Hypo-perfusion and hyper-resistance affect different cognitive functions

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Research Article

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Abstract

Cognitive impairment and dementia are conventionally categorised according to their causative disease, such as Alzheimer's disease and cerebrovascular disease. Cognitive impairments of different aetiologies often share pathological cerebral blood circulation patterns, characterised by perfusion and resistance. Here, we show that these two features are associated with distinct types of cognitive impairment. Using carotid ultrasonography, we evaluated the circulation status of individuals with little to no subjective cognitive symptoms. We assessed individuals' cognitive status using the Frontal Assessment Battery for executive function and Mini-Mental State Examination for learning and memory. Regression analysis showed that the hyper-resistance and hypo-perfusion components predicted the Frontal Assessment Battery and Mini Mental State Examination scores, respectively. These results are consistent with previous findings of hyper-resistance being associated with atherosclerosis, which disproportionately affects the frontal lobe and contributes to executive function impairments; meanwhile, hypo-perfusion disproportionately affects temporal lobe functions associated with learning and memory. We propose a novel concept that cognitive impairments fall into two subtypes regardless of the brain disease: hyper-resistance and hypo-perfusion subtypes. As these subtypes can be measured noninvasively and are treatable, this distinction would help design preventive and therapeutic strategies for dementia.

Introduction

Dementia is a medical condition defined by its symptoms, namely progressive deterioration in heterogonous cognitive functions (*e.g.*, memory, language, problem-solving, attention, and behavior), which interferes with daily life activities. Dementia is caused by various neurological diseases and is conventionally categorized by the underlying disease, such as dementia due to Alzheimer's disease (DAD), and not by the symptoms. Cerebrovascular disease is the second most common cause of dementia, and vascular dementia (VaD) accounts for approximately 10–20% of dementia cases in Europe and North America and 30% of cases in Asia and other developing countries[1]. Impairment of blood flow to the brain and damage to the blood vessels, resulting from events such as stroke, affect cognitive function[2]. The major pathological factors of vascular diseases are atherosclerosis[3] and arterial embolism (*i.e.*, micro infarction)[4]. These 'vascular risk factors' affect both intracranial and extracranial arteries. Recent studies revealed that the vascular risk factors play an important role in other types of cognitive impairment such as DAD[5], which is the most common type of dementia, accounting for over half of all cases[6]. Previous studies using positron emission tomography and single-photon emission computed tomography have shown that reduced cerebral blood flow predicts the progression of DAD and VaD[7,8]. Furthermore, magnetic resonance imaging has shown that vascular damage due to atherosclerosis is associated with dementia[3]. Carotid ultrasonography is also used to evaluate these vascular risk factors, and ultrasonographic parameters are associated with cognitive functions, which are measured using neuropsychological assessments[9–11]. Ultrasonography evaluates vascular risk factors by measuring (i) blood flow velocity and (ii) flow resistance[12]. The former reflects impaired cerebral blood perfusion[13], while the latter reflects atherosclerotic damage in the brain[14]. Interestingly, atherosclerosis

disproportionately affects the frontal lobe while relatively sparing the temporal lobe[15]. These regions contribute differently to cognitive function: the frontal lobe is important for executive function[16], while the temporal lobe is essential for learning and memory[17].

If impaired cerebral blood perfusion (*i.e.*, blood flow velocity) and atherosclerotic damage (*i.e.*, flow resistance) are quantitively associated with distinct types of cognitive impairment, an alternative dementia categorization scheme based on symptoms might be feasible. The conventional categorization of dementia is based on causative pathology and its drawback is that these pathologies do not always reflect the patients' symptoms[18,19]. Here, we hypothesized that the two vascular risk factors have distinct influences on cognitive functions. We evaluated our hypothesis using ultrasonographic parameters and neurological assessment scores in middle-aged and old individuals.

Results

Neuropsychological scores

Clinical data of 39 individuals ranging from middle-aged to old was analyzed retrospectively in the present study. The average scores and standard deviations of the MMSE and FAB were 28.2 ± 1.9 (range: 23–30) and 13.8 ± 2.4 (range: 9–17), respectively (Supplementary Table S1). Among the 39 individuals, six showed a lower MMSE score than the cut off (26/27)[20] [*i.e.*, MMSE-positive (Mp)] and nine showed a lower FAB score than the cut off (12/13)[21] [*i.e.*, FAB-positive (Fp)] (Fig. 1). Four individuals showed lower scores in both the MMSE and FAB (MpFp) than their respective cut offs, while five were MMSE-negative (Mn) with Fp (MnFp) and two were FAB-negative (Fn) with Mp (MpFn). When assessing within-modality relationships, there was a positive correlation between the MMSE and FAB scores ($r = 0.53$, $p < 0.01$, bootstrap statistics).

