). There was no significant difference in treatment effects from CEA or CAS between men and women in the meta-analysis of randomized clinical trials of symptomatic patients (11). In CREST, the rates of the primary end point for CAS compared with CEA were similar, and there was no significant interaction between sexes (52, 53). However, periprocedural risk of events seems to be higher in women who have CAS than those who have CEA (6.8 versus 3.8%, $p = 0.047$) whereas there is little difference in men. A retrospective study based on a national database of carotid revascularizations in the United States found that women and men had equivalent rates of periprocedural stroke when

undergoing CEA (1.0 versus 1.0%) and CAS (2.7 versus 2.0%) (54). Nevertheless, symptomatic women had a significantly higher rate of periprocedural stroke than symptomatic men (3.8 versus 2.3%; $p = 0.03$). Among those with symptomatic stenosis, there was no difference between CAS and CEA in periprocedural events among men, but there was a non-significant trend toward fewer events with women who received CEA versus CAS (3.4 versus 6.2%, $p = 0.1$). In asymptomatic women, rates of periprocedural strokes were significantly lower after CEA than after CAS (0.9 versus 2.1%, $p < 0.001$) Therefore, in elderly women, CEA is recommended rather than CAS.

However, the Italian study of carotid revascularization for patients greater than 80 years old showed a 5-year mortality of 49.4%, higher in males (39.5% for females and 52.5% for males) and ischemic stroke-related mortality of 20.2%, higher in females (40.0% for females and 15.6% for males) (55). Comparing data from octogenarian residents of the same geographical territory, ischemic stroke-related mortality hazard was significantly higher in the study females: OR 3.2 95% CI 1.16–9.17; $p = 0.029$ (for males: OR 0.97, 95% CI 0.89–1.10; $p = 0.99$). Five-year Kaplan–Meier estimates of any stroke was 84.8% (78.7% symptomatic versus 90.3% asymptomatic; $p = 0.003$). Therefore, invasive treatment of carotid stenosis may not be warranted in patients more than 80 years of age with carotid stenosis, especially when female and asymptomatic.

Because the proportion of women is higher in older patients, various medical conditions including age and sex should be considered together in the selection of CAS and CEA. In addition, for elderly women with asymptomatic carotid stenosis, some researchers asserted medical treatment is recommended as a priority (5, 23, 52).

Coronary Artery Disease Risk

Because atherosclerosis is a systemic disease, coronary and carotid artery disease frequently coexist. The older the patient's age, the greater the likelihood of coronary disease. The performance of either combined or staged coronary artery bypass grafting and CEA consistently has been associated with increased likelihoods of perioperative stroke, death, and MI compared with standalone CEA. In contrast, CAS among patients with concomitant severe coronary disease seems relatively safe in comparison with CEA (40).

Inclusion of MI in the primary end point was different across trials, and the results were influenced by this component (**Tables 1** and **2**). The SPACE and EVA-3S, which did not include MI for the composite outcome, failed to prove non-inferiority of periprocedural events in CAS group compared with CEA group (28, 29). However, SAPPHIRE, CREST, and ACT-1, which included MI in the primary end point, showed higher risk of MI with CEA during the periprocedural period (12, 24, 32). Especially in CREST, the rate of MI was higher in the CEA group rather than the CAS group (2.3 versus 1.1%, HR 0.50, 95% CI 0.26–0.94, $p = 0.03$) (12). In addition, both the patients with MI defined as biomarker elevation plus either chest pain or electrocardiography (ECG) evidence of ischemia and the patients with biomarker only (biomarker elevation with neither chest pain nor ECG abnormality) were independently associated with increased future mortality (56).

In some studies, the risk of MI did not increase with age in either treatment group (12, 44, 46, 47, 57). However, in other studies, postoperative MI after CEA or CAS was independently associated with older age (44, 58–60). A meta-analysis showed an increased risk of developing MI in older patients compared with younger patients after CEA [2.2 and 1.4%, respectively; OR 1.64 (95% CI 1.57–1.74)] and CAS [2.3 and 1.5%, respectively; OR 1.30 (95% CI 1.16–1.45)] (44).

To reduce the risk of MI after CEA or CAS, more detailed preoperative cardiovascular evaluation might be needed. Because asymptomatic coronary stenosis can influence periprocedural vascular events, intensive preoperative evaluation such as coronary computed tomography angiography can be helpful (61). In addition, patients in CREST undergoing CEA with regional anesthesia had a similar risk of periprocedural MI as those undergoing CAS, whereas the risk for CEA with general anesthesia was twice that compared with patients undergoing CAS (62). Thorough perioperative management and assignment to CAS instead of CEA may minimize ischemic cardiac complications even in elderly patients (63). In addition, the use of dual antiplatelet therapy, statins, cardioprotective pharmacotherapy with or without coronary revascularization, or regional anesthesia could be recommended in patients with coronary disease.

Atrial Fibrillation

The prevalence of atrial fibrillation increases with age and ranges from 0.1% among adults less than 55 years of age to 9% in those ≥80 years of age (64). It is well known that atrial fibrillation increases the risk of stroke and is associated with poor stroke outcomes. In general practice, atrial fibrillation is a common comorbid condition among patients who undergo carotid revascularization. The rate of chronic atrial fibrillation in patients undergoing CEA ranges from 4 to 7% (65–67). Because many previous randomized controlled trials have excluded patients with cardiac arrhythmias (NASCET, ACAS, SAPPHIRE, CREST), the effect of atrial fibrillation on outcomes of patients is not well understood (6, 8, 12, 32).

Some studies revealed atrial fibrillation was associated with an increased risk of postoperative stroke in patients undergoing CEA but not in patients undergoing CAS. The relative risk of the composite outcome of postoperative stroke, cardiac complication, and mortality was increased in both groups with atrial fibrillation (65, 66). However, there were no long-term outcome results from the studies of CAS or CEA. The combined use of antiplatelets and anticoagulants in patients with atrial fibrillation after CAS may increase the bleeding risk, so additional studies are needed.

Miscellaneous

The prevalence of concomitant severe steno-occlusion on the contralateral carotid artery and vertebrobasilar artery and/or aortic arch stenosis increases with age. Theoretically, patients with contralateral carotid or vertebrobasilar occlusion have an increased risk of intolerance to ipsilateral carotid clamping, distal cerebral embolization, or cerebral hyperperfusion syndrome. Aortic arch stenosis and severe angulation can induce technical failure of CAS. There have been conflicting data regarding the

relationship between these concomitant atherosclerotic disease and risk of carotid revascularization (40, 68). However, recently both carotid revascularization methods can be applied in most patients, and final selection depends on individual situation.

White matter hyperintensities reflect small vessel burden and is associated with cognitive decline. The development of white matter lesions correlates with age. In a substudy of ICSS, CAS was associated with a higher risk of stroke compared with CEA in patients with moderate to severe white matter changes [an age-related white matter changes (ARWMC) score of 7 or more, HR for any stroke 2.98, 1.29–6.93; $p = 0.011$; HR for non-disabling stroke 6.34, 1.45–27.71; $p = 0.014$], but there was no difference in risk in patients with an ARWMC score of less than 7 (69). Therefore, it is necessary to be careful when selecting CAS in patients with more extensive white matter lesions. Nevertheless, there was a study reporting patients who underwent CAS tended to achieve higher scores in some cognitive function tests (70).

BEST MEDICAL TREATMENT VERSUS CAROTID REVASCULARIZATION

Medical treatment with antihypertensive, single or multiple antiplatelets, and lipid-lowering drugs has advanced since most clinical trials have been completed comparing CEA with best medical therapy alone. Recent studies suggest that the annual rate of stroke in medically treated patients with an asymptomatic carotid artery stenosis has decreased (22, 23).

The population-based Oxford Vascular Study (OXVASC) assessed the risk of TIA and stroke in 1,153 patients with ≥50% carotid stenosis recruited consecutively in 2002–2009 (23). During 301 patient-years of follow-up (mean of 3 years), there were 6 ischemic events in the territory of an asymptomatic stenosis, 1 minor stroke, and 5 TIAs. The average annual rates on medical treatment were 0.34% for any ipsilateral ischemic stroke, 0% for disabling ipsilateral stroke, and 1.78% for ipsilateral TIA. A systematic review of the stroke risk in the medical treatment group of patients with severe asymptomatic carotid stenosis for the past 25 years was presented (22). The development of pharmacotherapy led to a decrease in the incidence of ipsilateral and total TIA or stroke since the mid-1980s. The risk of stroke in the medical arms in the post-2000 studies has been similar or lower than that of the CEA arms of major clinical trials in the 1990s.

Therefore, there is an urgent need for clinical trials comparing carotid revascularization therapy with optimal medical treatment in the patients with asymptomatic carotid stenosis. The aggressive medical treatment evaluation for asymptomatic carotid artery stenosis (AMTEC) study was the first randomized controlled trial comparing CEA and modern medical treatment (aggressive lipid-lowering and antihypertensive medication, and aspirin). However, the trial was stopped after a median follow-up of 3.3 years because of the obvious superiority of CEA (71). CREST 2 and SPACE-2 are now ongoing, and will compare intensive medical management alone versus CEA plus intensive medical management or CAS plus intensive medical management in patients who are asymptomatic (72–74). The results of these trials and a subgroup analysis of elderly patients may be helpful to answer the questions about best management of these patients.

Regardless, it is important to maintain optimal medical treatment in patients with carotid stenosis whether or not carotid revascularization procedures are performed. However, elderly patients may be at greater risk for side effects because adverse drug reactions and drug–drug interactions are more common in older patients than the general population due to polypharmacy, age-related changes in physiology, and/or underlying chronic disease (75). Aggressive antihypertensive treatment in elderly is highly associated with orthostatic hypotension, falls, and dementia (76). Hypoglycemia can lead to worse outcomes in elderly diabetic patients, which leads to a change in the recommended glycated hemoglobin levels (7.5–9% rather than <7%) (77). Therefore, prescription of these medications needs to be carefully performed in these elderly patients.

FUTURE DIRECTIONS FOR THE PATIENTS WITH CAROTID STENOSIS—THE IMPORTANCE OF PLAQUE

Carotid stenosis in the 60–99% range has been an inadequate predictor of future vascular events. The ACAS and ACST trials did not show stenosis degree in this range as a predictor of future events (8, 20). Therefore, stenosis degree alone is not a reliable predictor to be used in decision making, and carotid plaque could be an important factor to improve the prediction of future stroke risk.

The disruption of atherosclerotic plaques precedes the onset of a clinical stroke syndrome. Vulnerability of carotid plaques, characterized by cap rupture, is significantly associated with the development of vascular events such as stroke (78, 79). There were several studies that found clinical indices for identifying high risk carotid plaques. Multiple non-invasive imaging modalities have shown their potential to differentiate high-risk vulnerable plaques from stable plaques. Atherosclerotic plaques can be characterized based on their surface irregularity, ulcerations, echolucency and gray-scale values by ultrasound (80–82). The Asymptomatic Carotid Emboli Study (ACES) investigated 1 h transcranial Doppler recording from the ipsilateral middle cerebral artery, and the absolute annual risk of ipsilateral stroke or TIA between baseline and 2 years was 7.13% in patients with embolic signals and 3.04% in those without, and for ipsilateral stroke was 3.62% in patients with embolic signals and 0.70% in those without (83). MRI has also been used to detect the presence of intraplaque hemorrhage as indicative of a high-risk plaque and vessel wall imaging by high-resolution MRI can be helpful to differentiate vulnerable from stable plaques (84, 85).

Other studies using albumin-binding MRI and 18F-fluoride position emission tomography have also investigated detection of vulnerable plaques, and someday these efforts to differentiate stroke-prone patients will be helpful for the decision of carotid treatment (86, 87). In the future, these approaches will be used for personalized and precision medicine in the treatment of complicated elderly patients (88).

Better understanding of risk factors for periprocedural and long-term outcome would help clinicians offer the best treatment option for carotid artery stenosis in elderly patients. Because individual risks are different according to the treatment method and stroke incidence has been decreasing by advanced drug therapy

and medical devices, clinicians should still be thoughtful while selecting patients for carotid revascularization therapy. Current guidelines may be changed in the future, depending on the results of ongoing trials of intensive medical management versus procedures plus medical management.

AUTHOR CONTRIBUTIONS

SH searched the literature, formulated the topics for the review, and wrote the manuscript. CB provided edits and contributed scientifically to the final draft.

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Determining the Association between Language and Cognitive Tests in Poststroke Aphasia

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Background: Individuals with aphasia are often excluded from studies exploring poststroke cognition because so many of the standard cognitive assessments rely on language ability. Our primary objective was to examine the association between performance on cognitive tests and performance on comprehension and naming tests in poststroke aphasia. Second, we aimed to determine the association between language performance and a real-life measure of cognition (Kettle Test). Third, we explored the feasibility of administering cognitive tests in aphasia.

Methods: Thirty-six participants with poststroke aphasia and 32 controls were assessed on a battery of pen-and-paper cognitive tests recommended in stroke. Auditory comprehension was measured using the Comprehensive Aphasia Test and naming was measured using the Boston Naming Test. Twenty-two community dwelling participants with aphasia and controls were also asked to complete the Kettle Test. Multiple linear regressions were used to explore the relationship between language performance and performance on the cognitive tests. Feasibility was determined by quantifying missing data.

Results: The cognitive tests with the highest variance accounted for by auditory comprehension and naming were animal fluency (R^2 = 0.67, R^2 = 0.78) and the Hopkins Verbal Learning Test (recognition discrimination index) (R^2 = 0.65, R^2 = 0.78). All cognitive tests were significantly associated with auditory comprehension and naming, except for the Star Cancellation Test and the Kettle Test. Thirty-three percent of participants with aphasia were unable to complete all the cognitive tests.

Conclusion: Language and non-linguistic cognitive processes are often interrelated. Most pen-and-paper cognitive tests were significantly associated with both auditory comprehension and naming, even in tests that do not require a verbal response. Language performance was not significantly associated with a real-life cognitive performance measure. Task instructions, stimuli, and responses for completion need to be tailored for individuals with aphasia to minimize the influence of language deficits when testing non-linguistic cognitive performance.

Keywords: aphasia, cognition, cognitive impairments, stroke, neuropsychological tests, pen-and-paper tests

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INTRODUCTION

Up to 30% of stroke survivors experience difficulty with receptive and expressive language—called aphasia (1). There is an assumed relationship between language and non-linguistic cognitive performance in poststroke aphasia, but the nature and management of this relationship is poorly understood. Studies show that impaired executive skills, working memory, and attention can adversely influence aphasia rehabilitation outcomes (2–4), and cognitive performance may predict aphasia recovery better than language performance (5). El Hachioui et al. (6) explored cognitive deficits in aphasia during the first year poststroke and the association with functional outcome. Participants with persisting aphasia had poorer cognitive performance, poorer functional outcome, and they were more depressed compared to participants with resolved aphasia. To optimize aphasia therapy, clinicians need to measure linguistic and non-linguistic performance to ensure all aspects of cognitive impairments are considered.

International guidelines recommend that all stroke survivors should be screened for cognitive impairments using valid and reliable tools, and comprehensive neuropsychological testing should be undertaken for those that fail screening (7–9). Pen-and-paper screening tools and assessments are used more frequently than alternative methods for assessing cognition poststroke (10, 11). Such tools are often linguistically loaded, and aphasic deficits may confound non-linguistic cognitive performance (12, 13). Consequently, patients with aphasia are often excluded from studies validating cognitive assessments and exploring cognitive outcomes in stroke (10, 14, 15).

A reliance on verbal response is an obvious barrier to obtaining accurate measures of non-linguistic cognitive performance in aphasia. For example, verbal fluency is task often used in standard language assessments (16), but it is also used to measure executive skills in stroke (17). This highly language-dependent task (18) is unlikely to accurately represent executive skills in aphasia. Yet, eliminating verbal responses may not resolve language deficits confounding non-linguistic cognitive performance in aphasia. Comprehension deficits associated with aphasia may also confound results. Cognitive tests are often complex, with detailed instructions requiring sophisticated comprehension skills to understand the tasks (19). Increased syntactical complexity negatively influences comprehension in aphasia (20), and the linguistic complexity of instructions needs consideration in this stroke subgroup.

To quantify the association between language performance and cognitive tests without a verbal response, Fucetola et al. (21) explored how much variance in the non-verbal subtests from the Wechsler Adult Intelligence Scale-III (block design, matrix reasoning, and picture arrangement) and Wechsler Memory Scale-III (spatial span) was accounted for by auditory comprehension and oral expression in aphasia. Auditory comprehension accounted for 41% of the total variance ($p < 0.001$), whereas no significant relationship was found with naming performance. This study suggests that non-verbal cognitive performance is related to auditory comprehension severity, but 59% of the variance remains unexplained.

