

Surgical Treatment in Our Institute

In Department of Neurosurgery, Tokyo Medical and Dental University, all patients with ischemic presentation and asymptomatic patients with hemodynamic impairment were treated by indirect bypass surgery, ie, encephalo-duro-arterio-synangiosis¹ and/or encephalo-duro-pericranial-synangiosis.²

Patients with hemorrhagic presentation who met the inclusion criteria of previous studies³ were treated by direct bypass surgery, ie, superficial temporal artery–MCA anastomosis.

Neurocognitive Assessments

The full neurocognitive batteries used in this study protocol included the WAIS-III, TMT, Word Fluency Test, and Stroop Test. These neurocognitive batteries were completed in a clinically feasible examination time and did not exhaust the patients, a condition that could lead to lower scores that do not reflect their typical abilities.

In addition to the Processing Speed Index, the WAIS-III and IV provide 3 indices measuring language and verbal ability (Verbal Comprehension Index), ability to organize nonverbal visual stimuli (Perception Organization Index), and auditory attention and mental manipulation (Working Memory Index). These indices have an average of 100 and an SD of 15 adjusted for age according to the standardized Japanese version.

The TMT⁴ contains Part A (TMT-A), which consists of randomly arranged numbers beginning with 1 and ending with 25, and Part B (TMT-B), which consists of numbers from 1 to 13 and 12 Japanese letters (hiragana).

During the Word Fluency Test,⁵ the participants were required to generate as many unique words as possible that started with a specific letter (letter fluency: Japanese “A,” “Ka,” and “Shi”) and belonged to a particular semantic category (category fluency: animals, sports, and occupations) within 1 minute. This test measures executive function.

The Stroop Test⁶ consists of the following 3 tasks performed with 24 stimuli and 4 colors: Word Naming (naming a color written in black Japanese letters [hiragana]), Color Naming (naming the color of a colored circle), and Incongruent Color Naming (naming the color of a word printed in an unmatched color). This test measures sustained attention. The result of Incongruent Color Naming was used in the analysis.

The TMT-A and -B, Word Fluency Test, and Stroop Test were converted to *z* scores using the reported normal ranges of each age group.

Low scores on the WAIS-III indexes, low *z* scores on the Word Fluency Test, and high *z* scores on the TMT and Stroop Test indicate neurocognitive dysfunction.

MR Imaging Acquisition

3D-T1WI was acquired by rapid acquisition with a gradient-echo sequence, TR = 1700 ms, TE = 2.61 ms, flip angle = 10°, TI = 800 ms, voxel size = 1 × 1 × 1 mm, parallel acquisition technique = GRAPPA, and acceleration factor = 2. The acquisition time was 3 minutes 9 seconds.

