RESEARCH ARTICLE OPEN ACCESS

Associations of Blood Cardiovascular Biomarkers With Brain Free Water and Its Relationship to Cognitive Decline

A Diffusion-MRI Study

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Abstract

Background and Objectives

There is an increasing awareness of the "Heart-Brain Connection," whereby cardiovascular function is connected with cognition. Diffusion-MRI studies reported higher brain free water (FW) was associated with cerebrovascular disease (CeVD) and cognitive impairment. In this study, we investigated whether higher brain FW was related to blood cardiovascular biomarkers and whether FW mediated the associations between blood biomarkers and cognition.

Methods

Participants recruited from 2 Singapore memory clinics between 2010 and 2015 underwent collection of blood samples and neuroimaging at baseline and longitudinal neuropsychological assessments up to 5 years. We examined the associations of blood cardiovascular biomarkers (high-sensitivity cardiac troponin-T [hs-cTnT], N-terminal pro-hormone B-type natriuretic peptide [NT-proBNP], and growth/differentiation factor 15 [GDF-15]) with brain white matter (WM) and cortical gray matter (GM) FW derived from diffusion MRI using whole brain voxel-wise general linear regression. We then assessed the relationships among baseline blood biomarkers, brain FW, and cognitive decline using path models.

Results

A total of 308 older adults (76 with no cognitive impairment, 134 with cognitive impairment no dementia, and 98 with Alzheimer disease dementia and vascular dementia; mean [SD] age: 72.1 [8.3]) were included. We found that blood cardiovascular biomarkers were associated with higher FW in widespread WM regions and in specific GM networks including the default mode, executive control, and somatomotor networks at baseline ($p < 0.01$, family-wise error corrected). Baseline FW in widespread WM and network-specific GM fully mediated the associations of blood biomarkers with longitudinal cognitive decline over 5 years. Specifically, in GM, higher FW in the default mode network mediated the relationship with memory decline (hs-cTnT: $\beta = -0.115$, SE = 0.034, $p = 0.001$; NT-proBNP: $\beta = -0.154$, SE = 0.046, $p = 0.001$; GDF-15: $\beta = -0.073$, SE = 0.027, $p = 0.006$); by contrast, higher FW in the executive control network was responsible for executive function decline (hs-cTnT: $\beta = -0.126$, SE = 0.039, $p = 0.001$;

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Glossary

AD = Alzheimer disease; **BBB** = blood-brain barrier; **BMI** = body mass index; **CeVD** = cerebrovascular disease; **CIND** = cognitive impairment no dementia; **DTI** = diffusion tensor imaging; **DMN** = default mode network; **dMRI** = diffusion MRI; ***DSM-IV*** = *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*; **ECN** = executive control network; **FAt** = tissue compartment fractional anisotropy; **FW** = free water; **GDF-15** = growth/differentiation factor 15; **GLM** = general linear model; **GM** = gray matter; **hs-cTnT** = high-sensitivity cardiac troponin-T; **NCI** = no cognitive impairment; **NT-proBNP** = N-terminal pro hormone B-type natriuretic peptide; **SMN** = somatomotor network; **TIV** = total intracranial volume; **VaD** = vascular dementia; **WM** = white matter; **WMH** = WM hyperintensity.

NT-proBNP: β = −0.110, SE = 0.038, p = 0.004; GDF-15: β = −0.117, SE = 0.035, p = 0.001). Similar full mediation effects of brain FW were also identified for baseline cognition.

Discussion

Results suggested a role of brain FW in linking cardiovascular dysfunction to cognitive decline. These findings provide new evidence for brain-heart interactions, paving the way for prediction and monitoring of domain-specific cognitive trajectory.

Cerebrovascular disease (CeVD) is related to an increased risk of developing cognitive impairment and dementia.[1] There is an increasing awareness of a "Heart-Brain Connection,"[2] where cardiac disease and vascular function may potentially contribute to CeVD, dementia due to Alzheimer disease (AD), and vascular cognitive impairment.[3-5] Studies have demonstrated that peripheral cardiovascular dysfunction may lead to blood vessel damage and neurovascular alterations through both vascular and AD pathophysiologic pathways in dementia, which eventually cause neuronal injury and cognitive dysfunction.[6] For example, the established circulating markers of cardiac diseases such as high-sensitivity cardiac troponin-T (hs-cTnT) and N-terminal prohormone B-type natriuretic peptide (NT-proBNP) exhibit upregulation in the early phases of cardiac dysfunction and myocardial injury.[7] These cardiovascular blood biomarkers have been associated with concomitant CeVD MRI markers such as cortical microinfarcts[8,9] and cognitive dysfunction.[10] BNP, particularly, was found to predict vascular cognitive impairment, independent of cardiovascular risk factors.[7,10] Growth/differentiation factor 15 (GDF-15), a cardiovascular biomarker with protective and trophic bioactivity in cardiomyocytes,[11] was related to small vessel CeVD in dementia.[10] However, the relationships between circulating cardiovascular markers and cerebrovascular function underlying cognitive decline are not yet fully understood.