Cognitive tests vary in the cognitive domain being tested, the task complexity, the delivery of instructions, and the responses needed for completion. There has been no systematic analysis of the relationship between language performance in poststroke aphasia (naming and comprehension) and performance on a broad range of widely used neuropsychological tasks. Exploring the potential variability in the association between language and scores on cognitive tests (including an everyday real-life measure of cognition, such as making a hot drink) in aphasia is necessary to better inform clinical practice.

Our primary objective was to examine the association between performance on cognitive tests and assessments of comprehension and naming in poststroke aphasia. Our second aim was to determine the association between auditory comprehension and naming performance and a validated real-life cognitive performance assessment in aphasia and controls. Our last aim was to determine the feasibility of all cognitive tests used by quantifying missing data in patients with aphasia compared to controls.

PARTICIPANTS AND METHODS

Participants

Thirty-six participants with poststroke aphasia and 32 controls were recruited from three Brisbane Hospitals, the Communication Registry at The University of Queensland, community posters, social groups, and newsletters. Participants with aphasia had diagnostic imaging evidence of stroke (or a clinical diagnosis if imaging was unavailable) and a diagnosis of aphasia according to the Comprehensive Aphasia Test (CAT) (using auditory comprehension subtests' cutoff scores) (16) or the Language Screening Test (cutoff < 15) (22). Patients were excluded if they: (1) had visual and hearing impairments that impeded testing; (2) needed an interpreter to participate if English was their second language; or (3) were too medically unwell. The included control participants passed a mood screen (The Patient Health Questionnaire) (23) to eliminate the potential influence of depression on cognitive performance (24, 25). Controls were excluded if they had a history of neurological disease or acquired injury, or if they needed an interpreter to participate if English was their second language.

Assessments

Demographic data collected included age, sex, education level, handedness, time poststroke, and clinical setting. We did not report localization of stroke lesion(s) because detailed neurological data could not be sourced for all community participants.

Language performance and severity of aphasia were assessed using the CAT (16) (auditory comprehension total score) and the 15-item abbreviated Boston Naming Test (26). The Boston Naming Test is one of the most widely used standardized aphasia measures in clinical practice (27). The 15-item abbreviated Boston Naming Test strongly correlates with the full Boston Naming Test ($r = 0.93$) (28), and it was recommended as part of neuropsychological testing for stroke survivors (17). Fifty percent of stroke survivors experience fatigue irrespective of time poststroke (29). The practicality of testing individuals with fatigue was considered in selecting our battery.

Our battery of pen-and-paper neuropsychological tests has been validated in stroke. The battery included as follows.

Star Cancellation (30)

A visual neglect test that includes small stars on an A4 sheet with visual distractors (large stars and letters). Participants are provided with a visual demonstration, along with brief verbal instruction, to cross out all the small stars using a pen.

The Brixton Spatial Anticipation Test (31)

An executive function test with a 56-page stimulus booklet. It is a visuospatial sequencing task with rule changes where participants are required to detect rules in sequences of stimuli. Each page contains 2 rows of 5 circles, numbered from 1 to 10. On each page, a single circle is colored blue, and the position of the blue circle changes from one page to the next, based on a series of patterns. Participants are provided with lengthy verbal instructions and a practice. The examiner clarifies understanding. Participants are required to point to where they predicted the filled circle will be on the following page, based on the pattern inferred from the previous page.

Trail Making Test (Parts A and B) (32)

Part A is often used to test attention. Participants are verbally instructed to connect circles numbered 1–25 in correct order as quickly as possible using a pen. Part B is an executive task where participants are verbally instructed to connect numbered and lettered circles in correct alternating order (i.e., 1-A-2-B, etc.) as quickly as possible. Both parts have practice trials for familiarization.

Digit Span Test (Forwards and Backwards) (33)

The forwards test is used to measure verbal short-term memory. Participants are verbally instructed to repeat strings of numbers of increasing length. The backwards test is used to measure verbal working memory and executive skills. Participants are presented with more number of strings, and they are verbally instructed to recall each number string in reverse order.

Hopkins Verbal Learning Test (HVLT)-Revised (34)

Hopkins Verbal Learning Test-Revised is used to assess verbal memory. The examiner reads a list of 12 words (from 3 taxonomic categories). Participants are instructed to try to remember, and verbally repeat, as many words as possible from the list. The examiner then reads the same list twice more, with recall each time. The immediate recall score is the total number of words recalled over these three trials. Subsequently, the participants are asked to recall the word list 20–25 min later (delayed recall). A retention score is calculated to determine the percentage of words retained (delayed recall as a percentage of the best immediate recall from trial 2 or 3). This is followed by a forced-choice recognition test [recognition discrimination index (RDI)], where 12 target words from the learning trials are included with 12 distractor words (six semantically related and six semantically unrelated). Participants are instructed to provide a yes/no response.

Rey Complex Figure (Copy, Immediate, and Delayed Recall) (35)

Rey Complex Figure (copy, immediate, and delayed recall) is used to assess visuospatial, visual memory, and executive skills. Participants are provided with a pen and paper and asked to reproduce the complex figure. The stimulus figure and reproduction are then removed. After a 5 min delay, the participants are verbally instructed to reproduce the figure from memory. Then, after a 20–30 min delay, the participants are instructed to reproduce the figure from memory again.

Animal Fluency (36)

A verbal fluency task where participants are verbally instructed to name as many different animals as possible within a minute. While fluency tasks (such as animal fluency) undoubtedly include facets of executive function in planning search and retrieval, they are predominantly a reflection of language skills (18).

Kettle Test (37)

Kettle Test is a real-life everyday performance measure designed to detect cognitive processes needed for independent community living. Observations are rated on 13 distinct steps to complete the hot drink making task and guidelines for cueing are provided. The participants are scored according to the degree of cueing needed to complete the individual steps (0–4). Total scores range from 0 to 52, with higher scores indicating more assistance.

Statistical Analysis

The relationships between auditory comprehension, naming, and cognitive function were tested using separate multivariate linear regressions (controlling for age and education) for each cognitive test. To determine the distinct effects of auditory comprehension and naming, the independent variables were entered into different models. Demographic variables included in the models were years of education and age. If assumptions were not met to perform the multiple linear regressions, logistic regressions were used. To explore the feasibility of performing cognitive tests in aphasia compared to controls, we recorded reasons for missing data and the frequency for each individual test. All analyses were performed with Stata 14 software.

RESULTS

The characteristics of the 36 participants with poststroke aphasia and 32 controls are shown in **Table 1**. Of the 36 participants with aphasia, 22 community dwelling participants and the controls were also asked to complete the Kettle Test. The Kettle Test was not performed in the acute phase of stroke due to practical restrictions on the ward.

The severity of auditory comprehension and naming impairments in the aphasia group ranged from very severe to mild language deficits. Total scores for auditory comprehension ranged from 5/66 to 63/66 (median = 53, interquartile range = 29–58) as measured by the CAT. The results from the Boston Naming Test ranged from 0/15 to 15/15 (median = 10, interquartile range = 1–12). Control participants completed all tests, while 33% ($n = 12$) of participants with aphasia had missing data. All participants completed the auditory comprehension and naming tasks. There were a total of 32 missed cognitive test scores.

Figure 1 shows the number and frequency of missing data for the cognitive tests. The Trail Making Test (part B) had more

missing data than any other test (28%). The non-verbal cognitive tests had more missing data compared to the tests that required a verbal response. For example, verbal fluency (0%) and the HVLT (0–2.8%) compared to the Brixton (8.3%) and the Rey immediate and delayed recall (8.3%). Reasons for missing data in the pen-and-paper tests were (1) refusal to attempt test (n = 3 participants), (2) incomplete due to task complexity (n = 3 participants), (3) unable to understand instructions (n = 3 participants), and (4) incomplete due to difficulty using a pen (n = 2 participants). Four of the 22 community dwelling participants with aphasia (15%) had missing data for the Kettle Test due to upper and lower limb hemiparesis. Participants with missing data had more severe auditory comprehension deficits (median = 27.5, interquartile range = 25.0–49.0) and more severe naming deficits (median = 1, interquartile range = 0–7.5), compared to participants without missing data (auditory comprehension median = 53, interquartile range = 45.8–58.0; naming median = 6.5–13.5, interquartile range = 7.0). The clinical setting did not influence missing data, where there was an equal distribution of participants in the acute versus community setting.

TABLE 1 | Characteristics of the aphasia and control groups.

	Aphasia	Controls
Age in years, mean ± SD	70.1 ± 9.0	67.3 ± 12.3
Sex, *n* (%)		
Female	12 (33)	17 (53)
Male	24 (67)	15 (47)
Handedness, *n* (%)		
Right-handed	34 (94)	30 (85.7)
Left-handed	2 (5.5)	2 (6.3)
Ambidextrous	1 (2.7)	0
Education in years, mean ± SD	11.0 ± 2.6	15.1 ± 3.4
Premorbid neurological disease/injury (*n*)	3	–
Time poststroke, mean ± SD by clinical setting		–
Acute setting (n = 12)	9.2 ± 13.2 days	–
Inpatient rehabilitation (n = 2)	23.5 ± 11.5 days	–
Community dwelling (n = 22)	6.35 ± 5.2 years	–

Table 2 shows the descriptive statistics for the language and cognitive tests. As expected, there was minimal variance in the auditory comprehension and the Boston Naming Test scores of the control group, and therefore no regressions associating language and cognitive performance were run in this group. The data for the regressions were sourced only from the participants with aphasia. We conducted a pairwise regression between the independent variables (auditory comprehension and naming), and confirmed that they were too closely related (pairwise correlation = 0.86) to be included in the same regression model.

Figure 2 shows that all cognitive tests were significantly associated with auditory comprehension (all $p < 0.01$) with a variance ranging from 40 to 67%, except for the Kettle Test [$F(3,14) = 0.75$, $p = 0.54$] with a variance of 14%, and the Star Cancellation [$F(3) = 4.9$, $p = 0.18$] with a variance of 24%. A multiple logistic regression was used for Star Cancellation due to a ceiling effect (refer to **Table 2**), and a pseudo R^2 was reported. Animal fluency had the highest variance explained by auditory comprehension (67%), closely followed by HVLT RDI (65%) and immediate recall (63%).

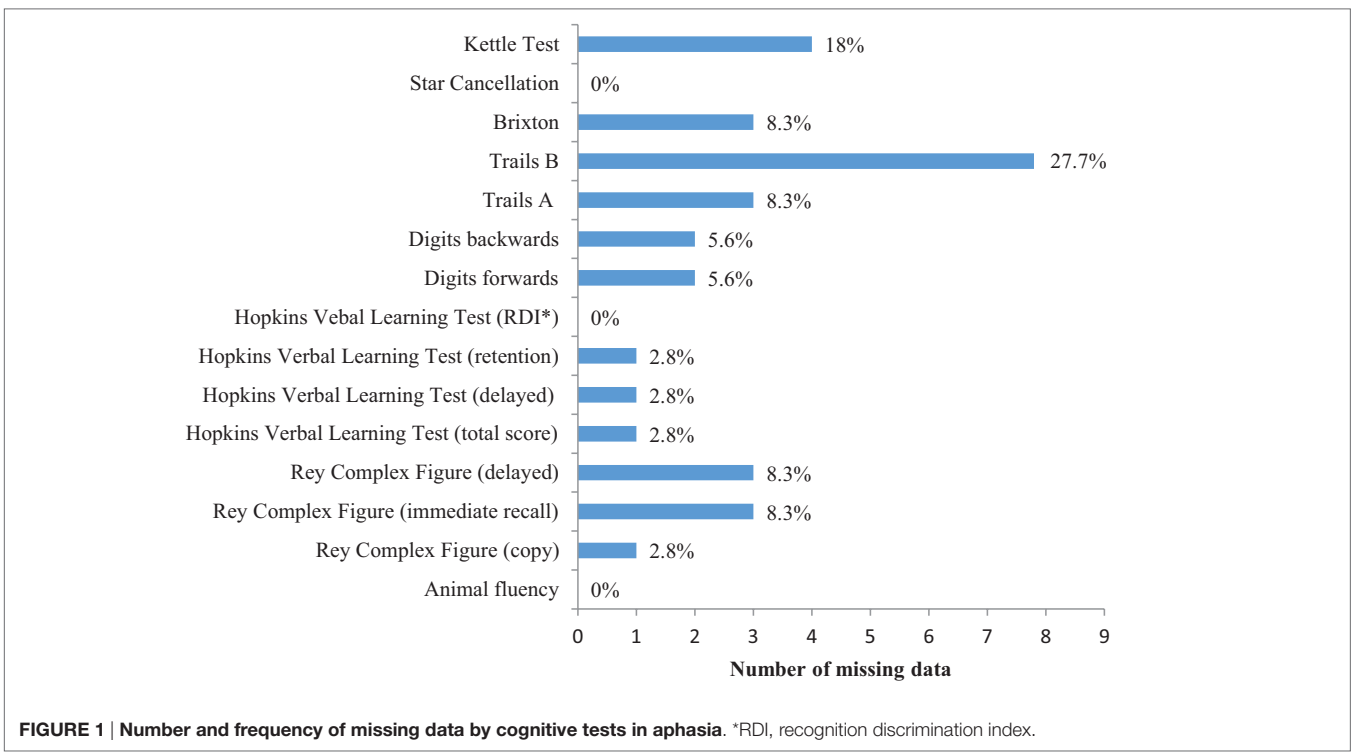

FIGURE 1 | Number and frequency of missing data by cognitive tests in aphasia. *RDI, recognition discrimination index.

TABLE 2 | Descriptive statistics of the language and cognitive tests.

Test	Aphasia group			Controls		
	Mean (SD)	Median	Range	Mean (SD)	Median	Range
Auditory comprehension	46.1 (15.5)	52.0	5–63	61.4 (3.2)	62.0	55–66
Boston Naming Test	8.2 (5.3)	9.5	0–15	13.8 (1.2)	14.0	11–15
Kettle Test	4.6 (4.0)	4.0	0–15	1.5 (1.6)	1.0	0–5
Star Cancellation	51.6 (6.3)	54.0	24–54	53.9 (0.4)	54.0	52–54
Brixton	28.9 (12.4)	28.0	4–52	22.6 (8.8)	20.0	7–40
Trails B	181.9 (85.4)	178.0	44.2–300	87.4 (33.7)	83.8	33–160
Trails A	91.9 (60.6)	75.0	20–300	36.6 (9.8)	35.6	17.5–63.7
Digits backwards	3.3 (2.9)	4.0	0–11	7.4 (2.6)	7.0	2–14
Digits forwards	5.8 (4.1)	6.0	0–14	10.2 (2.2)	10.0	6–14
HVLT (RDI)	6.0 (3.9)	7.0	0–12	9.7 (1.8)	10.0	6–12
HVLT (delayed)	3.6 (2.9)	3.5	0–9	7.3 (2.8)	7.0	3–12
HVLT (total)	11.6 (7.8)	13.0	0–23	23.3 (4.9)	23.5	13–32
Rey Complex Figure (delay)	10.0 (9.2)	8.5	0–30	18.2 (6.6)	17.8	7–32
Rey Complex Figure (immediate)	11.2 (9.0)	9.0	0–29	19.5 (6.6)	19.3	7.5–32
Rey Complex Figure (copy)	23.9 (11.7)	26.0	0–36	34.5 (2)	35.0	28.5–38
Animal fluency	10.2 (7.5)	10.5	0–25	24.7 (7)	24.0	16–44

HVLT, Hopkins Verbal Learning Test; RDI, recognition discrimination index.