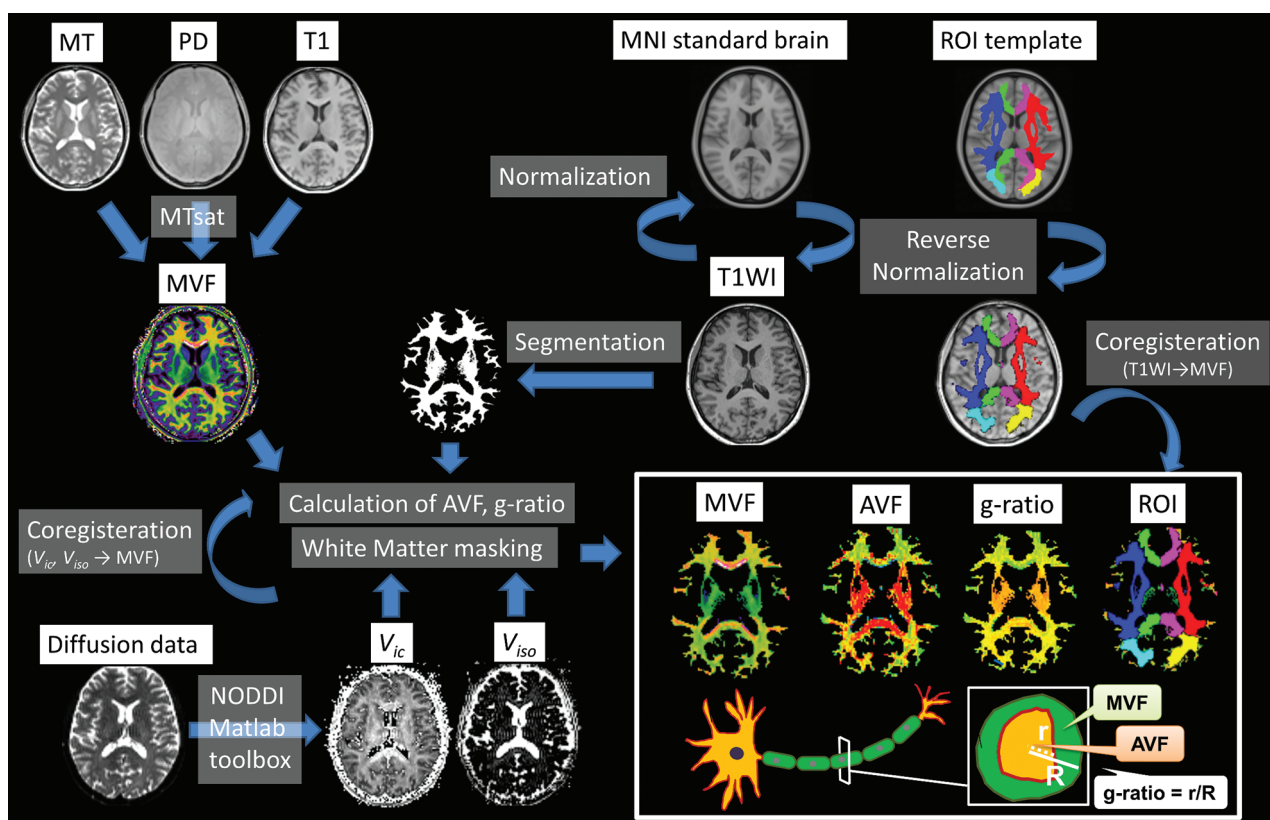
FLAIR was acquired with TR = 12,000 ms, TE = 96 ms, flip angle = 150°, TI = 2750 ms, section thickness = 3 mm, gap = 0.6 mm; SWI, with TR = 27 ms, TE = 20 ms, flip angle 15°, section thickness = 1.6 mm, and gap = 0 mm; and MRA with TR = 24 mm, TE = 3.69 mm, flip angle = 18°, section thickness = 0.70 mm, and FOV = 100.

PET Data Acquisition

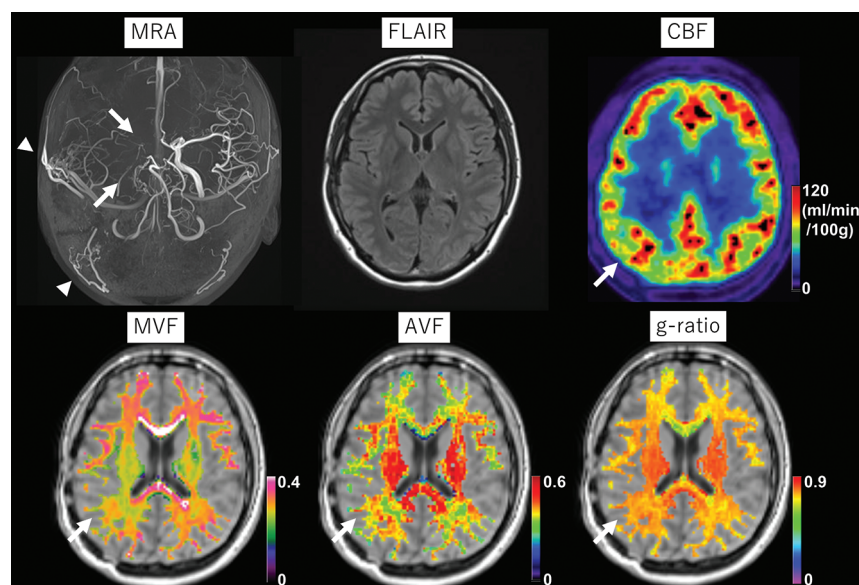
The PET data were acquired using a Discovery 710 PET/CT scanner (GE Healthcare).⁷ The 3.5-minute acquisition of the scans was initiated simultaneously with a 1.5-minute inhalation of [¹⁵O]-labeled carbon dioxide (C¹⁵O₂) (2000 MBq/min) using a neck shield.⁸ The amount of radioactivity in arterial whole blood was manually collected at 0, 2, and 4 minutes, and images of inhaled C¹⁵O₂ were acquired. The images were reconstructed under the following conditions: a 3D-ordered-subset expectation-maximization algorithm, 128 × 128 matrix, 47 slices, 2.0 mm/pixel, 3.27 mm/section, 4 iterations, 16 subsets, and a Gaussian filter of 3.0 mm. The amount of radioactivity in arterial blood was used to create CBF images using the PET autoradiographic method with Xeleris software (GE Healthcare).^{9–11}