Diffusion MRI (dMRI) has emerged as an important method for studying CeVD and dementia.[12] Free water (FW) volume derived from dMRI[13] using a bitensor model reflects the relative contribution of freely diffusing extracellular water molecules that are unrestricted by their local microenvironment.[13] Higher FW in the white matter (WM) was found in patients with CeVD or AD dementia compared with that in controls and associated with dementia severity and cognitive decline.[14-17] Of interest, a recent study demonstrated that FW alternations in the gray matter (GM) may indicate neuronal microstructure perturbations in the AD continuum[18] and was associated with cognition.[19] However, there is a lack of understanding of whether cardiovascular dysfunction is related to these CeVD-related FW abnormalities and eventually leads to general and domain-specific cognitive impairment. Furthermore, it is unclear whether such relationships are specific to certain brain networks or regions.

Accumulating evidence suggests that the executive control network (ECN) and somatomotor network (SMN) changes were related to cerebrovascular dysfunction.[20-22] By contrast, AD pathology (i.e., amyloid plaques and neurofibrillary tangles) leads to targeted large-scale brain network disorganization specifically in the default mode network (DMN).[23,24] Reduced network connectivity (through resting-state functional MRI) and metabolism (through [^{18}F]Fluorodeoxyglucose-PET) in the ECN and DMN were associated with deficits in executive function and memory.[25-27] Nevertheless, it remains unknown whether brain cortical FW changes relate to cardiovascular dysfunction and domain-specific cognitive decline in a network-specific manner.

To investigate these research questions, we examined the associations of brain FW in WM and GM with cardiovascular blood biomarker levels and cognitive measures in an Asian memory clinic population with a high CeVD burden. We hypothesized that (1) higher cardiovascular biomarkers levels would be associated with higher FW mainly in the frontal-parietal regions related to executive and somatomotor functions; (2) both baseline GM and WM FW would mediate the associations of cardiovascular biomarkers with baseline and longitudinal changes of global cognition; and (3) cortical GM FW would influence cognitive function in a brain network–specific manner.

Methods

Participants

This study was part of an ongoing prospective memory clinic study. Participants with no cognitive impairment (NCI),

cognitive impairment with no dementia (CIND), AD dementia and vascular dementia (VaD) were recruited from the National University Hospital of Singapore and Saint Luke's Hospital.[17,28,29] AD dementia was diagnosed in accordance with *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (*DSM-IV*) for dementia and internationally established criteria for the clinical diagnosis of AD dementia.[30] VaD was diagnosed using the *DSM-IV* criteria for dementia and internationally established criteria for the clinical diagnosis of VaD.[31] CIND was determined based on objective impairment in at least 1 domain of the neuropsychological assessment but did not meet the *DSM-IV* criteria for dementia.[28] Participants were classified as NCI if they had no objective impairment in the neuropsychological assessment.[29] Participants of the cohort study were aged 50 years and older and had no major vascular risk factor–related encephalopathy or significant neurologic comorbid conditions or loss of functional independence (detailed diagnoses, significant CeVD, and inclusion/exclusion criteria are provided in eMethods, links.lww.com/WNL/C813).

Of 471 participants enrolled between August 2010 and August 2015, we studied 308 participants (76 with NCI, 134 with CIND, and 98 with AD and VaD) according to the following criteria (see flowchart in eFigure 1, links.lww.com/WNL/C813): (1) passed the MRI data quality control (details in imaging data processing) and (2) had blood and cognitive test information (Table 1). A total of 271 participants (68 with NCI, 121 with CIND, and 82 with AD and VaD) with baseline cognitive scores and at least 1 follow-up were included in the longitudinal analysis (eTable 1). Characteristics of the included and excluded participants were similar (eTable 2).