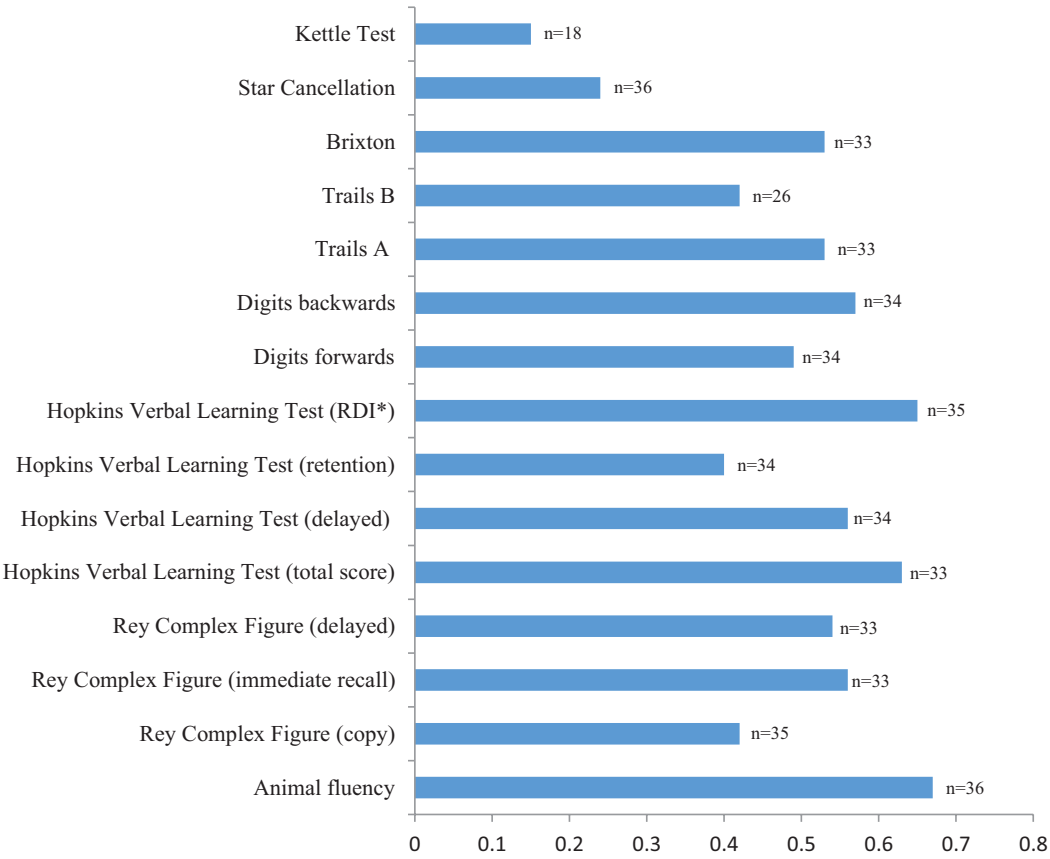

FIGURE 2 | Association between auditory comprehension and the cognitive tests (R^2), with demographic factors included in the models. *RDI, recognition discrimination index.

Figure 3 displays the results of the multiple linear regressions used to determine the relationship between the naming and the cognitive tests, with age and education included in the models. A multiple logistic regression was again used for the Star Cancellation Test. All cognitive tests were significantly associated with naming (all $p < 0.01$) with a variance ranging from 33 to 78%, except for the Kettle Test [$F(1,16) = 3.44$, $p = 0.08$] with a variance of 18%, and the Star Cancellation [$F(3) = 3.8$, $p = 0.28$] with a variance of 18%. Animal fluency and the HVLT RDI had the highest variance explained by naming (both 78%).

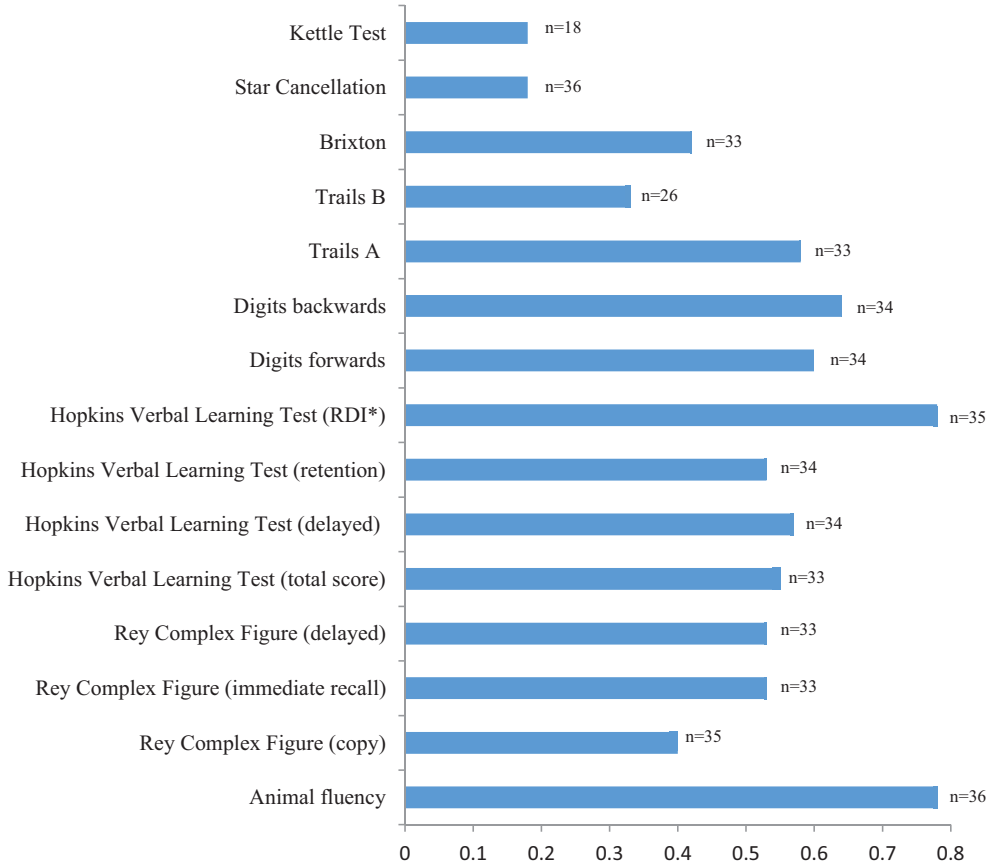

FIGURE 3 | Association between naming and the cognitive tests (R^2), with demographic factors included in the models. *RDI, recognition discrimination index.

DISCUSSION

Both auditory comprehension and naming performance in aphasia were significantly associated with all pen-and-paper cognitive tests, with the lone exception of Star Cancellation. The total variance explained by auditory comprehension performance differed between the cognitive tests. The cognitive tests requiring a verbal response showed more variance explained by naming compared to the non-verbal cognitive tests. We also confirmed that auditory comprehension and naming were not significantly associated with an everyday real-life measure of cognition (Kettle Test). Feasibility was an issue, with substantial missing data for the pen-and-paper cognitive tests, and also missing data for the Kettle Test due to upper and lower limb hemiparesis, in aphasia. While non-linguistic cognitive impairments co-occur with aphasia (2–4), non-verbal cognitive tests may not necessarily overcome the potential confounding influence of aphasia-related deficits. The Kettle Test shows that individuals with aphasia can undertake a real-life cognitive task without the confounding influence of language impairments.

Animal fluency and the HVLT RDI had the highest variance explained by both auditory comprehension and naming. Our animal fluency results are supported by Whiteside et al. (18) where factor analysis was used to verify that animal fluency loaded exclusively to language, rather than executive functioning. Although executive skills may be impaired in aphasia (38) using the animal fluency task to determine executive skills in people with aphasia may mislead diagnoses.

The RDI component of the HVLT requires a yes/no response to identify previously learned words. Eliciting a yes/no response from a person with aphasia is a suggested technique to overcome verbal barriers and facilitate communication (39), yet the variance was largely explained by auditory comprehension (65%) and naming (78%). These results may not be surprising given the HVLT requires participants to remember linguistic targets, thus impaired language will influence recognition performance. Also, to identify a correct response, participants need to discriminate between semantically related distractors. The literature supports observed semantic deficits in both auditory comprehension and naming in aphasia (40). Thus, using semantically related distractors in a verbal recognition task will likely be confounded in aphasia, even when the response is restricted to a yes/no response.

The total variance explained by auditory comprehension for the pen-and-paper cognitive tests without language stimuli or

a verbal response (i.e., Star Cancellation, Rey Complex Figure, and the Brixton) was variable (24–56%). This means a large amount of variance remains unexplained, which may be attributed to concomitant non-linguistic cognitive deficits. Auditory comprehension was not significantly associated with the Star Cancellation Test. A weak association between neglect and language comprehension stroke is verified in the literature (41), but the simplicity of the Star Cancellation's instructions, and the simplicity of the response (crossing out stars with a pen), will assist comprehension in aphasia. The Star Cancellation Test was able to be completed by all participants with aphasia, and it is a reliable assessment to use poststroke (30) where visual spatial screening is recommended.

There was a significant association between all subtests of the Rey and auditory comprehension. Pyun et al. (42) explored visuospatial skills in 23 participants with aphasia and found that the Rey copy scores were significantly correlated with the severity of the overall language performance ($r = 0.654$, $p < 0.05$). Visual perceptual deficits may be underestimated in aphasia. While the Rey copy is supported by simple verbal instructions, the complex copy task has been shown to involve planning and organization skills for successful completion (43). Thus, the relationship with language performance and the Rey copy task could be partly explained by concomitant executive deficits in aphasia. The association between non-linguistic memory performances in the Rey immediate task can be compared with Lang and Quitz (44), where 99 participants poststroke (49 with aphasia and 50 without aphasia) were assessed using linguistic and non-linguistic memory tests. Participants with aphasia performed worse than participants without aphasia in the memory tests, even when participants had similar cerebral lesions, which the authors attributed to a common working memory impairment in aphasia.

The total variance explained by auditory comprehension for the Brixton was 53%. The aphasia group, and to a lesser degree the controls, experienced difficulty understanding the Brixton's lengthy verbal instructions. This was evidenced by the need to repeat instructions for clarity. However, as part of the Brixton assessment, direct feedback is provided for each response (e.g., participants are aware of a correct or incorrect response based on where the blue dot appears on the following sheet). This immediate visual feedback may have assisted with participants learning what is needed. Thus, executive tests that necessitate lengthy verbal instructions can incorporate non-linguistic prompts to facilitate understanding.

Fucetola et al. (21) explored the association between auditory comprehension and non-verbal subtests of the WAIS-III and WMS-III [e.g., block design (constructional), matrix reasoning (reasoning by visual analogy), picture arrangement (sequencing), and spatial span (visual working memory)]. Auditory comprehension accounted for 41% of the total variance in the non-verbal cognitive tests. Naming was also significantly associated with the non-verbal cognitive tests in the present study, which contrasts with the findings of Fucetola et al. (21). It is difficult to distinguish between a confounding language influence and a co-occurring non-linguistic cognitive impairment in cognitive tests that are not tailored for individuals with aphasia.

Auditory comprehension was not significantly associated with the Kettle Test. This everyday real-life cognitive test contains verbal instructions, but understanding is maximized by using a meaningful task with familiar everyday objects. The kitchen setting may further support understanding by incorporating a multisensory environment. Using multiple sensory modalities facilitates the ability to identify, discriminate, and recognize stimuli, and learning can be optimized (45, 46). Our results demonstrate that using a familiar, real-life functional measure of cognitive performance may minimize the language skills needed to complete the task. The Kettle Test may be appropriate for individual with aphasia, but participants needed adequate motor skills to complete the task. Upper and lower limb hemiparesis was the sole reason for missing data associated with the Kettle Test. While the Kettle Test is regarded as an executive task (37), it may underestimate the potential association between language and cognitive skills needed for more complex community living activities. Further testing using functional cognitive performance measures in aphasia is needed.

Testing cognition in aphasia was not feasible in a number of participants, particularly those with more severe language impairments. There were no missing data for the language tests in both the aphasia and control group. Primary reasons for missing data in the pen-and-paper cognitive tests were participant refusal and an inability to understand the tasks. Chapman (47) explored the association between semantic comprehension deficits and executive skills in aphasia and semantic dementia and reported that participants found many executive tests too difficult to understand. If an individual is unable to undertake task instructions, performance may reflect comprehension deficits rather than the target non-linguistic cognitive domain intended for testing. This may result in inaccurate information being used to guide cognitive therapy, inaccurate education given to stroke survivors and their families, and the potential for misinformed discharge planning. Missing data associated with the Kettle Test were due to upper and lower limb hemiparesis. Participants with aphasia were particularly resistant to participate in the Trail Making Test (part B). This executive task has linguistic stimuli and requires a more complex response (i.e., participants use a pen to sequentially track the alternate numbers and letters). In contrast to another executive task, the Brixton, a simple response is required (i.e., pointing to a colored circle), and participants were more likely to attempt and complete it. It appears that feasibility of testing participants with aphasia not only relates to complexity of instructions but it may also be influenced by the complexity of the response needed for completion.

To determine feasibility of cognitive testing, we minimized the exclusion criteria to be inclusive of participants that represent clinical practice. A limitation is that the high frequency of missing data for the cognitive tests may have biased the regression findings to exclude the association of participants with profound comprehension deficits and cognitive performance.

Assessing non-linguistic cognitive skills in aphasia is challenging, which results in people with aphasia being excluded from studies that have validated cognitive assessments in stroke (10). Using non-verbal cognitive tests may not ensure accurate results due to potentially confounding auditory comprehension

impairments observed in aphasia. Difficulty understanding the tasks may also influence an individual's willingness to participate in testing, creating feasibility barriers for both clinical and research practice. Clinical guidelines for poststroke aphasia (48, 49) require further evidence of the association between linguistic and non-linguistic cognitive skills in aphasia, to warrant the inclusion of non-linguistic cognitive assessment in clinical recommendations. The Star Cancellation Test and the Kettle Test were the only cognitive assessments not significantly associated with auditory comprehension and naming performance in aphasia. To maximize the accuracy and feasibility of cognitive testing in aphasia, cognitive tests need to be tailored to enhance understanding of the tasks. Multidisciplinary expertise is needed to look beyond typical pen-and-paper methods and consider multisensory input for cognitive testing in aphasia.

ETHICS STATEMENT

Ethical clearance was obtained through relevant Human Research Ethics Committees in Brisbane, Australia, including the Royal Brisbane and Women's Hospital. Written consent was sourced for all participants and a substitute decision maker was used for patients with cognitive deficits that precluded informed consent.

AUTHOR CONTRIBUTIONS

KW, TC, and DC contributed to the conception and design of the work. KW was responsible for data collection, data analysis, and drafting the manuscript. TC and DC critically revised the work and contributed to the interpretation of the data. All authors gave their final approval of the version to be published and agreed to be accountable for all aspects of the work.

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Apolipoprotein E ε4: A Possible Risk Factor of Intracranial Pressure and White Matter Perfusion in Good-Grade Aneurysmal Subarachnoid Hemorrhage Patients at Early Stage

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Aneurysmal subarachnoid hemorrhage (aSAH) is a devastating and complicated disease with significant morbidity and mortality. Previous studies have shown that genetic susceptibility may play an important role in the outcome of a given individual with aSAH. This study evaluates the potential association in effects of the APOE allele on the early brain injury (EBI) in light of elevated intracranial pressure (ICP) and cerebral perfusion disorders in a consecutive series of non-comatose Chinese patients with aSAH. A total of 122 patients with aSAH (54 males and 68 females) were enrolled in this study. Demographic and clinical data were collected. We measured ICP before microsurgical clipping or endovascular coiling during the first 72 h after aneurysm rupture. Computed tomography perfusion (CTP) examination in patients was performed before treatment. The distributions of APOE genotypes and alleles matched Hardy–Weinberg law ($p > 0.05$). In this study, 68 patients (55.7%) had a normal ICP, whereas 54 (44.3%) had an elevated ICP. Fourteen of 21 patients with APOE ε4 had an elevated ICP, which was significantly different from those without APOE ε4 ($p = 0.03$). The patients with the ε4 allele had a higher incidence of elevated ICP [$p = 0.009$, 95% confidence interval (CI) = 1.481–15.432, odds ratio = 4.780] than those without this allele. For CTP measurements, a lower mean cerebral blood flow (difference, −4.74; 95% CI, 0.53–8.94 s, $p = 0.03$), longer mean transit time (difference, 0.47; 95% CI, −0.87 to −0.78, $p = 0.02$), and time-to-peak (difference, 2.29; 95% CI, −3.64 to −0.93 s, $p = 0.02$) were observed in patients with ε4 allele than in those without in the internal capsule regions. In conclusion, the APOE ε4 allele predisposes patients to elevated ICP and perfusion disorders in white matter regions during the first 72 h after aSAH. The presence of an APOE ε4 allele plays an important role in the EBI response to aSAH.

Keywords: apolipoprotein E, subarachnoid hemorrhage, early brain injury, intracranial pressure, computed tomography perfusion, white matter injury

INTRODUCTION

Aneurysmal subarachnoid hemorrhage (aSAH) is a devastating and complicated disease with significant morbidity and mortality (1). Traditionally, cerebral vasospasm (CVS) and aneurismal rebleeding have been considered to be major complications that significantly worsen the prognosis of aSAH (2). In recent years, early brain injury (EBI) during the first 72 h after aSAH has been shown to play an important determinant of clinical outcome (3). Notably, global cerebral ischemia as a hallmark of EBI is thought to be related to raised intracranial pressure (ICP) and cerebral perfusion (4–6). Cerebral perfusion is related to mean arterial blood pressure and ICP, which reduces the cerebral perfusion and threatens the brain function.

Increasing evidence has shown that aSAHs with similar pathologies might have different clinical statuses and outcomes. However, the Hunt and Hess grade, sex, and age of the patient can explain only part of this variability. Alternatively, genetic susceptibility may play an important role in the outcome of a given individual with aSAH (7, 8). Recently, apolipoprotein E (APOE = gene; apoE = protein) has become one of the most widely studied genes in aSAH research (9). There are three common isoforms (apoE2, apoE3, and apoE4) encoded by three gene alleles (APOE ε2, APOE ε3, and APOE ε4) (10). Although the presence of the APOE ε4 allele predisposes poorer outcome in patients with aSAH, the conclusions of investigations are still conflicting (11, 12).