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ON-LINE FIG 1. Postprocessing of MR imaging data and schematic illustration of myelin volume fraction, axon volume fraction, and myelin g-ratio. PD indicates proton density.



ON-LINE FIG 2. A 28-year-old woman who previously had frequent episodes of transient ischemic attacks of the left arm and was surgically treated by indirect bypass surgery 1 year before. Her ischemic symptoms disappeared several months after the operation, and her current MRA shows stenosis of the right internal carotid artery and posterior cerebral artery (arrows) and marked development of the extracranial arteries (arrowheads). CBF on the right hemisphere that had decreased before the surgery shows improvement (arrow). However, the myelin volume fraction seems to be decreased on the right side of the brain under the surgical site (arrow) compared with the left side. While the right-left difference in axon volume fraction is unclear (arrow), the g-ratio seems to be higher in the right parietal lobe (arrow).

On-line Table 1: Patient details

Patient No	Age (yr)	Sex	Presentation History	MRA Stages		PCA Lesion		Previous Surgery	Interval between Surgery and MR Imaging	Family History of MMD	<i>p.R4810K</i> Gene Variant	History
				Rt	Lt	Rt	Lt					
1	44	M	TIA→ IVH	4	3	Yes		Lt/D	344 days		Hetero	
2	17	F	TIA	2	3			Lt/I	334 days		Hetero	
3	28	F	TIA	3	2	Yes		Rt/I	316 days		Hetero	
4	45	F	TIA	3	3						Hetero	HTN
5	43	F	TIA	4	4			Lt/I	782 days		Hetero	
6	45	F	None	3	2	Yes					Hetero	HTN
7	28	F	TIA	4	4	Yes	Yes	Bil/I	8 yr	Yes	Hetero	HTN, cervical disk herniation
8	41	F	TIA	2	1						Hetero	Gastric cancer (removed)
9	41	F	TIA/infarction	3	3		Yes	Lt/I	13 yr		Hetero	
10	20	F	TIA	3	4	Yes	Yes	Bil/I	10 yr		Hetero	
11	44	F	HA	3	4		Yes				Wild	HTN
12	21	M	TIA	4	4			Bil/I	9 yr		Hetero	
13	29	F	HA	4	3	Yes			3 yr		Hetero	
14	42	F	TIA	3	3						Wild	HTN, DM, DLP
15	23	M	TIA	4	4			Bil/I	19 yr		Homo	
16	33	F	Infarction	4	4	Yes	Yes				Hetero	
17	49	F	TIA	4	4	Yes	Yes				Wild	DM, strabismus (cured)
18	55	F	ICH	4	4	Yes					Hetero	

Note:—IVH indicates intraventricular hemorrhage; ICH, intracerebral hemorrhage; D, direct bypass surgery; I, indirect bypass surgery; Rt, right; Lt, left; Bil, bilateral; HTN, hypertension; DM, diabetes mellitus; DLP, dyslipidemia; Homo, homogeneous; Hetero, heterogeneous; HA, headache; Wild, wild-type.