Neuropsychological Assessments

Neuropsychological assessments were performed using a locally validated comprehensive neuropsychological battery[32] at

Table 1 Demographic, Cognition, and Circulating Cardiovascular Biomarker Levels of Participants

	NCI (n = 76)	CIND (n = 134)	Dementia (n = 98)	*p* Value
Age, y, mean (SD)	68.5 (6.1)	71.0 (8.2)	76.3 (8.2)[a,b]	**<0.001**
Sex, female/male	44/32	62/72	62/36	**0.03**
Ethnicity, Chinese/non	67/9	103/31	73/25	0.07
Education, y, mean (SD)	10.3 (4.7)	7.6 (4.9)[a]	4.8 (4.9)[a,b]	**<0.001**
Handedness, right/left	73/3	131/3	98/0	0.12
MMSE (max = 30), median (IQR)	28.0 (3.0)	25.0 (4.0)[a]	16.0 (7.0)[a,b]	**<0.001**
Global CDR, mean (SD)	0.1 (0.2)	0.3 (0.2)[a]	1.2 (0.5)[a,b]	**<0.001**
Hypertension, yes/no	43/33	91/43	83/15	**<0.001**
Hyperlipidemia, yes/no	51/25	105/29	71/27	0.19
Diabetes mellitus, yes/no	17/59	51/83	42/56	**0.02**
History of heart disease, yes/no	5/71	15/119	8/90	0.50
History of stroke, yes/no	12/64	51/83	27/71	**0.003**
Antiplatelet therapy, yes/no	18/58	48/86	34/64	0.17
Smoking, yes/no	20/56	40/94	25/73	0.74
BMI, kg/m^2, mean (SD)	24.6 (4.1)	24.1 (3.6)	23.8 (3.9)	0.38
GDF-15, pg/mL, median (IQR)	n = 76	n = 134	n = 98	
	827.1 (350.9)	1132.2 (1057.0)[a]	1555.4 (1549.7)[a,b]	**<0.001**
NT-proBNP, pg/mL, median (IQR)	n = 45	n = 93	n = 80	
	65.4 (58.8)	111.5 (152.7)[a]	179.5 (316.7)[a,b]	**<0.001**
hs-cTNT, pg/mL, median (IQR)	n = 45	n = 93	n = 80	
	6.2 (4.1)	9.6 (7.9)[a]	13.9 (10.4)[a,b]	**<0.001**

Abbreviations: ANOVA = analyses of variance; BMI = body mass index; CDR = Clinical Dementia Rating; CIND = cognitive impairment no dementia; GDF-15 = growth/differentiation factor 15; hs-cTnT = high-sensitivity cardiac troponin-T; IQR = interquartile range; MMSE = Mini-Mental State Examination; MoCA = Montreal Cognitive Assessment; NCI = no cognitive impairment; NT-proBNP = N-terminal pro hormone B-type natriuretic peptide.
Superscript letters indicate whether the group mean was significantly different compared with [a]NCI; [b]CIND; following 1-way ANOVA or nonparametric Kruskal-Wallis ANOVA (for MMSE and blood biomarkers). X^2 tests were conducted on sex and ethnicity and binarized vascular-related covariates, while the Fisher exact test was conducted for handedness. Bold indicates $p < 0.05$.

baseline and at years 2, 4, and 5, which assesses memory, executive function, language, attention, visuomotor speed, and visuoconstruction (individual subtests in each domain are summarized in eTable 3, links.lww.com/WNL/C813). Standardized domain scores were calculated following the previous study[33] (see eMethods).

Vascular Risk Factor Assessment and Medications

Data on various risk factors associated with vascular health were collected through a combination of clinical interview, examination of medical records, and physical examination.[9] Hypertension was defined as systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg or the use of antihypertensive medication. Hyperlipidemia was defined as total cholesterol levels ≥4.14 mmol/L or the use of lipid-lowering medication. Diabetes mellitus was defined as glycated hemoglobin ≥6.5% or the use of diabetic medication. Heart disease was defined as the presence of coronary artery disease, ischemic heart disease, or atrial fibrillation. History of stroke was defined as having a clinical history of rapid-onset focal or global neurologic deficits for >24 hours and confirmed on medical records. Antiplatelet therapy was defined as the use of antiplatelet medication. In addition, smoking history and body mass index (BMI) were also recorded. BMI was calculated by participant's weight in kilograms divided by the square of height in centimeters.

Blood Cardiovascular Biomarkers

Nonfasting blood was drawn from study participants. NT-proBNP and hs-cTnT were measured using electrochemiluminescence immunoassays on an automated Cobas-e411 analyzer, while GDF-15 levels were measured using quantitative sandwich immunoassays (see eMethods, links.lww.com/WNL/C813).