Increased ICP is common after SAH, even in patients with a good clinical H–H grade. Elevated ICP post-SAH is associated with a worse patient outcome (13). Patients with good-grade aSAH (Hunt and Hess grades I–III) can also die or present severe deficit due to increased ICP leading to cerebral ischemia (14). Elevated ICP post-SAH is associated with good-grade patient outcomes (13). Our previous study indicated that APOEε4 as an independent risk factor for cerebral perfusion dysfunction (6). However, the risk of APOE genotype on ICP and cerebral perfusion of good-grade aSAH patients has never been investigated in detail. The present study aimed to evaluate the potential association between APOE allele and the progression of EBI in light of increased ICP and cerebral perfusion in a consecutive series of good-grade Chinese patients with aSAH.

MATERIALS AND METHODS

Study Design and Inclusion and Exclusion Criteria

A total of 122 consecutive patients with onset of aSAH shorter than 72 h were enrolled to the two departments of neurosurgery in this prospective pilot study from December 2014 to July 2016 (The Affiliated Hospital of Southwest Medical University: 67 patients and The First Affiliated Hospital of Chongqing Medical University: 55 patients). aSAH was confirmed using CT scans and lumbar puncture. The sample group of adult patients included 54 males and 68 females, aged 48–72 years old, with a diagnosis of SAH from a ruptured cerebral aneurysm, which was verified using digital subtraction angiography or CT angiography.

The following inclusion criteria were applied: (i) the clinical grade before treatment was I–III, according to the Hunt and Hess grading system (e.g., good-grade non-comatose patients); (ii) all of the patients were treated within 72 h with early microsurgical clipping; and (iii) clinical data were recorded completely.

We excluded patients with the following characteristics: (i) cerebral lesions other than aneurysms because they can be independent predictors of ICP increases and can render the attribution of ICP less reliable; (ii) displayed symptomatic CVS with a PMV $\geq$ 120 cm/s (15) or severe narrowing of the involved artery on cerebral angiogram within the first 72 h; and (iii) aneurysmal rebleeding, intra-ventricular hemorrhage, or hydrocephalus observed by CT scan within 72 h.

Recording of Clinical Information

The clinical data of the included patients were recorded; this information included the patient's age, sex, neurological condition before treatment (Hunt–Hess grade), and Fisher grade on admission as well as the site of the ruptured aneurysm, and the type of treatment (clipping or coiling).

APOE Genotype

APOE genotype was determined from genomic DNA extracted from venous blood that was collected from the patients upon admission. DNA was extracted from frozen blood using standard techniques, and APOE ε2, ε3, and ε4 genotyping was performed using the polymerase chain reaction–restriction fragment length polymorphism method, as previously described (16). Briefly, a 250-bp fragment containing the coding region was amplified. The following primers were used: P1: 5′-TAAGCTTGGCACGGCTGTCCAAGGA-3′ (upstream) and P2: 5′-ACAGAATTCGCCCCGGCCTGGTACAC-3′ (downstream). The PCR products were digested using the *Hha*I restriction enzyme, and the fragments were separated by electrophoresis on 4% ethidium bromide-containing agarose gels for genotype determination.

ICP Monitoring

Lumbar puncture allowed us to gage the ICP of the SAH patients (17). Thus, lumbar pressure (LP) was used in this study as a surrogate measurement of ICP. After the source of SAH was identified, either aneurysm clipping or coiling was performed within 72 h. Before the operation, a silicon lumbar catheter was introduced through a 16-G lumbar needle into the subarachnoid space at the L4–L5 level. This catheter was connected to a sterile collecting system fixed above the point of catheter insertion. The LP was measured *via* a hydrostatic pressure transducer, which was immediately connected to the drainage system. The zero reference pressure was the atmospheric pressure at the level of the foramen of Monro. The ICP threshold was set at 20 mmHg because this pressure is the recommended threshold for routine initiation of ICP treatment in neurosurgery in adults.

Computed Tomography Perfusion (CTP) Screening

To characterize the region-specific response to cerebral perfusion, CTP examination in patients was performed before treatment. After injection 30 ml of non-ionic contrast agent (iopromide

Ultravist, 370 mg iodine/ml; Schering, Berlin, Germany) and 15 ml of normal saline through the cubital vein (4 ml/s), head scanning was performed by a Lightspeed VCT 64-slice CT machine. The following parameters were used: 80 kVp, 200 mAs, 5 mm slice thickness. Original data were transferred to an Adw4.2 workstation for subsequent analysis. The measurements of arterial input (anterior cerebral artery) and venous output (superior sagittal sinus) functions were semiautomatic. We cooperated with the clinical radiologists because they will likely become expert in distinguishing CT images on a region-by-region basis. Hand-drawn, multi regions of interest (ROIs) were defined by prespecified anatomical boundaries on CT images. One side and the contralateral mirror area of caudate nucleus, internal capsule, thalamus, external capsule, and whole cortex were scanned as the ROI. The cerebral blood volume, cerebral blood flow (CBF), mean transit time (MTT), and time-to-peak (TTP) were obtained. To ensure the accuration of each ROI, we narrowed ROIs in regions with indistinguishable boundary, and all the ROIs of each patient were drawn by the same assessor.

Statistical Analysis

SPSS software (version 19.0) was used for statistical analyses. After counting the number of alleles, the allele frequencies in aSAH patients were calculated from the sample proportions. The constituent ratio of each correlation factor in the clinical data between the groups (with ε4 allele and without ε4 allele) was analyzed using the χ^2 test for nominal variables. Univariate logistic regression was performed to analyze the associations of age (≤65 years old vs. >65 years old), Hunt–Hess grade (1 and 2 vs. 3), Fisher grade (1 and 2 vs. 3 and 4), aneurysm site (anterior communicating artery vs. other sites), type of treatment (clipping vs. coiling), and APOE genotype (with ε4 vs. without ε4) with elevated ICP. After adjusting the clinical data, further multivariate logistic regression analyses (stepwise backward conditional and Wald functions, as appropriate) were used to analyze the associations of the APOE genotype (with ε4 vs. without ε4) with elevated ICP. Variables entered into the multivariate regression at $p < 0.05$, while some variables were removed at $p > 0.1$. Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were calculated from the logistic regression model coefficients. In addition, we compared differences in mean values of cerebral perfusion between patients with and without ε4 allele by calculating the 95% CIs of the mean difference. The statistical significance of the correlation between the investigated quantitative variables was determined by the p value, and a p value <0.05 was considered significant.

RESULTS

The department admitted 210 patients with aSAH during the study period. Seventy-one patients were not included in the study because their clinical conditions were classified as IV or V on the Hunt and Hess grading scale. Seventeen good-grade patients met the exclusion criteria and were disqualified: two patients had cerebral lesions other than aneurysms, six patients had aneurysmal rebleeding or hydrocephalus within 72 h, three patients had intracerebral hematomas, and six patients displayed symptomatic CVS, with a PMV ≥ 120 cm/s, or suffered from severe narrowing of the involved artery as observed on cerebral angiography within 72 h. The remaining 122 aSAH patients were enrolled in the current study.

Of the 122 patients, allele frequencies were 9.4% for the ε4 allele and 90.6% for the non-ε4 allele. The distributions of the APOE allele frequencies and genotypes are presented in **Table 1**. The samples demonstrated Hardy–Weinberg equilibrium ($p > 0.05$).

The clinical data of the included patients are summarized in **Table 2**; these data include age, sex, Hunt and Hess grade and Fisher grade of CT scans, aneurysm site, and the type of treatment. The distribution of the baseline characteristics between the groups of patients with and without an APOE ε4 allele was not different ($p > 0.05$).

Effect of APOE ε4 Allele on ICP

All of the ICP analyses were based on values obtained from lumbar drainage. The patients were separated into two groups based on their LP values before treatment. ICP values of 20 mmHg were chosen because an ICP greater than 20 mmHg is a well-known threshold for treating patients with neurosurgery. Therefore, the normal ICP group included patients who had an ICP less than 20 mmHg, and the elevated ICP group consisted of patients with an ICP greater than 20 mmHg. In this study, 68 patients (55.7%) had a normal ICP, whereas 54 (44.3%) had an elevated ICP. The ICP was increased in good-grade patients with a Hunt and Hess grade of I–III. Fourteen of 21 patients with APOE ε4

TABLE 1 | Distribution of APOE genotype.

Genotype						Allele frequency		
ε2/2	ε2/3	ε2/4	ε3/3	ε3/4	ε4/4	ε2	ε3	ε4
0	15	4	86	15	2	7.8%	82.8%	9.4%

TABLE 2 | Baseline characteristics of patients with and without ε4 allele.

	Total series (n = 122)	Patients with ε4 allele (n = 21)	Patients without ε4 allele (n = 101)
Age			
≤65 years	80	10	70
>65 years	42	11	31
Sex			
Male	54	9	45
Female	68	12	56
H–H grade			
1 and 2	64	11	53
3	58	10	48
Fisher grade			
1 and 2	53	13	40
3	69	8	61
Site			
AcoA	50	9	41
Other	72	12	60
Treatment			
Clipping	98	16	81
Coiling	24	5	19

had an elevated ICP, which was significantly different from those without APOE ε4 ($p = 0.03$). According to the univariate analysis, patients with the ε4 allele had a higher incidence of elevated ICP than those without this allele ($p = 0.03$, 95% CI = 1.132–8.217, OR = 3.1). When the data were adjusted for significant risk factors in the multivariate analysis (age, sex, Hunt and Hess grade, Fisher grade, etc.), the association of the ε4 allele with the risk of elevated ICP was even more significant ($p = 0.009$, 95% CI = 1.481–15.432, OR = 4.780). Furthermore, elevated ICP was also associated with a worse Hunt–Hess grade ($p = 0.004$, 95% CI = 1.536–9.116, OR = 3.742) (**Table 3**). The patient's age, sex, Fisher grade, and aneurysm site were not statistically associated with ICP.

Assessment of the APOE ε4 Allele and Cerebral Perfusion

As shown in **Table 4**, in the internal capsule area, CBF was 33.03 mL/100 g/min in patients with ε4 allele and 37.77 mL/100 g/min in those without ε4 allele (difference, −4.74; 95% CI, 0.53–8.94 s, $p = 0.03$). In patients with APOE ε4, MTT was 6.29 s, and in those without ε4 allele, MTT was 5.33 s in internal capsule (difference, 0.47; 95% CI, −0.87 to −0.78 s, $p = 0.02$). As was TTP, patients with ε4 allele had a significantly longer TTP than patients without ε4 allele both in internal capsule (difference, 2.29; 95% CI, −3.64 to −0.93 s, $p = 0.02$) and external capsule (difference, 1.09; 95% CI, −2.16 to −0.01 s, $p = 0.04$). These results suggested that patients with ε4 allele had a significant abnormality in brain cerebral perfusion in internal capsule and other whiter matter regions, such as external capsule (**Figure 1**).

DISCUSSION

From the study of 122 good-grade aSAH patients, our major finding is that those aSAH patients carrying the APOE ε4 allele are predisposed to elevate ICP within 72 h of the ictus, after controlling for age, the severity of the hemorrhage, the aneurysm location, and other factors. Moreover, patients with ε4 allele had a significant abnormality in brain cerebral perfusion in white matter (especially in the internal capsule area). The current study provides some initial clinical evidence that the APOE ε4 allele is associated with a detrimental effect on a patient's early response to aSAH.

Recently, particular attention has been paid to the APOE gene. apoE is associated with complex neuroprotective functions in the biochemical network of SAH (10, 18, 19). However, the neuroprotective effectiveness of the apoE4 isoform is reduced when compared with the other isoforms, and this decreased effectiveness has designated the ε4 allele as a sort of "frailty protein" and a potential risk factor. Several possible mechanisms might be involved in different ways (10, 18): (i) apoE4 might be a defective free radical scavenger; (ii) patients with the apoE4 protein could have impaired modulation of the brain inflammatory response to SAH, due to unregulated cytokine cascades; or (iii) reduced membrane repair and synaptic plasticity might occur.

Although controversial, increasing evidence indicates that the APOE ε4 genotype predisposes the patient to a poor outcome following aSAH (11, 12). In the Chinese population, the ε4 allele is also thought to be a possible risk factor for poor outcomes following aSAH (20). In our previous work, a series of follow-up clinical studies also demonstrated that patients with the APOE ε4 allele were prone to CVS and brain dysfunction, instead of rebleeding, after spontaneous SAH, which can also contribute to poor outcomes (21, 22).

In aSAH patients, global hypoperfusion caused by increased ICP and focal ischemia induced by vasospasm are common and devastating outcomes. In recent decades, CVS has become the focus of a large number of clinical and experimental research efforts. Although vasospasm is regarded as the primary cause of mortality and neurological morbidity in patients initially surviving aSAH, therapies designed to prevent and treat vasospasm remain limited (4, 23). Increasing evidence has led researchers to cast doubt on the importance of vasospasm in the setting of SAH. In recent years, EBI has been suggested to play a key role in aSAH patients' clinical deterioration and subsequent poor outcomes.

A previous study conducted on non-comatose patients with aSAH found that the presence of the ε4 allele increased the risk of clinical vasospasm, enhanced cognitive morbidity, and delayed ischemic neurologic deficit recovery (24). As increased ICP is common after aSAH, even in patients with good clinical grades, outcomes are negatively correlated with increased ICP. ICP appears to be a stronger predictor than the influence of vasospasm (25). To our knowledge, this relationship has not been reported in the clinical studies exploring the APOE gene's influence on ICP in the early stages of aSAH. In the present study, we measured ICP using lumbar drainage before surgery as a surrogate measurement, and we demonstrated that patients with the APOE ε4 polymorphism

TABLE 3 | Intracranial pressure logistic regression.

Characteristic	Univariate			Multivariate		
	p Value	OR	95% CI	*p* Value	OR	95% CI
APOEε4	0.027*	3.1	1.132–8.217	0.009*	4.780	1.481–15.432
Sex	0.256	0.7	0.320–1.355	0.438	0.717	0.309–1.664
Age	0.821	0.9	0.432–1.947	0.416	0.669	0.254–1.762
H–H grade	0.022*	2.4	1.132–4.879	0.004*	3.742	1.536–9.116
Fisher grade	0.866	1.1	0.517–2.189	0.133	2.013	0.809–5.008
Site	0.247	1.5	0.740–3.218	0.022	3.013	1.176–7.717

OR, odds ratio; CI, confidence interval.
**Significant difference ($p < 0.05$).*

TABLE 4 | Cerebral perfusion in patients with and without ε4 allele.

APOEε4	Mean CBV (mL/100 g)		Mean CBF (mL/100 g/min)		Mean MTT (s)		Mean TTP (s)	
	Yes	No	Yes	No	Yes	No	Yes	No
Caudate nucleus	4.28 ± 2.36	4.19 ± 2.58	52.01 ± 6.56	54.45 ± 7.78	4.58 ± 2.93	4.17 ± 1.7	24.36 ± 1.52	23.43 ± 1.28
Difference of means (95% CI; *p* value)	0.09 (−1.79 to 1.61; $p = 0.91$)		−2.44 (−2.59 to 7.46; $p = 0.33$)		0.41 (−2.08 to 1.26; $p = 0.62$)		0.93 (−1.91 to −0.52; $p = 0.06$)	
Internal capsule	3.07 ± 0.86	3.15 ± 1.29	33.03 ± 5.50	37.77 ± 6.49	6.29 ± 0.71	5.82 ± 0.25	28.43 ± 1.89	26.14 ± 1.98
Difference of means (95% CI; *p* value)	0.08 (−0.69 to 0.85; $p = 0.83$)		−4.74 (0.53 to 8.94; $^*p = 0.03$)		0.47 (−0.87 to −0.78; $^*p = 0.02$)		2.29 (−3.64 to −0.93; $^*p = 0.02$)	
Thalamus	3.78 ± 1.14	3.62 ± 1.04	41.98 ± 6.93	43.95 ± 6.68	5.36 ± 0.91	5.04 ± 1.01	21.87 ± 1.81	22.11 ± 2.26
Difference of means (95% CI; *p* value)	0.16 (−0.93 to 0.61; $p = 0.67$)		−4.04 (−2.78 to 6.72; $p = 0.40$)		0.32 (−0.98 to 0.35; $p = 0.35$)		−0.24 (−1.18 to 1.67; $p = 0.73$)	
External capsule	3.34 ± 0.86	3.20 ± 1.05	36.21 ± 7.21	39.96 ± 7.64	6.24 ± 1.41	5.99 ± 1.30	25.69 ± 1.46	24.60 ± 1.61
Difference of means (95% CI; *p* value)	0.14 (−0.81 to 0.53; $p = 0.67$)		−3.75 (−1.44 to 8.94; $p = 0.15$)		0.26 (−1.2 to 0.69; $p = 0.59$)		1.09 (−2.16 to −0.01; $^*p = 0.04$)	
Cortex	4.17 ± 1.13	4.00 ± 1.04	50.71 ± 8.40	52.31 ± 7.32	4.91 ± 1.21	4.83 ± 1.39	24.08 ± 2.61	22.40 ± 2.66
Difference of means (95% CI; *p* value)	0.17 (−0.93 to 0.57; $p = 0.63$)		−1.60 (−3.90 to 7.10; $p = 0.15$)		0.08 (−0.99 to 0.82; $p = 0.86$)		1.68 (−3.53 to 0.16; $p = 0.07$)	

CBV, cerebral blood volume; CBF, cerebral blood flow; MTT, mean transit time; TTP, time-to-peak; CI, confidence interval.