On-line Table 2: Summary of results of cognitive tests

Test (n = 18)	Mean	<1 SD
Verbal Comprehension Index	87.9 ± 12.9	6 (33%)
Perceptual Organization Index	89.8 ± 12.9	5 (28%)
Working Memory Index	85.1 ± 15.2	9 (50%)
Processing Speed Index	90.3 ± 10.4	5 (28%)
Word Fluency (letter, z score)	−0.35 ± 0.93	5 (28%)
Word Fluency (category, z score)	−0.22 ± 1.16	4 (22%)
Stroop (Incongruent Color Naming, z score)	0.66 ± 1.28	2 (11%)
TMT-A (z score)	0.49 ± 1.84	1 (7%)
TMT-B (z score)	−0.26 ± 0.72	0

On-line Table 3: Correlation among cognitive tests and regional parametric values

Test: <i>r</i> (<i>P</i>)	Rt ACA	Lt ACA	Rt MCA	Lt MCA	Rt PCA	Lt PCA
MVF						
Verbal Comprehension Index	0.08 (.79)	0.05 (.86)	0.21 (.45)	0.03 (.90)	0.06 (.84)	0.00 (.99)
Perceptual Organization Index	-0.01 (.98)	0.04 (.87)	0.21 (.40)	0.12 (.64)	0.16 (.53)	0.30 (.24)
Working Memory Index	0.15 (.57)	0.17 (.51)	0.33 (.19)	0.20 (.44)	-0.24 (.87)	0.33 (.19)
Processing Speed Index	-0.37 (.13)	-0.36 (.14)	-0.20 (.43)	-0.23 (.36)	-0.24 (.34)	-0.14 (.57)
Word Fluency (letter, <i>z</i> score)	0.15 (.60)	0.14 (.63)	0.28 (.31)	0.17 (.54)	0.13 (.65)	0.12 (.68)
Word Fluency (category, <i>z</i> score)	0.10 (.73)	-0.02 (.95)	0.28 (.32)	0.02 (.93)	-0.01 (.96)	-0.22 (.43)
Stroop (Incongruent Color Naming, <i>z</i> score)	-0.25 (.38)	-0.29 (.29)	-0.25 (.37)	-0.23 (.40)	-0.27 (.33)	-0.20 (.48)
TMT-A (<i>z</i> score)	-0.06 (.82)	0.05 (.83)	-0.15 (.56)	-0.03 (.89)	-0.24 (.33)	-0.08 (.75)
TMT-B (<i>z</i> score)	0.34 (.16)	-0.29 (.24)	-0.49 (.04 ^a)	-0.31 (.21)	-0.37 (.13)	-0.22 (.38)
AVF						
Verbal Comprehension Index	0.19 (.51)	-0.08 (.79)	0.29 (.30)	-0.09 (.76)	0.06 (.82)	-0.09 (.74)
Perceptual Organization Index	0.12 (.63)	0.12 (.63)	0.15 (.55)	0.06 (.82)	0.36 (.14)	0.10 (.69)
Working Memory Index	0.06 (.73)	-0.03 (.89)	0.09 (.72)	-0.08 (.76)	0.00 (.98)	0.00 (1.00)
Processing Speed Index	0.18 (.47)	0.33 (.18)	0.24 (.32)	0.27 (.29)	0.54 (.02 ^a)	0.32 (.20)
Word Fluency (letter, <i>z</i> score)	-0.04 (.88)	-0.13 (.64)	0.16 (.57)	-0.17 (.55)	0.29 (.30)	-0.04 (.89)
Word Fluency (category, <i>z</i> score)	0.08 (.78)	-0.06 (.83)	0.40 (.14)	-0.08 (.78)	0.23 (.42)	-0.22 (.44)
Stroop (Incongruent Color Naming, <i>z</i> score)	0.15 (.60)	0.28 (.32)	0.18 (.52)	0.23 (.41)	0.28 (.32)	0.30 (.29)
TMT-A (<i>z</i> score)	-0.23 (.36)	-0.2 (.44)	-0.36 (.15)	-0.13 (.61)	-0.54 (.02 ^a)	-0.16 (.52)
TMT-B (<i>z</i> score)	-0.40 (.10)	-0.25 (.32)	-0.55 (.02 ^a)	-0.16 (.51)	-0.52 (.03 ^a)	0.00 (1.00)
G-ratio						
Verbal Comprehension Index	0.03 (.91)	-0.12 (.67)	0.07 (.80)	-0.14 (.62)	-0.02 (.95)	-0.09 (.74)
Perceptual Organization Index	0.08 (.77)	0.05 (.500)	0.07 (.81)	-0.06 (.82)	0.21 (.39)	-0.24 (.35)
Working Memory Index	-0.09 (.83)	-0.16 (.54)	-0.22 (.40)	-0.26 (.31)	0.00 (.99)	-0.08 (.73)
Processing Speed Index	0.45 (.06)	0.49 (.04 ^a)	-0.28 (.08)	0.38 (.13)	0.64 (.004 ^b)	0.40 (.10)
Word Fluency (letter, <i>z</i> score)	-0.17 (.54)	-0.21 (.45)	-0.12 (.66)	-0.32 (.24)	0.14 (.62)	-0.14 (.63)
Word Fluency (category, <i>z</i> score)	-0.04 (.88)	-0.05 (.87)	0.09 (.75)	-0.11 (.69)	0.20 (.48)	-0.04 (.90)