Resistance And Perfusion Components

Carotid ultrasonography helped determine six ultrasonographic parameters on either side of the CCA: four local parameters (*i.e.*, blood flow velocity) [diameter of artery (DA), peak systolic velocity (PSV), end diastolic velocity (EDV), and mean velocity (MV)], and two downstream parameters (*i.e.*, flow resistance) [pulsatility index (PI) and resistance index (RI)][11,22]. Correlation analysis showed that the ultrasonographic parameters were positively correlated within each group (represented by the red cells in Fig. 2).

Parameters were subdivided into two vascular risk components using principal component analysis (PCA). These components had eigenvalues of 6.55 and 2.11, which explained 74.1% of the overall variance (primary component: 56.0%, secondary component: 18.1%). The promax-rotated coefficients of all 12 ultrasonographic parameters are shown in Fig. 3A and Supplementary Table S2. The primary component was closely related to downstream factors (red biplots in Fig. 3A) and was named the

resistance component, whereas the secondary component was closely related to local factors (blue biplots in Fig. 3A) and was named the perfusion component. The component scores (vascular risk component scores) for each individual (scatterplots in Fig. 3A) were used in the following analysis.

Vascular Risk Components And Cognition

To examine our hypothesis (*i.e.*, two vascular risk factors differently influence cognitive function), each neuropsychological score (MMSE and FAB) was subjected to a linear mixed-effect model (LMEM), including the two vascular risk component scores as fixed predictors, where the individuals' profile biases (*i.e.*, age and sex) were considered as nuisance predictors, as fixed covariate (age) and random intercept/slopes (for each sex). The perfusion risk component contributed significantly to the MMSE (estimated coefficient 4.472 ± 3.504) but not to the FAB (0.321 ± 3.038), whereas resistance component contributed significantly to the FAB (-5.980 ± 3.846), but not to the MMSE (-1.896 ± 3.779). Thus, the two vascular risk components significantly and predominantly contributed to the MMSE and FAB scores, respectively (Fig. 3B).

Discussion

This study revealed that the resistance and perfusion components of the ultrasonographic parameters unequally contribute to the MMSE and FAB scores (Fig. 3B). The MMSE score was predicted by the perfusion component, which has a close relationship with local ultrasonography parameters (DA, PSV, EDV, and MV). Meanwhile, the FAB score was predicted by the resistance component, which has a close relationship with downstream ultrasonography parameters (PI and RI) (Fig. 4).

The concept of dementia has existed throughout recorded history. It was long considered a consequence of healthy aging[23], whereas now, it is regarded an outcome of a disease, such as Alzheimer's disease. Although memory loss (*i.e.*, dysfunction of the temporal lobe) was considered the major symptom of DAD[24], with the preservation of frontal function till the late stage[24], recent studies have revealed that impairment in executive function (*i.e.*, dysfunction of the frontal lobe) presents from an early stage[25]. It is consistent with the fact that MMSE cannot screen one third of all patients with mild cognitive impairment[26]. Hence, it is important to assess frontal and temporal function to appropriately diagnose dementia, especially at an early stage. A previous review introduced the concept that cognitive impairments associated with the temporal lobe arise from the pathology of Alzheimer's disease, while impairments associated with the frontal lobe occur in healthy ageing[27]. Although this concept provides a new insight, it has two limitations for clinical use: (i) it is not possible to quantify the degree of contribution of causative diseases in vivo as it requires autopsy, which is not available in clinical practice. (ii) The definition of 'healthy ageing' is vague (*e.g.*, brain age is affected by lifestyle and does not correspond to the biological/chronological age[28]).