**Significant difference ($p < 0.05$).*

were predisposed to the presence of elevated ICP during the early phases of aSAH. In one TBI study, APOEε4 could increase cellular and tissular vulnerability (26), Olivecrona and coworkers found that there was no statistically significant difference in the ICP or cerebral perfusion pressure (CPP) of ε4 and non-ε4 patients with severe TBI who were treated with an ICP-targeted therapy (24). These results are apparently in contrast with those of our study. However, the two reports are not actually comparable because of their different neurological diseases, inclusion/exclusion criteria, and so on.

Early brain injury is believed to arise from significant pathophysiological mechanisms that occur in the brain during aSAH (2, 3). The acute rise in ICP, which has been demonstrated in both clinical studies and experimental animal models, results from the initial mass effect of the blood flowing into the subarachnoid space (27, 28), impeded CSF drainage (29), cerebrovascular dysfunction (30), and the development of cerebral edema (31). Elevated ICP may be correlated with the extent of EBI (32). As the pressure rises, a compensatory decrease in CPP occurs. The mechanism behind this relationship may be related to the Monroe–Kelly hypothesis. If the compensatory mechanism is not sufficient to support critical levels of brain perfusion, increased ICP and subsequently decreased CPP can result in significant reductions in CBF, leading to the deterioration of neurological function. apoE4 exerts a strong influence of cerebrovasculature dysfunction and disrupts CBF (33). In our previous study, APOEε4 carriers exhibit MTT prolongation in CTP scanning within 24 h (6). We further measured the region-specific response to cerebral perfusion in this study. We found a significant prolongation of MTT and TTP in the internal capsule and TTP in the external capsule of patients with ε4 allele. Although the reduction of values are of small differences, the ε4 aSAH patients presented a lower CBF in regions measured in this study, while the internal capsule region presented a significant difference. Furthermore, the MTT prolonged over 5.9 s in some regions, such as internal capsule. Our previous study indicated APOEε4 as an independent risk factor for prolonged MTT over 5.9 s, suggestive of increased risk of DCI and poor outcome in APOEε4 patients (6). Meanwhile, a significant reduction of CBF was seen in internal capsule of patients with ε4 allele. Previous study demonstrates that astrocytes are capable of eliciting both vasoconstriction and vasodilation, then control of CBF in brain (34). The apoE4-induced detrimental changes may be linked to astrocyte activation (33). Although several limitations of CTP should be considered, this technology may reflect the white matter injury indirectly according to regional perfusion. The abnormality in brain cerebral perfusion in white matter regions suggested that patients with ε4 allele might suffer more serious white matter injury after aSAH.

White matter injury has recently been reported in clinical and experimental SAH (35, 36). Victims of SAH suffer most from global emotional and cognitive dysfunction and associated diffuse cerebral atrophy, and diffuse axonal injury may also be an important feature of SAH (37, 38). van Asch and coworkers also observed an abnormalities perfusion of white matter in acute hydrocephalus aSAH patients (39). Studies support the hypothesis that white matter injury is due to CVSs and perfusion disorders after a brain injury (40–42). Although this has been

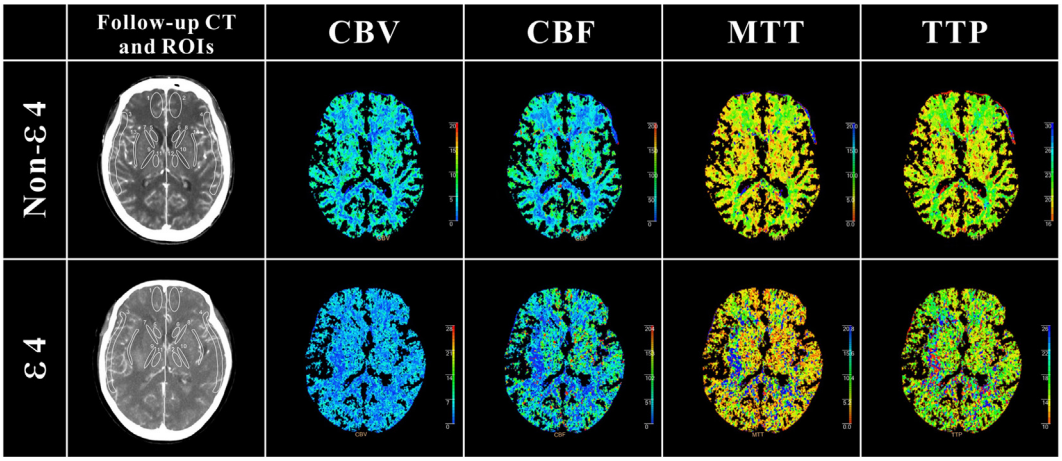

FIGURE 1 | **Definition of regions of interest (ROIs) in follow-up CT and cerebral perfusion images in ε4 and non-ε4 SAH patients**. ROIs were drawn in 5 different regions: cortex: ROIs 1 and 2 (anterior cerebral artery), ROIs 3 and 4 (middle cerebral artery); caudate nucleus: ROIs 5 and 6; internal capsule: ROIs 7 and 8 (anterior limb), ROIs 9 and 10 (posterior limb); thalamus external: ROIs 11 and 12; capsule: ROIs 13 and 14. As shown in cerebral perfusion images, APOE ε4 allele aneurysmal subarachnoid hemorrhage patients suffered more severe perfusion disorders, especially in white matter regions.

identified as the only proven drug to improve patients' outcomes after SAH, nimodipine, a kind of calcium antagonist, needed to advance the understanding of its effects on microcirculatory changes and cerebral perfusion after SAH. Thus, development of feasible SAH therapeutic strategies still needs more effort. Our previous study has identified ApoE-mimetic peptide COG1410 in EBI by preventing white matter injury after experimental SAH (43). Because ApoE-mimetic peptide is a modified peptide sequence from human apoE, this could indicate that apoE4 lacks a protective effect found in apoE2 and apoE3 in the biochemical network of SAH. Hence, APOEε4 may induce cerebral perfusion impairment *via* elevated ICP in the early phase, contributing to white matter injury in EBI following aSAH. Furthermore, increased postoperative ICP is common after early clipping, especially in poor-grade aSAH patients, and this might precipitate CVS-induced ischemic events in aSAH patients including the deterioration of neurological function and poor outcomes (44, 45). Patients with symptomatic CVS were excluded in this study, the results indicated that one of the most important factors in predicting the outcomes is correlated with elevated ICP, including good H–H grade aSAH patients with ε4 allele.

Although no previous clinical studies have specifically focused their attention on ICP after SAH, these results are supported by the experimental observations that wild-type mice treated with ApoE-mimetic peptide after experimental SAH decreased mortality, functional deficits and vasospasm (25), neurons apoptosis (46), and BBB disruption (47) as compared with vehicle-treated mice. Notably, in that study, SAH-affected mice expressing the human ε4 allele were prone to higher mortality rates and greater functional deficits compared to their human ε3 counterparts during the first 72 h after experimental SAH. These deficits were associated with a greater degree of cerebral edema and vasospasm in mice expressing the apoE4 isoform. Modulation of the CNS inflammatory response might be one mechanism by which APOE genotype affects EBI after SAH.

Limitations

There were several potential limitations of the current study. First, as blood is mainly located in the basal cisterns in aSAH patients, CSF outflow from the ventricles into the subarachnoid space should not be substantially impaired. At the same time, the location of the blood clot can present a barrier to the downstream flow of CSF from the convex subarachnoid space of the cerebral hemispheres through the foramen magnum into the spinal compartment. Thus, a partial obstruction might be present and render the LP lower than the actual ICP. Second, although lumbar drainage has been shown to be safe in SAH patients, the formation of pressure gradients remains a potential threat that could result in herniation and rebleeding. Therefore, lumbar drainage was only performed in the present study before aneurysm clipping or coiling. An additional method, such as continuous ICP monitoring, might be needed to verify our findings. Third, abnormality in brain cerebral white matter perfusion of ε4 allele aSAH patients was observed in this study. However, the specific reason of white matter injury after SAH is not entirely clear. The detail pathophysiological processes and clinical diagnosis strategy of white matter injury after SAH need to be further investigated both in experimental and clinical studies.

Conclusion and Outlook

We evaluated the association between the presence of the APOE ε4 allele and elevated ICP *via* invasive (LP) in this prospective study. Despite the limitations of the present study, these preliminary findings provide new evidence that the APOE ε4 allele predisposes patients to elevated ICP after aSAH. Meanwhile, APOE ε4 allele aSAH patients suffered more severe perfusion disorders in white matter regions. These clinical observations support the hypothesis that APOE plays an important role in the response of the CNS to EBI, possibly involving the adverse effects of apoE4 on white matter injury, neurobiology, and its potential links to certain risk factors, such as elevated ICP. To improve the

precision medicine, further studies are needed to elucidate the mechanisms by which the APOE ε4 allele can adversely affect a patient's response to EBI after aSAH.

ETHICS STATEMENT

The study was approved by the ethics committee of the coordinating institution and has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. All the patients gave their informed consent prior to their inclusion in the study. Informed consent was obtained from each patient directly.

AUTHOR CONTRIBUTIONS

Conception and design: YJ and J-hP. Acquisition of data: J-wP, X-hQ, and X-bY. Analysis and interpretation of data: YW, J-hD, W-fW, and C-rH. Drafting the article: J-hP and YJ. Reviewed submitted version of manuscript: YJ, X-cS, and L-gC. Statistical analysis: YW, J-hD, and J-wP. Study supervision: YJ, X-cS, and L-gC.

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Alberta Stroke Program Early CT Score Infarct Location Predicts Outcome Following M2 Occlusion

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Background: Although it is generally thought that patients with distal middle cerebral artery (M2) occlusion have a favorable outcome, it has previously been demonstrated that a substantial minority will have a poor outcome by 90 days. We sought to determine whether assessing the Alberta Stroke Program Early CT Score (ASPECTS) infarct location allows for identifying patients at risk for a poor 90-day outcome.

Methods: We retrospectively analyzed patients with isolated acute M2 occlusion admitted to a single academic center between January 2010 and August 2012. Infarct regions were defined according to ASPECTS system on the initial head computed tomography. Discriminant function analysis was used to define specific ASPECTS regions that are predictive of the 90-day functional outcome as defined as a modified Rankin Scale score of 3–6. In addition, logistic regression was used to model the relationship between each individual ASPECT region with poor outcome; for evaluation and comparison, odds ratios, *c*-statistics, and Akaike information criterion values were estimated for each region.

Results: Ninety patients with isolated M2 were included in the final analysis. ASPECTS score ≤6 predicted poor outcome in this cohort (sensitivity = 0.591, specificity = 0.838, $p < 0.001$). Using multiple approaches, we found that infarction in ASPECTS regions M3 and M6 were strongly associated with poor functional status by 90 days.

Conclusion: Infarction in ASPECTS regions M3 and M6 are key predictors of functional outcome following isolated distal M2 occlusion. These findings will be helpful in stratifying outcomes if validated in future studies.

Keywords: M2 occlusions, outcome, Alberta Stroke Program Early CT Score, stroke, thrombolysis

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INTRODUCTION

The site of arterial occlusion represents one of the most important factors determining outcome after anterior circulation ischemic stroke (1, 2). However, relatively little is known regarding outcome predicting variables in patients with distal middle cerebral artery (MCA) occlusion.

The Alberta Stroke Program Early CT Score (ASPECTS) was introduced to provide a structured infarct size and location analysis to aid clinical decision making (3). Its availability on initial evaluation of non-contrast head computed tomography (CT) makes it a relevant neuroimaging marker that does not require complex image post-processing. Its utility for acute treatment decision making in acute stroke patients with MCA occlusion has previously been documented (4). Specifically, stroke patients with a high pre-treatment ASPECTS are more likely to have a favorable outcome. However, because patients with distal MCA occlusion (M2) tend to have a high ASPECTS related to the sparing of subcortical tissues (5–7), a more granular understanding of the association of the ASPECTS with outcome in these patients is needed.

A better understanding of this issue is highlighted by the transformative results from the recent positive endovascular stroke trials (2, 4, 8–10). However, less than 3% of enrolled patients had an isolated M2 occlusion and the majority of patients experience a favorable outcome irrespective of endovascular therapy (4, 7, 11). Hence, identifying imaging parameters that predict poor outcome in this population may aid in the proper patient selection for therapy.

Therefore, we sought to determine whether information regarding infarct location encoded in the ASPECTS allows for defining patients at high risk for a poor functional outcome after isolated M2 occlusion in addition to the total ASPECTS score. We hypothesized that infarction in distinct ASPECTS location will be associated with a poor outcome.

MATERIALS AND METHODS

Study Sample

We performed a retrospective analysis of consecutive acute ischemic stroke patients admitted to a single academic center from January 2010 to August 2012. Only patients with isolated M2 occlusion on admission CT-angiography (CTA) were included. This study was approved by the Institutional Review Board of the University of Massachusetts Medical School. Because this was a retrospective analysis the consent requirement was waived. Included patients have been described as part of a prior study (12).

All patients had head CT performed on presentation to the emergency room. Patient demographics, comorbidities, pre-admission medications, laboratory data, treatment modality [conservative management versus acute intervention (intravenous thrombolysis and endovascular recanalization)], and stroke etiology (according to the Trial of Org 10172 in Acute Stroke Treatment classification) (13) after completion of diagnostic evaluation, were collected on all patients. Admission National Institutes of Health Stroke Scale and modified Rankin Scale (mRS) scores were assessed at the time of presentation and at 90 days by a stroke-trained physician or study nurse certified in the mRS (12). Good outcome at 90 days was defined as mRS ≤2.

Neuroimaging Protocol

All CT sequences were obtained on a 64-row detector Philips scanner. NCCT was performed in a non-helical mode at 120 KvP and 200 mA with data reconstruction at 5 mm axial slices. CTA was performed using 64 mm × 0.625 mm detector configuration with a pitch of 0.673, from the arch of aorta to the vertex using 120 KvP, 300 mA, and 0.5-s rotation time. Patients received 60–80 mL of Isovue 370 (Bracco Diagnostics, Princeton, NJ, USA) in the antecubital vein at a rate of 4 mL/s through a power injector followed by 40 mL saline. Three-dimensional orthogonal maximum intensity projection images were created in three planes.

Image Review and Analysis

Image review and analysis has been described in detail earlier (12). Briefly, CT and CTA were reviewed independently by study physicians masked to clinical data, follow-up scans, patient variables, and outcomes. The M2 segment was defined as the segment extending from the bifurcation/trifurcation of the MCA to the top of the Sylvian fissure to further division (12). For the purpose of this study, we performed an infarct location analysis on the initial head CT as defined by ASPECTS system (3). These areas included the insula (I), caudate nucleus (C), lentiform nucleus (L), internal capsule (IC), superior parietal lobe (M6), precentral and superior frontal lobe (M5), anterior superior frontal lobe (M4), inferior parietal and posterior temporal lobe (M3), temporal lobe (M2), and anterior inferior frontal lobe (M1) (14). Scoring was conducted by an experienced reader (Muhib Khan) trained in ASPECTS (http://www.aspectsinstroke.com).

Statistical Methods

All analyses were conducted using SAS Software 9.4 (SAS Inc., Cary, NC, USA). Poor outcome (mRS 3–6) was modeled with ASPECTS score using multivariable logistic regression, both as an ordinal measure and dichotomized >6 versus ≤6. Discriminant function analysis (DFA) was used to derive a single statistical function from all ASPECTS regions that distinguishes between a poor and favorable outcome; ASPECT regions were then evaluated by how well each region correlated with the derived discriminant function distinguishing between a poor and favorable outcome. DFA was used as it is more robust than multivariable logistic regression for small sample sizes. DFA was produced using the CANDISC procedure. In order to confirm and quantify the relationship between each region and outcome, logistic regression was used to model the relationship between each individual ASPECT region with poor outcome using the LOGISTIC procedure; odds ratios (OR) (effect size), *c*-statistics [area under the receiver operating characteristics curve (AUC)], and Akaike information criterion (AIC) (AIC-relative model fit) values were, therefore, estimated for each region. In addition, sensitivity, specificity, as well as positive and negative predictive values and likelihood ratios were determined for each ASPECTS region predicting poor outcome using generalized estimating equations (GEE), which allowed multiple observations (regions) to be nested within patients, using the GLIMMIX procedure. Group differences examined in **Table 1** were compared using the χ^2-square test or Wilcoxon test. A two sided $p < 0.05$ (when applicable) was considered significant and all estimates were calculated for 95% confidence interval (95% CI).