Stroop (Incongruent Color Naming, <i>z</i> score)	0.32 (.24)	0.42 (.12)	0.39 (.15)	0.38 (.16)	0.42 (.12)	0.44 (.10)
TMT-A (<i>z</i> score)	-0.12 (.64)	-0.17 (.50)	-0.16 (.52)	-0.09 (.73)	-0.37 (.13)	-0.12 (.78)
TMT-B (<i>z</i> score)	0.00 (1.00)	0.04 (.88)	0.02 (.94)	-0.13 (.61)	-0.19 (.46)	0.15 (.06)
MD						
Verbal Comprehension Index	-0.06 (.81)	0.13 (.62)	-0.44 (.07)	0.03 (.89)	-0.31 (.21)	0.03 (.91)
Perceptual Organization Index	-0.03 (.90)	-0.02 (.94)	-0.26 (.30)	-0.03 (.89)	-0.41 (.09)	-0.18 (.47)
Working Memory Index	-0.19 (.46)	0.06 (.80)	-0.29 (.25)	0.10 (.68)	-0.28 (.25)	-0.04 (.88)
Processing Speed Index	0.03 (.90)	-0.16 (.53)	-0.17 (.61)	-0.12 (.63)	-0.56 (.02 ^a)	-0.37 (.13)
Word Fluency (letter, <i>z</i> score)	0.06 (.81)	0.14 (.58)	-0.26 (.29)	0.14 (.58)	-0.51 (.03 ^a)	-0.09 (.74)
Word Fluency (category, <i>z</i> score)	0.16 (.52)	0.33 (.19)	-0.47 (.05)	0.14 (.58)	-0.50 (.04 ^a)	0.11 (.66)
Stroop (Incongruent Color Naming, <i>z</i> score)	0.22 (.37)	-0.02 (.95)	0.08 (.75)	-0.05 (.83)	-0.31 (.20)	-0.28 (.26)
TMT-A (<i>z</i> score)	-0.06 (.82)	-0.04 (.88)	0.20 (1.00)	-0.05 (.84)	0.65 (.003 ^b)	0.18 (.48)
TMT-B (<i>z</i> score)	0.14 (.57)	-0.05 (.85)	0.59 (.01)	0.09 (.72)	0.54 (.02 ^a)	0.04 (.88)
FA						
Verbal Comprehension Index	0.09 (.73)	0.09 (.73)	0.20 (.42)	0.00 (1.00)	0.37 (.11)	0.06 (.82)
Perceptual Organization Index	0.13 (.61)	0.15 (.55)	0.14 (.58)	-0.05 (.84)	0.45 (.06)	0.29 (.24)
Working Memory Index	0.18 (.48)	0.17 (.51)	0.29 (.24)	0.06 (.81)	0.42 (.09)	0.14 (.59)
Processing Speed Index	0.04 (.87)	0.07 (.77)	-0.13 (.13)	-0.08 (.74)	0.35 (.16)	0.26 (.29)
Word Fluency (letter, <i>z</i> score)	-0.05 (.84)	-0.09 (.72)	-0.10 (.68)	-0.28 (.26)	0.23 (.37)	-0.15 (.55)
Word Fluency (category, <i>z</i> score)	0.00 (.99)	-0.11 (.67)	0.07 (.78)	-0.24 (.34)	0.24 (.34)	-0.26 (.29)
Stroop (Incongruent Color Naming, <i>z</i> score)	-0.06 (.83)	-0.04 (.88)	-0.18 (.49)	-0.03 (.89)	-0.01 (.97)	-0.00 (.97)
TMT-A (<i>z</i> score)	-0.14 (.57)	-0.03 (.92)	0.00 (1.00)	0.17 (.51)	-0.32 (.20)	0.05 (.86)
TMT-B (<i>z</i> score)	-0.31 (.20)	-0.15 (.56)	-0.30 (.23)	-0.06 (.82)	-0.56 (.015 ^b)	-0.08 (.76)
AD						
Verbal Comprehension Index	-0.09 (.72)	0.27 (.29)	-0.45 (.06)	0.01 (.96)	0.03 (.92)	0.11 (.66)
Perceptual Organization Index	0.15 (.54)	0.13 (.62)	-0.23 (.35)	-0.15 (.56)	-0.06 (.83)	0.18 (.48)
Working Memory Index	-0.05 (.85)	0.27 (.27)	-0.14 (.57)	0.21 (.42)	0.08 (.74)	0.15 (.55)
Processing Speed Index	-0.04 (.88)	-0.29 (.24)	-0.37 (.87)	-0.36 (.14)	-0.38 (.12)	-0.20 (.43)
Word Fluency (letter, <i>z</i> score)	-0.20 (.44)	0.04 (.87)	-0.54 (.02 ^a)	-0.17 (.51)	-0.49 (.04 ^a)	-0.43 (.07)
Word Fluency (category, <i>z</i> score)	0.19 (.55)	0.42 (.08)	-0.63 (.005 ^b)	-0.08 (.74)	-0.44 (.07)	-0.27 (.28)
Stroop (Incongruent Color Naming, <i>z</i> score)	0.25 (.32)	-0.06 (.80)	-0.06 (.82)	-0.14 (.58)	-0.49 (.04 ^a)	-0.51 (.03 ^a)
TMT-A (<i>z</i> score)	-0.22 (.38)	-0.07 (.78)	0.32 (.19)	0.16 (.53)	0.59 (.01 ^b)	0.40 (.10)
TMT-B (<i>z</i> score)	-0.10 (.69)	-0.21 (.39)	0.58 (.01)	0.13 (.60)	0.14 (.57)	0.00 (1.00)