In this study, we showed that the two aspects of cognitive impairment (*i.e.*, learning/memory and executive function) can be quantified using ultrasonography, which is an objective measurement tool available at ordinary clinics and hospitals. Six ultrasonographic parameters were subdivided into resistance and perfusion components using PCA (Fig. 3A). The LMEM analysis showed that the MMSE and FAB scores were predicted by the perfusion and resistance components, respectively (Fig. 3B). The mismatch between the MMSE and FAB scores (Fig. 1) indicates that they reflected dysfunctions in different cognitive domains, such as memory and executive function. This supports our hypothesis that two subtypes of vascular risk factors (perfusion and resistance components) are associated with different types of cognitive impairment (MMSE and FAB) (Fig. 4). The FAB is a neurophysiological assessment originally developed for rapid and easy assessment of frontal functions, such as executive function[16,29]. The frontal lobe is susceptible to atherosclerosis[15,30], which is associated with downstream factors (PI and RI). The PI represents the hyper-pulsatility of the carotid blood flow and reflects the transmission of pulsatile energy into the cerebral microcirculation. It is positively associated with the development of stroke[31], which is a major risk factor for VaD. Patients with VaD tend to show executive dysfunction dependent on the frontal lobe and show little or no memory impairment[32], which heavily depends on the temporal lobe. The RI reflects impaired blood flow caused by the microvascular bed, and is correlated with arteriosclerotic risk factors[12,14]. In short, there is an interplay between the resistance component, downstream parameters (PI and RI), atherosclerosis, the frontal lobe, and executive dysfunction (Fig. 4, left). We speculate that the FAB score is sensitive to cognitive impartments as atherosclerosis mainly affects the frontal lobe rather than the temporal lobe. The MMSE is another neurophysiological assessment originally developed for dementia screening[33]. It primarily evaluates learning and memory resources, which depend on medial temporal lobe structures such as the hippocampus[34]. The MMSE score is associated with grey matter atrophy, mainly in the medial temporal lobe[34], a region not susceptible to atherosclerosis[15]. This study showed that the MMSE score was associated with the perfusion component, which is closely associated with local parameters such as PSV. Previous studies showed that PSV was correlated with MMSE scores[10,35] and cerebral blood flow, especially in the mesial temporal area[13]. Further, cerebral blood flow measured using positron emission tomography was negatively associated with changes in MMSE scores during a 3-year observation period[7]. Cerebral blood flow is associated with the hippocampal volume[36], and the left hippocampal volume is correlated with the MMSE score[37]. Furthermore, hippocampal blood flow is associated with the memory function[38]. Taken together, there is an interplay between the perfusion component, local factors (*e.g.*, PSV), cerebral blood circulation, temporal lobe (*i.e.*, hippocampus), and learning and memory (Fig. 4, right). It is reasonable to assume that the perfusion component is associated with the MMSE score via its involvement in temporal functions. On the other hand, the temporal lobe is not susceptible to atherosclerosis[15], which is associated with the resistance component. This is consistent with the present finding that the MMSE score was not predicted by the resistance component.

Conventional classification of dementia depends on the pathology of the causative diseases. However, it has some limitations. Accurate pathological diagnosis requires autopsy, which is not available in clinical

practice. A previous autopsy study revealed that up to 75% of cases had multiple brain pathologies[39]. So far, we have few effective treatment strategies that act directly on the causative pathology. Meanwhile, dementia is intrinsically defined by its neuropsychological symptoms. Therefore, it is desirable to have a classification system based on an objective and practical medical examination, which corresponds to the assessment of its symptoms rather than causative disease to prevent and treat cognitive impairment and dementia.

There are three potential limitations of this study. First, we chose the MMSE and FAB because these assessments are routinely used in medical health-check services. However, we believe that the arbitrary selection of neuropsychological assessment scores does not affect our results in a major way, and the combination of the MMSE and FAB evaluations comprehensively proved the proposed hypothesis. Second, the MMSE and FAB scores are not entirely dependent on temporal and frontal lobe functions, respectively [40,41]. The MMSE was originally developed for distinguishing old individuals with and without neuropsychiatric disorders and it is insensitive to frontal dysfunction[42]. The FAB was intendedly developed as an assessment tool for evaluating frontal function[16]. In this study, we focused on cognitive functions based on the individuals' symptoms during task performance that was measured by neuropsychological assessments, rather than scrutinizing the pathology or anatomy of dementia. Our approach is consistent with the concept of dementia, which is a syndrome rather than a disease defined by a pathology. Finally, the number of individuals was limited, since it was not easy to enroll more individuals without severe cognitive impairment (See Methods). However, increasing sample size was not imperative for this study, because bootstrap statistics allowed us to obtain robust results even with small sample sizes.