RESULTS

Overall, 90 patients with isolated M2 occlusions were included for analysis. Among these, 66 (73%) patients had an ASPECTS of >6 and the majority of patients (69%) had a good 90-day outcome. Baseline characteristics of included patients as stratified by ASPECTS ≤6 versus >6 (15) are summarized in **Table 1**.

The mean ASPECTS score was 7.1, 95% CI 6.8–7.4. An ASPECTS score ≤6 was associated with poor outcome (sensitivity = 0.591, specificity = 0.838, $p < 0.001$). Logistic regression analysis indicated that for every unit decrease in ASPECTS score, the odds of poor outcome increased more than twofold (OR: 2.32, 95% CI 1.50–3.59, AUC = 0.799, $p < 0.001$). We then sought to determine whether distinct infarct regions encoded by the ASPECTS allow for defining patients at risk for a poor functional outcome. Because more than one ASPECTS region was frequently infarcted in a given patient, DFA was used to model the relationship of region on poor outcome. **Table 2** summarizes each region's relationship with poor outcome derived from the DFA whereby larger loading and coefficient values indicate a stronger relationship with the statistically derived discriminant function that distinguished between and poor and favorable outcome. In particular, infarction in M3 had the strongest relationship with the discriminant function relative to all other regions, followed by M6. The relationship with each region, alone, was then quantified using logistic regression, which indicated that infarction in M3 and M6 had statistically significant and relatively large OR (right M3 = 115, left M3 = 14.9, right M6 = 25.7, left M6 = 10.4), indicating a relationship with poor outcome. Moreover, infarction in M3 and M6 had the largest AUCs indicating superior discrimination between good and poor outcomes, relative to all other areas. M3 and M6 also had the smallest AIC values, indicating that models of poor outcome using M3 and M6 were superior to models using other ASPECTS encoded regions, i.e., the combined analysis with logistic regression and DFA indicates that infarction in cortical M3 and adjacent M6 ASPECTS regions on either side are the strongest predictors of a poor outcome after M2 occlusion. Infarction in the left M5, right M2, and right M5 should also be considered as indicators of poor outcome as they were statistically significant or approached significance relative to the remaining regions.

TABLE 1 | Baseline characteristics (unadjusted) of the patient sample as stratified by Alberta Stroke Program Early CT Score (ASPECTS).

Characteristics	ASPECTS ≤6 ($n = 24$)	ASPECTS >6 ($n = 66$)	*p*-Value
Age, years (IQR)	79.5 (67–85.5)	75.5 (62–85)	0.430
Female (%)	66.7	51.5	0.200
Admission NIHSS (IQR)	16 (6–24)	7 (4–10)	0.009
i.v. rtPA (%)	21	27	0.536
Hypertension (%)	71	82	0.259
Dyslipidemia (%)	46	61	0.211
Diabetes (%)	25	38	0.255
Prior stroke or TIA (%)	13	15	0.751
Atrial fibrillation (%)	29	32	0.810

IQR, interquartile range, i.v., intravenous; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; PH, parenchymal hemorrhage Type 1 and 2; rtPA, recombinant tissue plasminogen activator; TIA, transient ischemic attack.

TABLE 2 | Discriminate function analysis, prediction, and performance of individual Alberta Stroke Program Early CT Score region infarction indicative of a poor outcome.

Area	Discriminant function		Prediction		Performance			
	Loading	Beta	OR	95% CI	AUC	95% CI	AIC	*p*
Right								
M1	0.15	0.22	1.97	(0.36–10.82)	0.56	(0.40–0.71)	47.72	0.4358
M2	0.43	0.51	5.54	(1.20–25.68)	0.70	(0.53–0.87)	43.19	0.0286
M3	0.93	0.93	115	(9.32–na)	0.91	(0.81–1.00)	23.12	0.0002
M4	−0.07	0.05	0.70	(0.12–4.20)	0.53	(0.38–0.68)	48.16	0.6998
M5	0.35	0.04	4.00	(0.85–18.84)	0.66	(0.49–0.83)	44.95	0.0795
M6	0.66	0.40	25.7	(2.76–239.81)	0.81	(0.69–0.94)	34.87	0.0044
C	0.02	0.36	1.15	(0.09–14.19)	0.51	(0.40–0.61)	48.30	0.9132
IC	0.02	0.09	1.15	(0.09–14.19)	0.51	(0.40–0.61)	48.30	0.9132
L	0.03	0.45	1.17	(0.18–7.56)	0.51	(0.37–0.65)	48.29	0.8715
Insula	0.06	0.21	1.25	(0.30–5.23)	0.53	(0.34–0.71)	48.22	0.7599
Left								
M1	−0.19	−0.28	–	–	0.53	(0.50–0.57)	57.18	0.9728
M2	0.27	0.22	2.43	(0.62–9.56)	0.61	(0.44–0.78)	56.91	0.2038
M3	0.77	0.69	14.90	(2.75–80.29)	0.79	(0.66–0.93)	45.61	0.0017
M4	−0.19	0.00	–	–	0.53	(0.50–0.57)	57.18	0.9728
M5	0.59	0.63	12.63	(1.48–107.53)	0.73	(0.62–0.85)	49.76	0.0203
M6	0.66	0.26	10.40	(1.97–54.87)	0.76	(0.62–0.90)	48.73	0.0059
C	−0.22	−0.32	–	–	0.55	(0.50–0.59)	56.69	0.9685
IC	−0.30	0.18	–	–	0.58	(0.53–0.58)	55.14	0.9581
L	−0.19	0.18	0.38	(0.04–3.35)	0.56	(0.45–0.67)	57.66	0.3821
Insula	−0.16	−0.09	0.60	(0.16–2.27)	0.56	(0.39–0.73)	58.02	0.4524

Loading and beta coefficients derived from discriminant function analysis, where stronger positive values relate to the function of poor outcome. Odds ratios (ORs), area under the receiver operating characteristics curve (AUC), and Akaike information criterion (AIC) are derived from logistic regression modeling, which estimate size of effect, diagnostic performance, and model fit, respectively.

TABLE 3 | Sensitivity, specificity, positive and negative predictive values, and likelihood ratios of individual Alberta Stroke Program Early CT Score region infarction for poor outcome (mRS >2).

Area	Sensitivity	Specificity	PPV	NPV	+LR	−LR
Right						
M1	0.27	0.84	0.43	0.72	1.70	0.87
M2	0.64	0.76	0.54	0.83	2.65	0.48
M3	0.91	0.92	0.83	0.96	11.36	0.10
M4	0.18	0.76	0.25	0.68	0.76	1.08
M5	0.73	0.60	0.44	0.83	1.82	0.45
M6	0.91	0.72	0.59	0.95	3.25	0.13
C	0.09	0.92	0.33	0.70	1.14	0.99
Internal capsule (IC)	0.09	0.92	0.33	0.70	1.14	0.99
L	0.18	0.84	0.33	0.70	1.14	0.97
Insula	0.46	0.60	0.33	0.71	1.15	0.90
Left						
M1	0.00	0.93	0.00	0.78	0.00	1.08
M2	0.64	0.58	0.28	0.86	1.52	0.63
M3	0.82	0.77	0.47	0.94	3.52	0.24
M4	0.00	0.93	0.00	0.78	0.00	1.08
M5	0.91	0.56	0.34	0.96	2.06	0.16
M6	0.82	0.70	0.41	0.94	2.71	0.26
C	0.00	0.90	0.00	0.78	0.00	1.11
IC	0.00	0.84	0.00	0.76	0.00	1.19
L	0.09	0.80	0.10	0.77	0.45	1.14
Insula	0.46	0.42	0.17	0.75	0.79	1.29

PPV, positive predictive value; NPV, negative predictive value; +LR, positive likelihood ratio; −LR, negative likelihood ratio.

Last, each region was evaluated for diagnostic performance of poor outcome. Using GEE, we found that M3, M5, and M6 for both the right and the left had a high sensitivity and specificity ($p < 0.01$) for predicting a poor outcome (**Table 3**). Specifically, infarction in right M3 region was highly sensitive (0.91) and specific (0.92) of poor outcome.

DISCUSSION

The most important findings of our study are that infarction in the M3 and M6 ASPECTS region predict a poor outcome after isolated M2 occlusion. We and others have previously shown that a substantial minority of patients with M2 occlusion have a poor outcome by 3 months (7, 11, 12, 16). Our results show that the anatomical and geometric information of the ASPECTS allows for more specific identification of patients at high risk for poor outcome after isolated M2 occlusion.

The ASPECTS template for anatomical lesion mapping within the MCA territory has the advantage that it does not require elaborate volumetric image analysis and allows for identifying patients likely to have a poor outcome in the emergency setting (4, 17, 18). The dichotomized ASPECTS score has been used to predict outcome in earlier studies, which found an ASPECTS greater than 6 to 7 to be predictive of good outcome (3, 4, 17, 19). Recent multicenter cohort of M2 occlusion patients undergoing thrombectomy also showed that ASPECTS ≥6 predicts a good outcome (7). Consistent with these prior results, we found that ASPECTS ≥6 predicted a good outcome.

Using DFA, we found that in our sample, infarction in M3 and M6 locations were most predictive of a poor outcome. This is not too surprising because even relatively small infarcts in the M3 region (which includes the language centers located within the inferior parietal and posterior temporal lobes) and M6 region (which includes the primary motor cortex) may cause significant disability (20, 21) related to ensuing motor deficits and aphasia (22, 23). Of note, though infarction of subcortical structures such as lentiform nucleus and IC have been identified as predictors of outcome (20, 24, 25), we did not find such an association in our study. However, this discrepancy may be explained by the fact that our study was underpowered to detect such an association due to low number of patients with a subcortical infarction. It is possible that subcortical infarction occurred mostly in patients who originally had an occlusion of the M1-segment of the MCA [which gives rise to the lenticulostriate arteries to supply the striatocapsular region (26, 27)] and then subsequent clot migration to the M2 segment [which predominantly supplies the cerebral cortex and adjacent white matter (26–28)] by the time of CTA.

We did not find any effect on outcome based on hemispheric laterality of stroke. Earlier studies have shown an impact of hemispheric laterality on functional outcomes after ischemic stroke (29–32). We feel that smaller infarct volume and neglect might have played a role in minimizing the effect of lateralization. Further study is required to determine the effects of lesion laterality and the impact on stroke outcome. Endovascular therapy in these patients has recently been shown to improve outcomes (7). Therefore, further research is needed using an external stroke cohort evaluating our findings to improve patient selection for this particular group. We envision the development of an imaging index that incorporates assessments of ischemic core volumes and location in conjunction with markers of collateral and perfusion status. Such an index will allow for accurate and rater unbiased selection of patients for emergent recanalization therapies for M2 occlusion.

The strengths of our study relate to the analysis of a well-defined patient population based on advanced intracranial vascular imaging. We utilized multiple statistical methods in a stepwise fashion to identify the ASPECTS regions, which predict outcomes in this population. The collection of a large number of clinically relevant variables contributed to improved data quality while limiting the potential for misclassification. Limitations of our study relate to its retrospective design and relatively small sample size. However, to account for the low sample size, we used DFA instead of logistic regression alone. Williams and Titus found that, as a general rule, sample size should be about 3xP variables [in our case $p = 10$, for each group (30)] (33). In addition to mitigate the risk of DFA-related model overfitting, we also provided the results of simple logistic regression as well as repeated measures logistic regression with modeling of the different ASPECTS regions within each patient. Importantly, our models were stable as indicated by the consistent results across model solutions (sensitivity, specificity, loadings, odds ratio, area under the receiver operator characteristics curve, AIC, and *p*-Values). Further, diagnostic and therapeutic modalities were used at the treating stroke physician's discretion, which may have introduced bias. Moreover, non-contrast CT head was used to determine ASPECTS, which might be less sensitive than newer imaging modalities. Our findings require confirmation

in further, prospective studies and should only be considered hypothesis generating.

CONCLUSION

In conclusion, this study shows that infarct topography as defined by ASPECTS allows for prediction of functional outcome after M2 occlusion. These findings may be helpful for stratifying outcomes if validated in other studies.

AUTHOR CONTRIBUTIONS

MK: study concept and design, data acquisition, statistical analysis, interpretation of data, and drafting the article. GB: statistical analysis, interpretation of data, and drafting the article. RG: data acquisition, interpretation of data, and critical revision of the manuscript for important intellectual content. BS: interpretation of data and critical revision of the manuscript for important intellectual content. NH: data acquisition, interpretation of data, drafting the article, and critical revision of the manuscript for important intellectual content.

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White Matter Correlates of Auditory Comprehension Outcomes in Chronic Post-Stroke Aphasia

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Neuroimaging studies have shown that speech comprehension involves a number of widely distributed regions within the frontal and temporal lobes. We aimed to examine the differential contributions of white matter connectivity to auditory word and sentence comprehension in chronic post-stroke aphasia. Structural and diffusion MRI data were acquired on 40 patients with chronic post-stroke aphasia. A battery of auditory word and sentence comprehension tests were administered to all the patients. Tract-based spatial statistics were used to identify areas in which white matter integrity related to specific comprehension deficits. Relevant tracts were reconstructed using probabilistic tractography in healthy older participants, and the mean values of fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD) of the entire tracts were examined in relation to comprehension scores. Anterior temporal white matter integrity loss and involvement of the uncinate fasciculus related to word-level comprehension deficits ($R_{FA} = 0.408$, $P = 0.012$; $R_{MD} = -0.429$, $P = 0.008$; $R_{AD} = -0.424$, $P = 0.009$; $R_{RD} = -0.439$, $P = 0.007$). Posterior temporal white matter integrity loss and involvement of the inferior longitudinal fasciculus related to sentence-level comprehension deficits ($R_{FA} = 0.382$, $P = 0.02$; $R_{MD} = -0.461$, $P = 0.004$; $R_{AD} = -0.457$, $P = 0.004$; $R_{RD} = -0.453$, $P = 0.005$). Loss of white matter integrity in the inferior fronto-occipital fasciculus related to both word- and sentence-level comprehension (word-level scores: $R_{FA} = 0.41$, $P = 0.012$; $R_{MD} = -0.447$, $P = 0.006$; $R_{AD} = -0.489$, $P = 0.002$; $R_{RD} = -0.432$, $P = 0.008$; sentence-level scores: $R_{FA} = 0.409$, $P = 0.012$; $R_{MD} = -0.413$, $P = 0.011$; $R_{AD} = -0.408$, $P = 0.012$; $R_{RD} = -0.413$, $P = 0.011$). Lesion overlap, but not white matter integrity, in the arcuate fasciculus related to sentence-level comprehension deficits. These findings suggest that word-level comprehension outcomes in chronic post-stroke aphasia rely primarily on anterior temporal lobe pathways, whereas sentence-level comprehension relies on more widespread pathways including the posterior temporal lobe.

Keywords: aphasia, stroke, white matter, diffusion tensor imaging, outcome

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INTRODUCTION

The era of modern neuroimaging has clarified that language extends well beyond the classical network composed of Wernicke's area, the arcuate fasciculus (AF), and Broca's area (1, 2). The putative location of Wernicke's area has shifted over time, and recent studies suggest that auditory comprehension of words relies on cortex considerably anterior to the traditional location of Wernicke's area in the posterior temporal lobe (3). A prominent study recently examined patterns of cortical atrophy in primary progressive aphasia, finding an anatomical dissociation, in which word-level auditory comprehension related to cortical thinning in the anterior temporal lobe, whereas sentence-level auditory comprehension related to thinning in a more widespread network of posterior temporal and frontal sites (4). The differences in localization of auditory comprehension in primary progressive aphasia from the classical localization based on stroke lesions were attributed to the white matter damage associated with stroke.

Indeed, language processing depends not only on cortical regions but also on the white matter fiber bundles that connect them (5). Recent diffusion tensor imaging (DTI) studies have suggested that the dual streams connecting frontal and temporal language areas differentially support particular aspects of language comprehension processing in the context of healthy participants (6, 7) and pathological conditions such as primary progressive aphasia (8). Only a few studies have used DTI to analyze white matter damage in post-stroke aphasia (9–12), and these have not come to a consensus regarding the contributions of specific tracts to particular auditory comprehension impairments. This likely relates to the small number of participants in these studies, and the investigation of either word- or sentence-level comprehension, but not both. Further, some these prior studies only either examined direct lesion load in tracts, or assessed relationships between comprehension and certain DTI metrics of white matter in the tract (9, 10). As such, the contributions of specific white matter tracts to different aspects of auditory language comprehension remain incompletely understood.