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On-line Table 3: Continued

Test: <i>r</i> (<i>P</i>)	Rt ACA	Lt ACA	Rt MCA	Lt MCA	Rt PCA	Lt PCA
RD						
Verbal Comprehension Index	−0.00 (.97)	0.05 (.83)	−0.36 (.15)	0.03 (.91)	−0.38 (.12)	−0.00 (.99)
Perceptual Organization Index	−0.06 (.83)	−0.08 (.75)	−0.21 (.39)	0.01 (.96)	−0.47 (.048 ^a)	−0.26 (.31)
Working Memory Index	−0.15 (.54)	−0.03 (.90)	−0.29 (.24)	0.05 (.86)	−0.38 (.12)	−0.09 (.73)
Processing Speed Index	0.04 (.87)	−0.10 (.68)	−0.04 (.87)	−0.02 (.94)	−0.51 (.03 ^a)	−0.34 (.17)
Word Fluency (letter, <i>z</i> score)	0.11 (.67)	0.15 (.55)	−0.08 (.74)	0.23 (.36)	−0.42 (.08)	0.05 (.85)
Word Fluency (category, <i>z</i> score)	0.14 (.59)	0.26 (.30)	−0.29 (.24)	0.21 (.41)	−0.42 (.08)	0.21 (.41)
Stroop (Incongruent Color Naming, <i>z</i> score)	0.15 (.56)	0.01 (.96)	0.13 (.61)	−0.01 (.95)	−0.18 (.48)	−0.14 (.58)
TMT-A (<i>z</i> score)	0.02 (.93)	−0.03 (.90)	0.10 (.69)	−0.13 (.62)	0.54 (.02 ^a)	0.06 (.80)
TMT-B (<i>z</i> score)	0.17 (.49)	0.01 (.98)	0.49 (.04 ^a)	0.07 (.78)	0.60 (.009 ^b)	0.04 (.88)

Note:—MD indicates mean diffusivity; FA, fractional anisotropy; AD, axial diffusivity; RD, radial diffusivity; Rt, right; Lt, left.

^a *P* < .05.

^b *P* < .05 (Bonferroni correction for comparison of 3 parameters).