This study showed that carotid ultrasonography could contribute to the development of a new classification for dementia. Herein, we have proposed a novel concept that cognitive impairment falls into two distinct subtypes: the hyper-resistance and hypo-perfusion subtypes, regardless of the underlying brain disease. The hyper-resistance type is pathologically associated with atherosclerosis mainly in the frontal lobe, while the hypo-perfusion type is associated with the temporal lobe and is caused by low cardiac output or lesions in the main blood vessels (Fig. 4). This concept allows us to evaluate the degree of cognitive impairment quantitatively along two axes (*i.e.*, hypo-perfusion and hyper-resistance) to overcome the difficulties faced in diagnosing the type of dementia due to an overlap between the various types (DAD, VaD, DLB, and FTD) in individual patients. The two subtypes proposed here should be considered when designing therapeutic strategies for cognitive impairment. Non pharmacological treatment is the first option for cognitive impairment, and previous studies have demonstrated their effectiveness[43]. Proper hydration or revascularization therapies (*i.e.*, carotid artery stenting and carotid endarterectomy) improve cerebral perfusion[44,45], and physical exercise reduces cerebrovascular resistance[46]. The outcome of these treatments can be regularly monitored using ultrasonography to maximise their outcome; this is suitable because ultrasonography is non-invasive, has a low running cost, and is available at ordinary clinics and hospitals. The proposed concept is treatment oriented and provides novel insights into the treatment of cognitive impairment and dementia.

Methods

Participants

We obtained cognitive assessment scores and ultrasonographic parameters from 42 individuals (24 women; mean age ± standard deviation: 74.0 ± 10.0 years old, range 43–89 years), with little or no subjective cognitive symptoms, who received medical health check services at the Kumagaya General Hospital between August 1, 2020, and April 1, 2021. Three of them were excluded following the criteria of the neuropsychological assessments described in the 'Neuropsychological assessments' section. Cognitive status was assessed by clinical psychologists using the Japanese version of the MMSE and FAB[47,48], and ultrasonographic parameters were evaluated by clinical laboratory technicians who examined the CCA[9,11] using a carotid ultrasonography system (ARIETTA 70 or Noblus, Hitachi, Tokyo, Japan). The CCA is one of the main sources of cerebral circulation (the other being vertebral arteries) and is located near the neck surface, where blood flow can be easily measured. After these assessments, a medical interview was conducted by a neurosurgeon who was a clinical instructor at the Japanese Society of Dementia Research. Twenty-five individuals were diagnosed as healthy or undergoing healthy ageing, 10 had mild cognitive impairment or were at the risk of developing it, five had dementia, and two were in a depressive state. All assessments and interviews were completed on the same day. The study was approved by the ethics committee of Kumagaya General Hospital (#40). All methods were performed in accordance with the relevant guidelines and regulations in Japan. All individuals provided written informed consent for participation in this research.

Neuropsychological Assessments

To specifically investigate the unique aspects of cognitive function, we focused on the dissociation between cognitive functions evaluated by the MMSE, which mainly assesses learning and memory[34], and the FAB, which examines executive function[16]. A previous study showed that the discrepancy between the MMSE and FAB scores is not clear among patients with severe cognitive dysfunction[49], and we excluded three individuals with severe cognitive impairments based on the following criteria: individuals who scored lower than 22/30 in the MMSE and/or lower than 7/18 in the FAB. All three individuals were diagnosed with dementia by the neurosurgeon.

Carotid Blood Flow Assessment

As strong correlations between ultrasonography parameters (Fig. 2) give rise to a multicollinearity problem when entered as predictors into the same regression model, the underlying components were scrutinised using PCA. The original dataset (39 individuals), with six ultrasonographic parameters on each side, were standardised (z-scored) and then used as input. Following the theoretical assumption that ultrasonographic parameters can be subdivided into two subcategories (local and downstream

factors), two components (*i.e.*, vascular risk components) were extracted[22]. To enhance the comprehensibility of the results, the coefficients were rotated using the promax rotation method and a sign convention imposed on the rotated coefficients, forcing the coefficient with the largest magnitude in each component to be positive. The component scores (*i.e.*, vascular risk component scores) were also rotated and scaled into the coefficient space (*i.e.*, each score was divided by the maximum absolute value of all scores and multiplied by the maximum length of the coefficient vector). The scores' signs were changed according to the sign convention for the coefficients. The calculated vascular risk component scores were stored and used for regression analysis.

Statistical Analyses

To examine the within-modality relationships (*i.e.*, between the MMSE and FAB and between ultrasonographic parameters), a correlation analysis was performed using a non-parametric bootstrapping approach. Bootstrapping statistics have methodological advantages over classical statistical inference (*e.g.*, Gaussian assumption)[50]. The Pearson's coefficient was calculated by resampling 20,000 times with replacement data across all individuals. The percentage of the resampled coefficients larger or smaller than 0 (the smaller value) was taken as the significance level (*p*-value). We report the grand mean of the correlation coefficient (*r*) across bootstrap iterations and *p*-values controlled for the false detection rate (FDR) using the Benjamini–Hochberg method[51].