In the present study, we adopted tract-based spatial statistics (TBSS) to identify critical regions of white matter lesions related to severity of word- and sentence-level comprehension deficits in chronic post-stroke aphasia. We then used probabilistic DTI tractography in a group of age-matched healthy older participants to reconstruct specific white matter tracts implicated by TBSS and examined the relationship between the integrity of these tracts in patients and both word- and sentence-level comprehension. We hypothesized that different ventral or dorsal white matter tracts sustain different aspects of comprehension in chronic post-stroke aphasia, in particular that word-level comprehension deficits relate to anterior temporal lobe white matter damage, whereas sentence-level comprehension deficits relate to more posterior temporal lobe white matter damage.

MATERIALS AND METHODS

Participants

Forty (14 females) chronic left hemisphere stroke survivors were recruited in the study with inclusion criteria as follows: native English speaker; at least 6 months post-stroke; able to follow testing instructions; and no history of other significant neurological illnesses. Demographics and language scores for the group are listed in **Table 1**. All patients had aphasia at the time of stroke based on medical records and received speech–language therapy.

Probabilistic tract reconstruction was performed in 27 healthy older participants (16 female) without neurological and psychiatric disorder. The mean age was 59.8 (±14.3) years; mean education was 16.3 (±2.6) years. Among them, 24 were right-handed, 2 left-handed, and 1 ambidextrous.

The study was approved by the Georgetown University Institutional Review Board, and written informed consent was obtained from all study participants.

Language Comprehension Assessment and Composite Scores

Word-level auditory comprehension was tested with the Auditory-Verbal Comprehension Word Recognition subtest of the Western Aphasia Battery-Revised (WAB-R) (13) and an in-house word-to-picture matching task, in which the tester speaks a word aloud and the participant must select a picture corresponding to the word from among five semantic foils presented on a computer screen. There are 48 trials, and all words are concrete nouns. There is no time limit for response. The test was previously normed on 22 healthy elderly participants matched for age and education (14). For sentence comprehension assessment, the tests included the Auditory-Verbal Comprehension Yes/No and Sequential Commands subtests of the WAB-R, and the Boston Diagnostic Aphasia Examination subtests: complex ideational materials, semantic probe, and embedded sentences tasks. Using these scores, we calculated word-level comprehension (WLC) and sentence-level comprehension (SLC) composite scores to provide robust measurements of these two aspects of comprehension.

TABLE 1 | Demographic data and language measures in patients.

Variables	Patients
Age at screening (years)	59.6 ± 10.1
Gender (F/M)	14/26
Education level (years)	16.3 ± 2.9
Handedness (R/L/ambidextrous)	33/6/1
Lesion volume (ml)	101.1 ± 74.1
Time from stroke (months)	45.3 ± 38.6
Language tests	
Word-level composite	0.91 ± 0.12 (0.45–1.00)
Word recognition (60)[a]	53.18 ± 9.31 (27–60)
Word-to-picture matching (48)	44.53 ± 5.32 (22–48)
Sentence-level composite	0.77 ± 0.16 (0.45–0.99)
AVCom Yes/No (60)[a]	55.43 ± 5.04 (39–60)
AVCom sequential commands (80)[a]	57.28 ± 18.50 (10–80)
Complex ideational materials (12)[b]	7.90 ± 3.09 (2–12)
Semantic total scores (60)[b]	54.68 ± 5.47 (34–60)
Embedded sentences (10)[b]	6.38 ± 2.72 (1–10)
Pyramids and Palm Trees test	44.28 ± 4.76 (27–49)

F, female; M, male; R, right-handed; L, left-handed; AVCom, auditory-verbal comprehension.

[a]*Western Aphasia Battery-Revised.*

[b]*Boston Diagnostic Aphasia Evaluation.*

For each language test, the maximum score is shown in brackets.

Raw scores were normalized by dividing by the maximum score of each task, and these normalized scores for each component of comprehension were averaged. Because sentence-level comprehension encompasses word-level comprehension, deficits in either could cause decreased SLC scores. Thus, the WLC scores were regressed out of the SLC scores to obtain a final residual SLC score that controls for word comprehension deficits. Nonverbal semantic performance was additionally assessed with the Pyramids and Palm Trees (PPT) test (15).

Image Acquisition

Subjects were scanned on a 3.0-T Siemens Trio scanner at the Georgetown University Medical Center. The high-resolution T1-weighted images were acquired with the following parameters: TR = 1,900 ms; TE = 2.56 ms; flip angle = 9°; 160 contiguous 1 mm sagittal slices; field of view = 250 mm × 250 mm; matrix size = 246 × 256, voxel size = 1 mm × 1 mm × 1 mm; slice thickness = 1 mm. Diffusion data were acquired using a single-shot echo-planar imaging sequence with the following parameters: TR = 7,500 ms; TE = 87 ms; flip angle = 90°; field of view = 240 mm × 240 mm; matrix size = 96 × 96, voxel size = 2. 5 mm × 2.5 mm × 2.5 mm; slice thickness = 2.5 mm; sagittal slice number = 64 slices. Sixty diffusion volumes weighted with a b_{max} value of 1,100 s/mm^2 and 10 volumes with no diffusion gradient were acquired. An additional 10 volumes with a low diffusion gradient (b_{min} = 300 s/mm^2) were collected to reconstruct a diffusion tensor from the combination of volumes with b_{min} and b_{max} diffusion weighting, which can reduce the vascular contribution to the diffusion parameters as well as partial volume effects as a result of the signal intensity of CSF (16–18).

Imaging Data Preprocessing

Structural MRI Lesion Delineation

Lesion masks of patients were created by manually tracing stroke damage on the native 3D T1 images by using MRIcron (19). Lesion masks were checked by two board-certified neurologists (Shihui Xing and Peter E. Turkeltaub). Structural T1 images were registered to a Montreal Neurological Institute (MNI) brain template in standard space using the unified segmentation tools implemented in Statistical Parametric Mapping software (SPM8)[1] running under Matlab R2014a (20). Deformations were then applied to warp the lesion masks into the MNI space (21). An overlap of patients' lesions is shown in **Figure 1**.

Diffusion MRI Lesion Analysis

Preprocessing of the diffusion images was performed using the FMRIB Software Library (FSL).[2] For each subject, the DWI datasets were preprocessed using FSL diffusion toolbox. Eddy current distortions and motion artifacts were corrected by registering each diffusion volume to the non-diffusion volume with an affine transform. Whole-brain maps of voxelwise DTI metrics were extracted including fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD).

Tract-Based Spatial Statistical Analysis

Whole-brain voxelwise analyses of the respective DTI metrics data were carried out with TBSS analyses (22). Briefly, FA maps were aligned to an averaged FA template in MNI standard space using a non-linear registration with FNIRT in FSL and individual lesion drawings were employed as masks to avoid deformation of the lesion area. An average FA map was created and a skeleton map representing the center of the white matter common to all patients was computed with a threshold at 0.2. All registered FA maps were finally projected into the skeleton. The same procedure was performed on MD, AD, and RD maps. Controlling for age and total lesion volume, separate regression analyses were conducted to identify voxels in which the white matter signal related to WLC and SLC with lesion masks to exclude lesioned voxels in each patient. All statistics were performed with 5,000 random permutations and a threshold-free cluster enhancement correction (23). Results were family wise error corrected and thresholded at $P < 0.05$.

Tract-Specific Analysis

To examine relationships of more comprehensive measures of entire tracts to behavioral performance, we conducted a tract-specific analysis. To precisely localize relevant tracts, we reconstructed the left inferior fronto-occipital fasciculus (IFOF), inferior longitudinal fasciculus (ILF), and uncinate fasciculus (UF) tracts implicated by the TBSS analysis (see Results) in 27 age-matched healthy subjects. For completeness, we also reconstructed the major dorsal language stream tract (AF) as well. Paired regions in the left hemisphere was defined as "seed" and "target" to reconstruct connections between these areas as previously described (24, 25). The regions were reversely transferred to the subject's native DWI space using non-linear registrations for FA images. Fiber tracking was performed using a probabilistic tractography algorithm based on Bayesian estimation of diffusion parameters (26). Fiber tracking was initiated from all voxels within the seed masks in the diffusion space to generate 5,000 streamline samples, with a step length of 0.5 mm and a curvature threshold of 0.2. The resultant tract density maps were normalized by dividing by the total number of streamline samples and thresholded at 0.005 to exclude spurious connections. Tracts were then non-linearly registered to MNI space using the registration parameters for FA images as above. The final groupwise probability map for each tract was generated with a threshold at least 50% (14/27 = 0.52) of healthy subjects (27, 28), and the respective binary map was generated as template to extract the mean values of DTI metrics for individual patient.

Statistical Analysis

To assess brain–behavior associations in the tracts identified above, we performed partial correlations between the mean values of FA, MD, AD, and RD (as indexes of white matter integrity) and WLC and SLC scores (as indexes of different level in

[1] http://www.fil.ion.ucl.ac.uk/spm.
[2] http://www.fmrib.ox.ac.uk/fsl/.

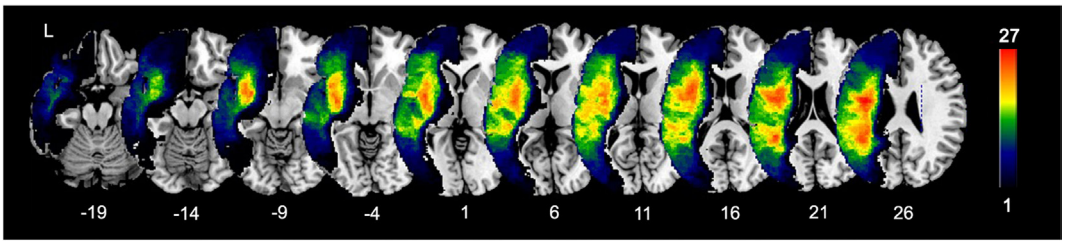

FIGURE 1 | **Lesion overlap of 40 patients**. Color bar indicates the number of patients with lesions in each voxel (maximum 27 out of 40).

comprehension processing) controlling for age and total lesion volume. Direct lesion volume within a tract may dramatically alter the mean values of the white matter integrity measures and could also covary with direct damage in neighboring tracts or gray matter yielding spurious tract–behavior relationships. Therefore, we further excluded the primary lesion load on each tract from analyses by including the number of lesioned voxels in the tracts as nuisance covariates in the analyses. Statistical analyses were performed using SPSS (version 22). As previously described (29), we considered tracts that showed significant correlations with behavior for the each DTI index at a threshold of $P < (0.05/4) = 0.0125$ (Bonferroni correction).

RESULTS

Localization of White Matter Correlates of Comprehension Deficits

Tract-based spatial statistics was conducted to localize areas in which white matter integrity related to WLC and SLC scores, controlling for age and total lesion volume. Because poor performance on word-level auditory comprehension tasks may relate to semantic impairment, rather than auditory comprehension *per se*, we added scores on the PPT test, a measure of non-verbal semantics, as an additional covariate for WLC. Because the SLC score already controlled for WLC (see Materials and Methods), further controlling SLC for non-verbal semantics was not necessary. TBSS analysis showed a strong association between WLC scores and DTI metrics (decreased FA and increased MD, AD, and RD) in a left anterior temporal region, which corresponds to a part of the ventral pathways where the IFOF, ILF, and UF run together (**Figure 2A**). SLC scores were significantly associated with DTI metrics in a left posterior temporal region, with decreased FA and increased diffusivities primarily located in parts of IFOF and ILF (**Figure 2B**). Notably, these results reflect only specific locations in which white matter integrity was associated with WLC or SLC scores. Thus, we next examined relationships between comprehension scores and DTI metrics of entire tracts implicated here.

Relationship between White Matter Tracts and Comprehension Deficits

To define potentially relevant white matter pathways, the left ventral tracts implicated by the TBSS analysis, along with the AF (for completeness), were reconstructed in healthy older participants (**Figure 3**). First, we examined the relationship between direct lesion burden in each tract and comprehension. Partial correlations showed that when controlling for total lesion volume, the number of lesioned voxels in the AF and ILF related to SLC scores, while the number of lesioned voxels in the UF related to WLC scores (all corrected $P < 0.05$, **Table 2**).

To test more specific measures of tract integrity, we next examined relationships between the comprehension scores and the average FA, MD, AD, and RD values in each tract. Partial correlations showed that when controlling for age, total lesion volume, and the number of lesioned voxels in each tract, reduced FA and increased diffusivity measures including MD, AD, and RD of the left IFOF were significantly associated with both WLC and SLC scores (corrected $P < 0.05$, **Figure 4A**). DTI metrics in the left ILF significantly related to the SLC scores, with significant correlations with MD, AD, RD, and a marginal correlation with FA (corrected $P < 0.05$, **Figure 4B**). In the left UF, DTI metrics significantly predicted the WLC scores (corrected $P < 0.05$, **Figure 4C**). When further controlling for PPT scores, correlations between the UF and WLC scores remained significant for MD, AD, and RD (all corrected $P < 0.05$), with a trend for FA (corrected $P = 0.08$). DTI metrics of the left AF did not relate to either WLC or SLC scores (all uncorrected $P > 0.10$). The full statistical results are shown in **Table 2**. Considering the potential confounding effect of handedness, we further performed the partial correlation analyses with the Edinburgh Handedness Index as an additional covariate and the results remained significant (data not shown). Taken together with the TBSS results, our findings showed that the anterior white matter connections *via* UF and IFOF were associated with WLC, while posterior white matter tracts including ILF and IFOF related to SLC.

DISCUSSION

We found that comprehension outcomes related primarily to damage in ventral stream white matter tracts in chronic left hemisphere stroke. Anterior temporal white matter integrity loss and involvement of the UF related primarily to word-level comprehension deficits. In contrast, posterior temporal white matter integrity loss and involvement of the ILF related primarily to sentence-level comprehension. Loss of white matter integrity in the IFOF related to both word- and sentence-level comprehension. Although lesion burden in the AF related to sentence-level

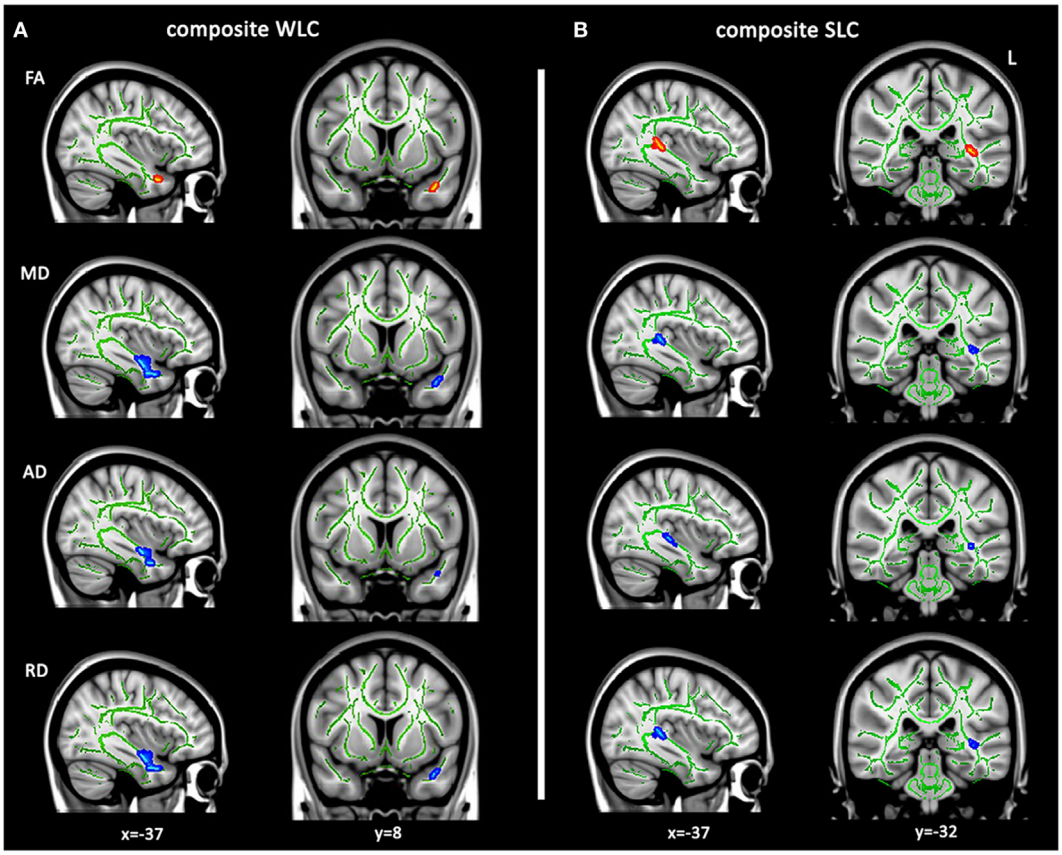

FIGURE 2 | **Tract-based spatial statistics analysis for white matter integrity related to language comprehension**. Altered diffusion tensor imaging metrics related to composite WLC **(A)** and SLC **(B)** scores controlling for age and lesion volumes (TFCE corrected $P < 0.05$). Regions with significantly positive correlates of mean fractional anisotropy (FA) (red–yellow) or negative correlates of mean diffusivity (MD), axial diffusivity (AD), and axial diffusivity (RD) (blue–light blue) with individual comprehension scores are overlaid on the FMRIB58 FA skeleton (green), displayed on a template in Montreal Neurological Institute space. WLC, word-level comprehension; SLC, sentence-level comprehension.

comprehension, more specific examination of white matter integrity metrics revealed no relationship. Taken together, these findings are among the first to map critical white matter pathways for different aspects of auditory comprehension in chronic stroke.

The finding that word-level comprehension relies on anterior temporal white matter corresponds with recent fMRI findings in healthy participants (3) and gray matter atrophy findings in people with primary progressive aphasia (4), collectively demonstrating that the classical posterior localization of Wernicke's area is incorrect. In line with these results, a previous study combining DTI and fMRI in a group of 10 patients with chronic post-stroke aphasia identified a relationship between UF damage and word-level comprehension (11). This study suggested that the left UF mediates semantic control during auditory word comprehension, by connecting inferior frontal cognitive control areas with anterior temporal areas storing word meanings. Another DTI study of post-stroke aphasia recently confirmed that lesion burden in left UF was associated with poor performance on word-to-picture matching and PPT tests, suggesting involvement of the left UF in semantic control during auditory word comprehension (10). We confirmed this prior result and extended it by showing that more specific measures of white matter integrity of the UF relate to word-level comprehension. Further, this relationship persists after controlling for non-verbal semantic performance on the PPT test, suggesting that the role of the UF in word-level comprehension does not simply reflect the role of the anterior temporal lobe in semantic knowledge (30), but that it plays a specific role in access to semantic information from auditory or perhaps amodal lexical representations.

The IFOF, like the UF, connects inferior frontal cortex to the temporal lobe. Whereas the UF connects to the anterior temporal lobe, the IFOF courses through the extreme capsule to posterior temporal areas, notably the middle temporal gyrus (31). We found that reduced IFOF integrity was significantly associated with both word- and sentence-level comprehension deficits. Previous lesion–symptom mapping studies implicated the posterior middle temporal gyrus in performance on both word and sentence comprehension tasks (31, 32). Although the authors suggested that involvement of the posterior middle temporal cortex in word-level comprehension could explain its relationship to deficits in all comprehension tasks, we found that the ventral stream connections between this area and the inferior frontal cortex *via*

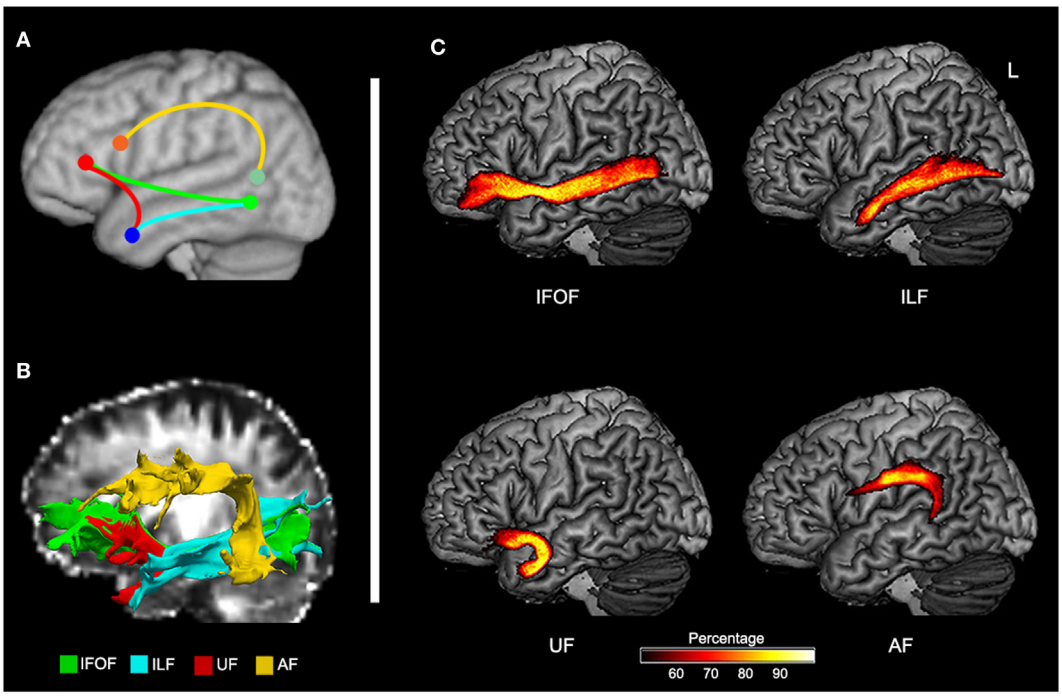

FIGURE 3 | Probabilistic maps of reconstructed ventral and dorsal pathways related to language. **(A)** Schematic representation of expected tracts in Montreal Neurological Institute space. **(B)** Reconstructed inferior fronto-occipital fasciculus (IFOF), inferior longitudinal fasciculus (ILF), uncinate fasciculus (UF), and arcuate fasciculus (AF) in native space of a control subject. **(C)** Group-based probability maps of IFOF, ILF, UF, and AF derived from probabilistic tractography in healthy older subjects (at least 50% subjects of each voxel).

TABLE 2 | Partial correlations between integrity of reconstructed tracts in left hemisphere and composite comprehension measures in patients controlling for age, total lesion volume, and lesions in each tract.

Tract	Tract size (mm^3)	Composite WLC					Composite SLC				
		Lesion	FA	MD	AD	RD	Lesion	FA	MD	AD	RD
IFOF	8,506	−0.214	0.410*	−0.447*	−0.489*	−0.432*	0.118	0.409*	−0.413*	−0.408*	−0.413*
ILF	5,451	−0.022	0.248	−0.378	−0.380	−0.369	−0.406*	0.382	−0.461*	−0.457*	−0.453*
UF	3,097	−0.400*	0.408*	−0.429*	−0.424*	−0.439*	−0.046	−0.010	−0.216	−0.232	−0.221
AF	3,447	−0.081	−0.127	0.129	0.110	0.138	−0.439*	0.074	−0.079	−0.088	−0.072

IFOF, inferior fronto-occipital fasciculus; ILF, inferior longitudinal fasciculus; UF, uncinate fasciculus; AF, arcuate fasciculus; FA, fractional anisotropy; MD, mean diffusivity; AD, axial diffusivity; RD, radial diffusivity; WLC, word-level comprehension; SLC, sentence-level comprehension.
For lesion-performance analyses, total lesion volume was considered as covariate.
**P < 0.05, Bonforroni corrections for multiple comparisons.*

the IFOF relate not only to word-level comprehension but also to sentence-level comprehension after regressing out word-level deficits. Indeed, some studies in healthy subjects have found that auditory sentence comprehension is mediated in part by the IFOF (6).

These frontal–posterior temporal connections may play a similar role in cognitive control to the UF connections discussed above. Structural and functional imaging studies suggest that inferior frontal regions contribute to access of semantic knowledge, and hence auditory comprehension (33–35). Furthermore, damage to prefrontal regions leads to more severe deficits of semantic control than damage to temporo-parietal regions alone (36). Thus, the IFOF, with its long course from the inferior frontal lobe through the temporal lobe, may be involved in linking control areas of the frontal lobe to multiple levels of semantic representations in the temporal lobe (37). It should be noted that another study in stroke patients also found that disruption of left ventral fronto-temporal connections *via* extreme capsule fiber systems related to sentence comprehension, although the specific findings suggested a role in syntax rather than semantics (12). Our sentence comprehension tasks do not allow us to discriminate between syntax and semantics, but the role of IFOF demonstrated here in word comprehension tasks involving only concrete nouns that require no syntactic processing suggests a role in semantics. Coupled with the relationship to sentence-level tasks after controlling for word-level comprehension, these

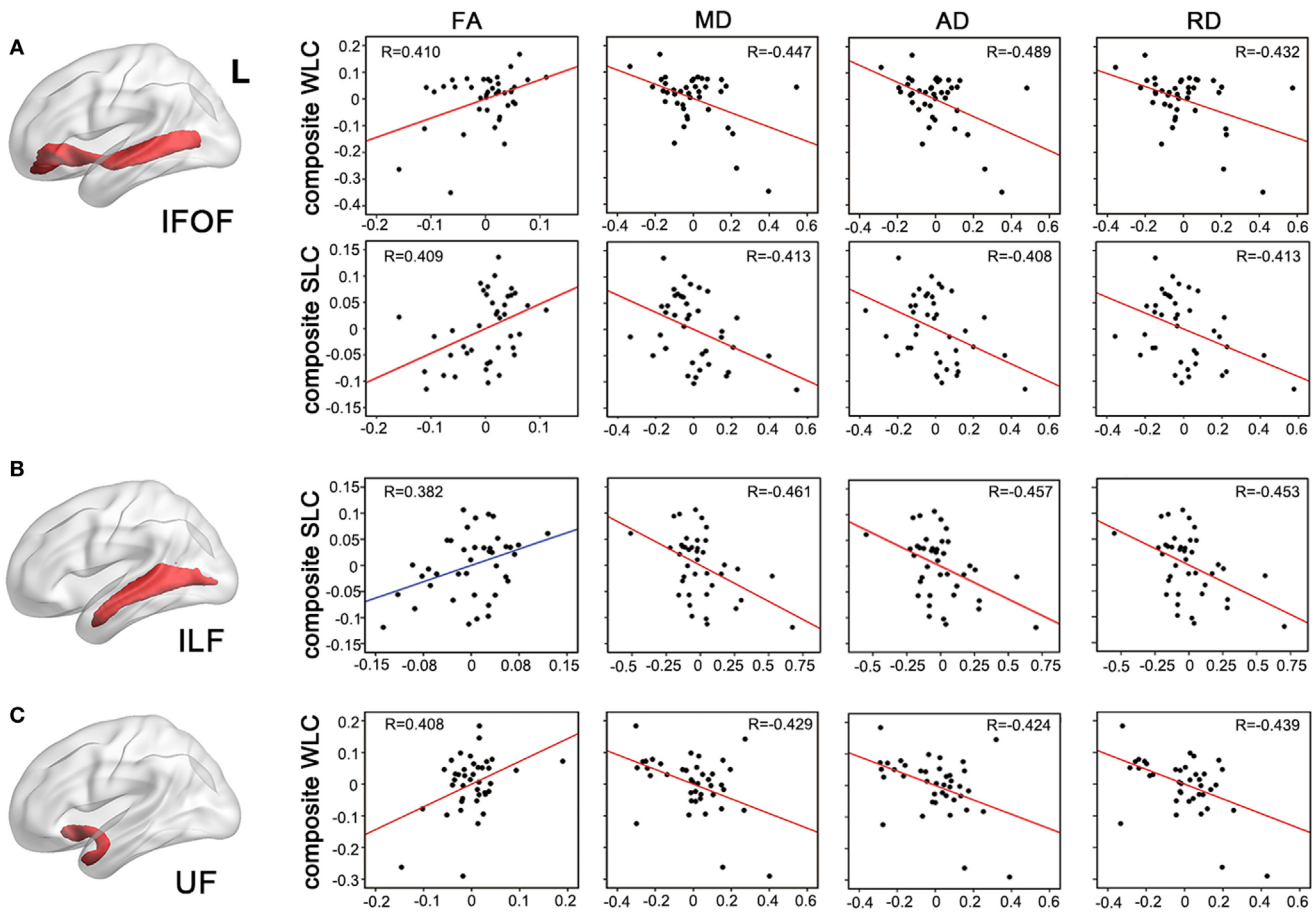

FIGURE 4 | **Partial correlations between integrity of entire tracts and auditory comprehension**. Mean measures of white matter integrity [fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD), and axial diffusivity (RD)] of left inferior fronto-occipital fasciculus [IFOF, **(A)**], inferior longitudinal fasciculus [(ILF), **(B)**], and uncinate fasciculus [(UF), **(C)**] were associated with WLC or SLC composite scores, controlling for age, lesion volume, and lesioned voxels in the respective tracts. $P < 0.05$ with Bonferroni correction. WLC, word-level comprehension; SLC, sentence-level comprehension.

findings suggest that the IFOF plays a role either in multi-level semantic processing or in domain general processes underlying comprehension in general, such as cognitive control.

In addition to the IFOF, our results also implicated the ILF in sentence comprehension. The TBSS analysis suggested that an area of posterior temporal white matter including segments of both the ILF and IFOF was especially critical. Auditory sentence comprehension involves a number of different cognitive subprocesses and so engages a widely distributed network of frontal, temporal, and parietal areas (38). The most critical portion of white matter for sentence comprehension in the TBSS analysis here underlies posterior temporal areas implicated in semantics, phonology, syntax, and working memory (2, 37). Previous studies on healthy participants have shown that temporo-parietal areas activated during sentence comprehension participate in a number of white matter pathways including the IFOF and the ILF (39). The ILF connects the posterior temporal lobe with anterior temporal cortex, which has been implicated in both semantic (30) and syntactic processing (40). Evidence from fMRI studies of healthy participants has indicated that auditory sentence comprehension simultaneously activates both posterior and anterior temporal regions (41), implying involvement of anterior/posterior connections *via* the ILF. However, the exact nature of the processing supported by the ILF remains unclear. Additional research will be needed to examine this question further.

It has been well established that the lateral AF supports sensory-articulatory integration involved in speech production (6, 42, 43). DTI studies have implicated the AF in syntactic processing during sentence comprehension in children (44) and people with primary progressive aphasia (8). Here, we found that direct lesion load on left AF related to sentence comprehension in post-stroke aphasia, consistent with recent studies in this population (9). However, when controlling for direct lesion overlap on the AF, we found no association between DTI measures within AF and performance. This finding contrasts with a previous study showing that integrity within left AF and ventral extreme capsule fiber systems related to syntactic comprehension in stroke patients (12). However, this prior study did not control for direct lesion burden on the tracts, so integrity measures in this study may reflect both direct lesion damage as well as secondary

axonal degeneration in the tracts. Different from this previous study, we factored out direct lesions to the tracts when examining white matter integrity metrics because the direct damage in a given tract likely covaries closely with damage in anatomically neighboring tracts. This covariance could result in false-positive findings in the tracts of interest. Factoring out the direct damage thus allowed us to examine the behavioral contributions of each white matter tract more specifically, by considering only the secondary degeneration. Two other considerations regarding the AF are worth noting. First, the prior studies above specifically examined syntax using tasks designed to control for semantics and other processes required for sentence comprehension. Since we focused on clinical tests, and not on disambiguating the subprocesses of sentence comprehension, our results may be less sensitive to a specific role of the AF in processing complex syntax. Additionally, the AF anatomically encompasses direct (fronto-temporal segment) and indirect (fronto-parietal or temporal–parietal segments) fiber bundles (42), and these bundles within AF may serve different functions in language processing (45). The roles of these different segments in auditory comprehension require further elucidation.

Several limitations should be noted. First, lack of objective measures of the individual tracts in patients is a main caveat of this study. Due to varied left hemisphere lesions, most of the left hemisphere white matter connections could not be reconstructed with probabilistic tractography in individual patients. Under this circumstance, white matter damage does not necessarily indicate that the adjacent cortical regions are crucial for comprehension behavior, but may rather indicate that connections between the posterior and the anterior cortical regions are associated with comprehension performance. Second, we did not determine the involvement of left hemisphere cortical areas in word or sentence comprehension. Previous studies have shown that regional gray matter damage in the left temporal lobe might support auditory comprehension processing in patients with post-stroke aphasia or primary progressive aphasia (4, 31, 32). Therefore, inter-relationships between both cortical structures and white matter pathways involved in different levels of auditory comprehension need further investigation.

CONCLUSION

The present findings implicate anterior temporal white matter and particularly the UF in word-level comprehension. In contrast, posterior temporal white matter damage and loss of integrity in the ILF related to sentence-level comprehension deficits. The IFOF, with its long course from the frontal lobe through the temporal lobe, was implicated in both word and sentence comprehension. These results demonstrate the importance of ventral stream white matter damage to auditory comprehension in stroke and suggest that anterior and posterior temporal white matter damage impairs different levels of auditory comprehension.

AUTHOR CONTRIBUTIONS

SX conceived the study, analyzed the data, and drafted the manuscript; EL contributed to the collection and analysis of the data; LS-K contributed to the data interpretation; PT contributed to the design of the study, the analysis and interpretation of the data, and editing of the manuscript. All the authors contributed to editing of the manuscript.

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