The influence of the ultrasonographic parameters on the neuropsychological assessments was tested using the linear mixed effects model (LMEM). The LMEM was applied to each of the assessment scores (MMSE or FAB) with three continuous predictors: two vascular risk component scores and age. Random intercept and slopes for all fixed predictors were entered into the model for each sex. Age and sex predictors were used for eliminating biases due to these profile factors affecting the results. The model was estimated using a least squares algorithm, provided by the fit liner mixed effects (fitlme) function of the Statistics and Machine Learning Toolbox in MATLAB (MathWorks, Natick, MA). To examine whether fixed predictors significantly contributed to the model, the estimated coefficients of the fixed predictors were tested for the null hypothesis of coefficient = 0 using a *t*-test. For visualizing these results, the 95% confidence intervals of the coefficients were calculated. All statistical analyses were performed using the Statistics and Machine Learning Toolbox and the Multiple Testing Toolbox [52] in MATLAB.

Declarations

Ethics approval and consent to participate

Reuse of the clinical data for the present study was approved by the ethics committee of Kumagaya General Hospital (#40). Additionally, written informed consents for using data were obtained.

Availability of data and materials

All data generated or analysed during this study are included in this published article and its supplementary information file.

Competing interests

Hideyuki Hoshi is now employed by RICOH Co., Ltd. Yoshihito Shigihara is now leading a joint research project with RICOH Co., Ltd.

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Authors' contribution

HH and YS designed the study, analysed the data, prepared the figures, and wrote the whole manuscript.

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Figures

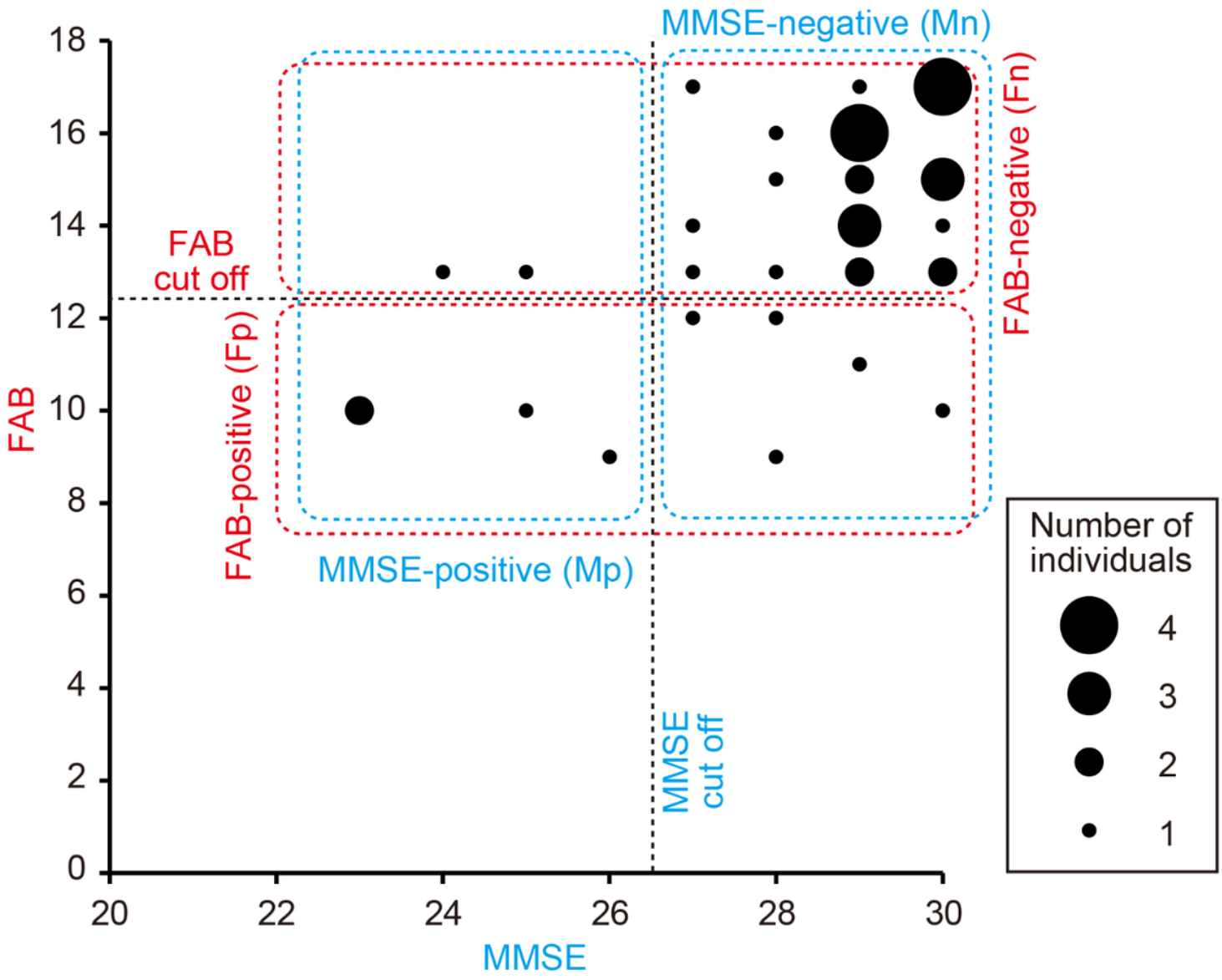

Figure 1

Relationship between Mini-Mental State Examination (MMSE) and Frontal Assessment Battery (FAB) scores. Seven out of 39 individuals showed discrepancies between the MMSE and FAB scores. Broken lines indicate cut off scores of MMSE and FAB. Five were MnFp and two were MpFn. Mn, MMSE-negative; Fn, FAB-negative; Mp, MMSE-positive; Fp, FAB-positive.

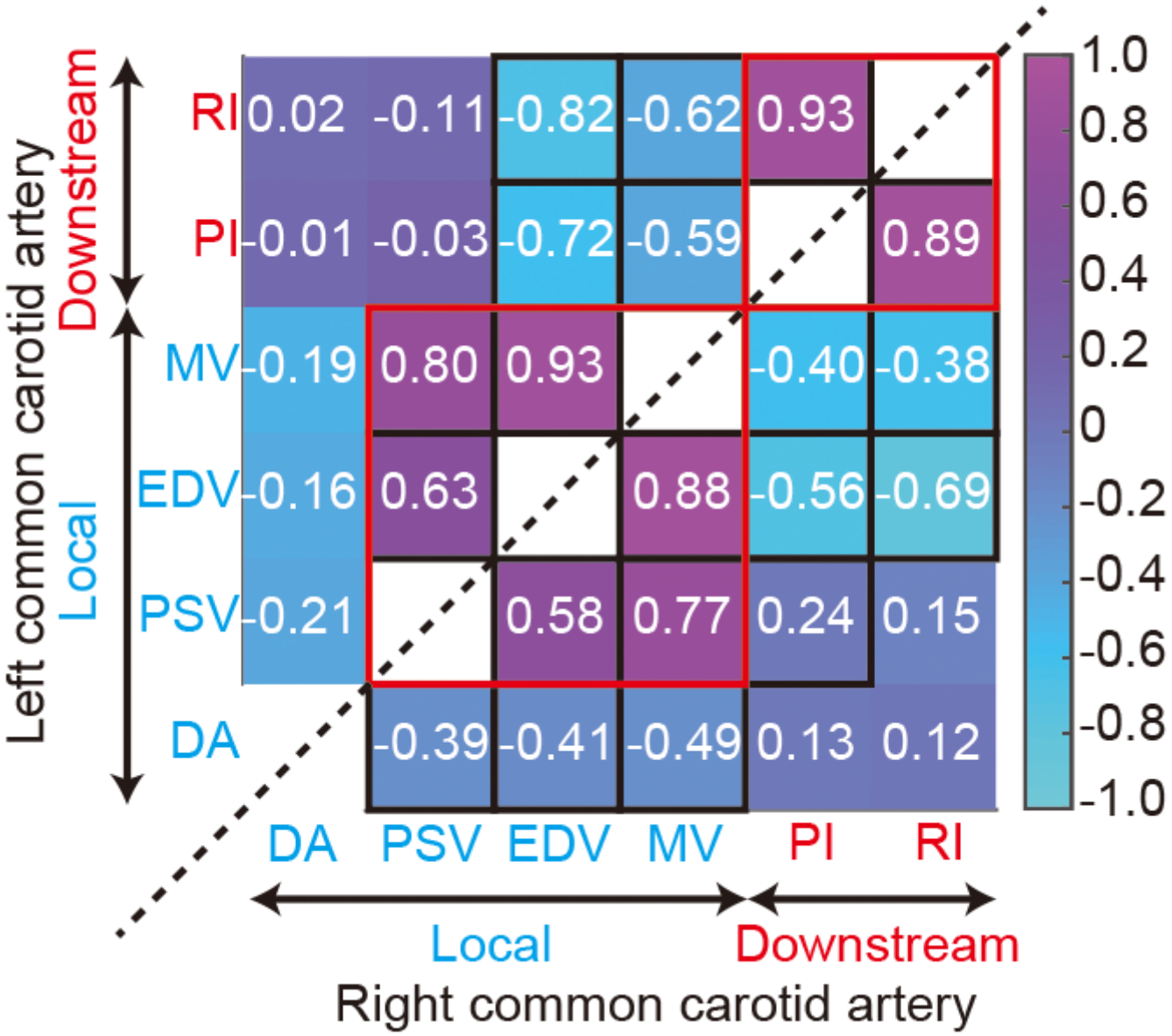

Figure 2

Correlation matrix of ultrasonographic parameters. Correlations between the six ultrasonographic parameters are examined using a non-parametric bootstrapping approach. The parameters are measured in the left common carotid artery (CCA; upper left half) and the right CCA (lower right half). The number and color in each cell represent the grand mean of the Pearson's correlation coefficient across bootstrap iterations. Black borders around cells highlight statistically significant correlations (after FDR correction). There are two salient positive clusters: one with the local parameters (PSV, EDV, and MV) and the other with downstream parameters (PI and RI), indicated with red borders. DA, diameter of artery; PSV, peak systolic velocity; EDV, end-diastolic velocity; MV, mean velocity; RI, flow resistance; PI, pulsatility index; RI, resistance index; TAMV, time-averaged maximum velocity.

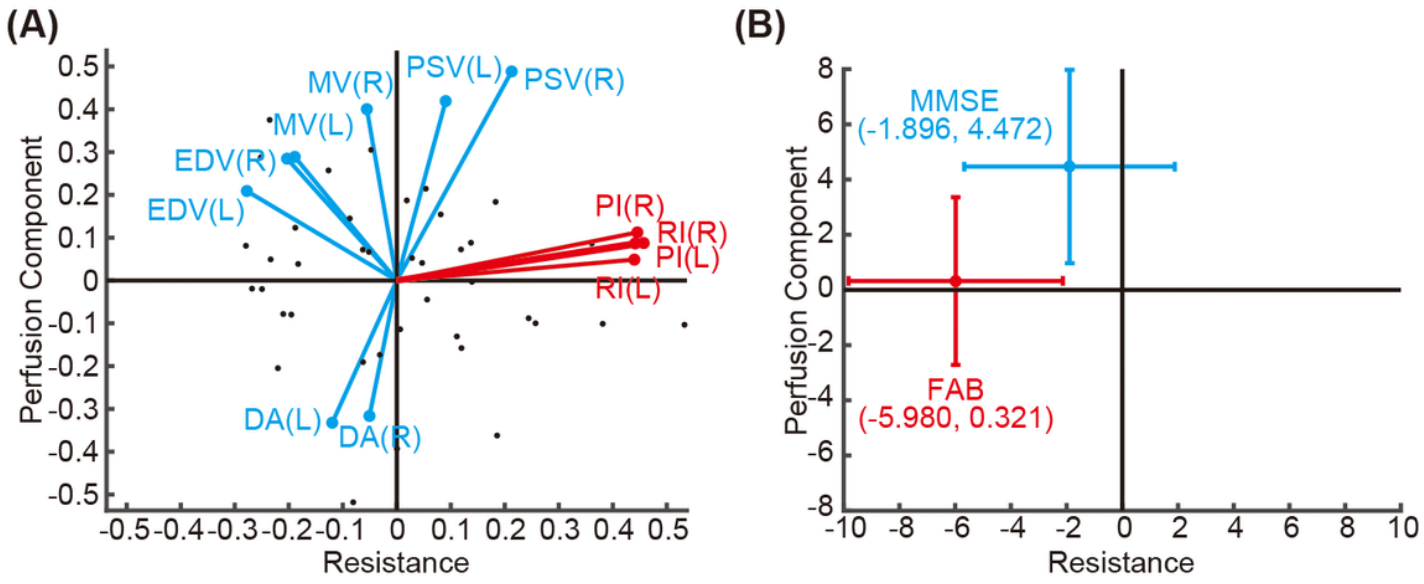

Figure 3

Principal component analysis (PCA) and linear mixed-effect model (LMEM). (A) Biplots show the coefficients of 12 ultrasonographic parameters acquired by PCA. X- and Y-coordinates correspond to the coefficients of the Resistance and Perfusion Components, given for each parameter. The scatterplot represents the component scores of 39 individuals. Coefficients and scores were rotated using the promax method. Blue and red letters indicate local and downstream parameters of ultrasonographic data, respectively. L, left; R, right. (B) Dots and lines represent the estimated coefficients of resistance and perfusion risk-component scores for predicting MMSE and FAB, and their 95% confidence intervals, respectively, acquired using an LMEM. Blue and red letters indicate the MMSE and FAB, respectively.

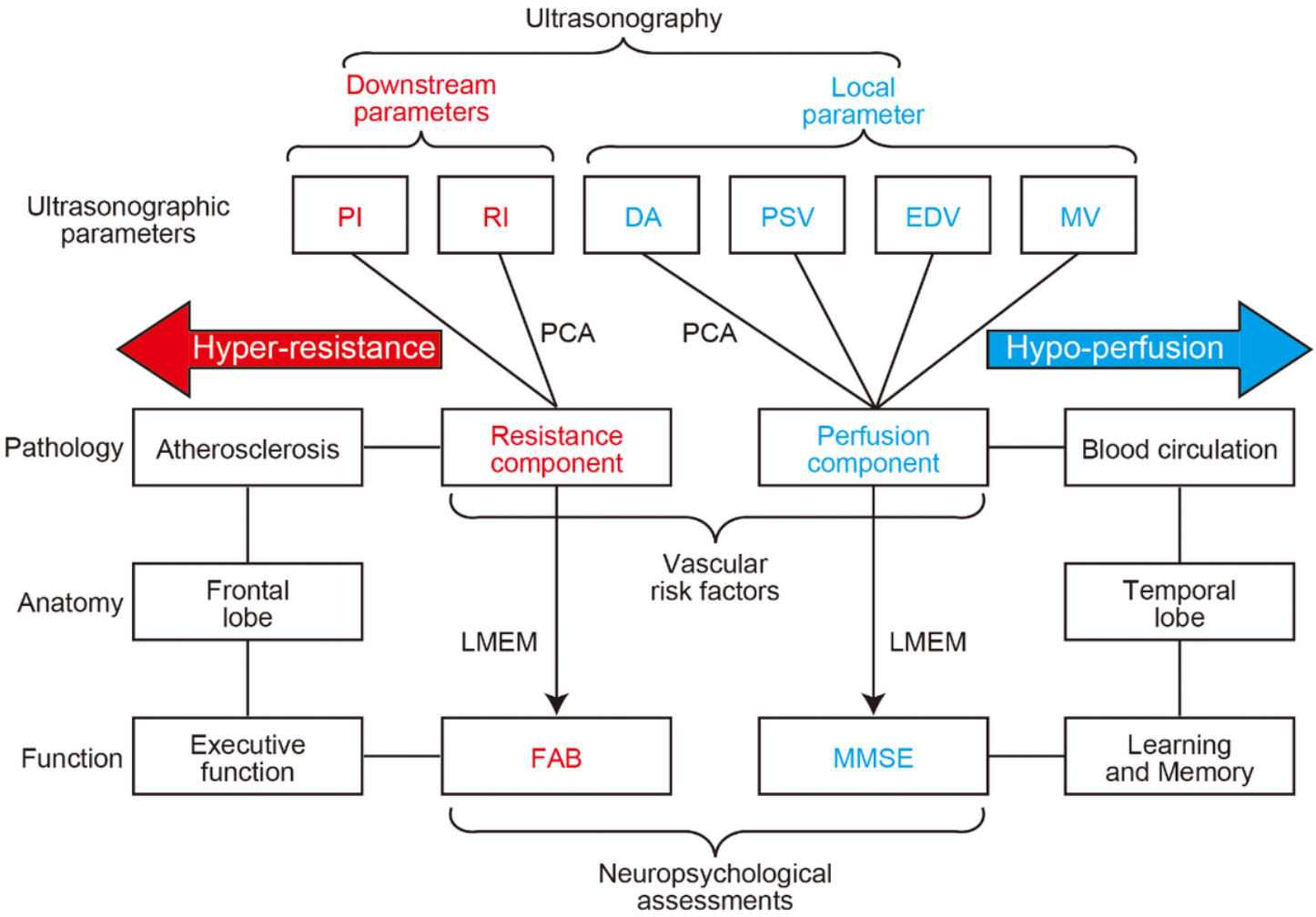

Figure 4

Summary of the findings. Lines and arrows indicate non-directional and directional associations, respectively. Red and blue represents factors associating hyper-resistance and hypo-perfusion respectively. DA, artery diameter; PSV, peak systolic velocity; EDV, end diastolic velocity; MV, mean velocity; RI, flow resistance; PI, pulsatility index; RI, resistance index; PCA, principal component analysis; LMEM, linear mixed-effect model; MMSE, Mini-Mental State Examination; FAB, Frontal Assessment Battery.

Supplementary Files

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- fbdussrsup2021827a.docx