Image Acquisition and Processing

Each participant underwent MRI scanning at the Center for Translational MR Research, National University of Singapore (3-T MAGNETOM Trio, Siemens, Germany). High-resolution T1-weighted structural MRI was performed using a magnetization-prepared rapid gradient echo. dMRI scans were acquired using a single-shot fast echo-planar imaging sequence (b value = 1,150 s/mm^2, 61 diffusion directions, and 7 b_0). Fluid-attenuated inversion recovery was also acquired.

The dMRI preprocessing was following previous work[17] including correction for head movements, eddy current distortions, and geometric distortions. We used the FW imaging method on the preprocessed dMRI data to estimate the fractional volume of freely diffusing extracellular water molecules (FW) and the tissue compartment fractional anisotropy (FAt).[13] Tract-based spatial statistics was applied to perform the WM FW maps,[17] while surface-based approach was used to derive cortical GM FW maps[18] of each participant. Please see eMethods (links.lww.com/WNL/C813) for details of image acquisition and processing.

Statistical Analyses

Associations Between Cardiovascular Biomarker Levels and Brain FW

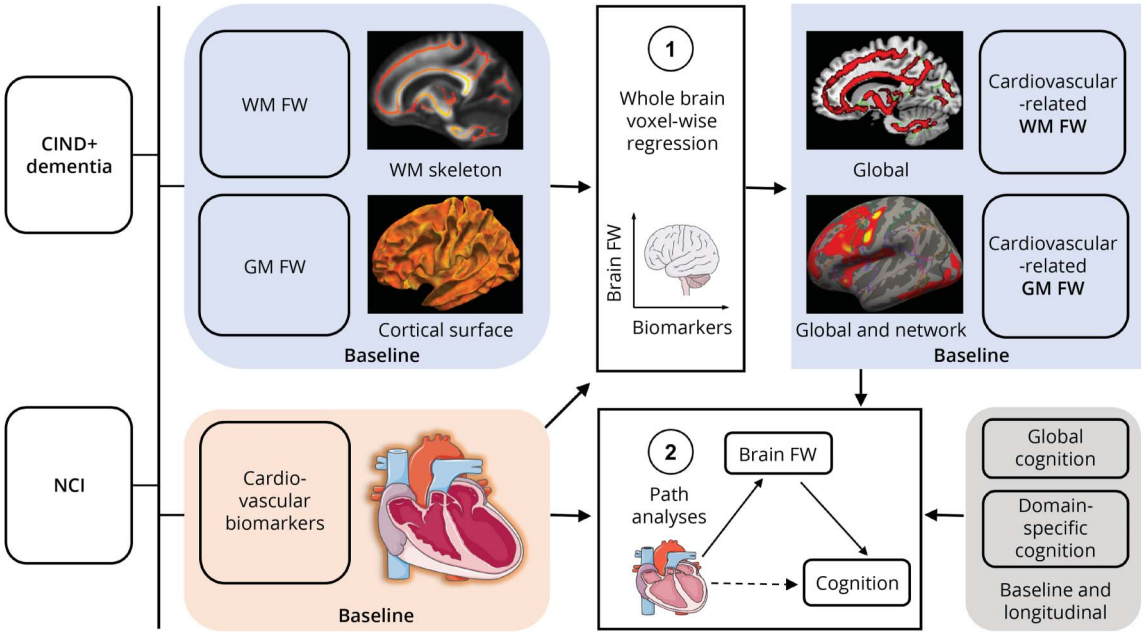
To identify region-specific associations between brain FW and the 3 logarithmically transformed blood cardiovascular biomarkers within each clinical group (CIND + dementia and NCI), we built general linear models (GLMs) for each blood biomarker separately (Figure 1, step 1). The FW in the vertex-wise surfaced GM or voxel-wise skeletonized WM images were entered as the dependent variables. Each blood biomarker level was the independent variable of interest. We included age, sex, education, ethnicity, total intracranial volume (TIV), cognitive status, and CeVD status as additional covariates for both GLMs. We tested the interaction effects of cognitive status (i.e., CIND/dementia) and CeVD status (i.e., with and without CeVD) for the GLM of CIND + dementia. We also tested the interaction effects of CeVD status for the GLM of NCI. For WM FW measures, skeleton regions were examined for statistical significance using threshold-free cluster enhancement and permutation-based nonparametric testing (FSL, Randomise). For GM FW measures, cortical regions were tested for significance using a Monte-Carlo simulation with 10,000 repeats (Freesurfer, Glmfit). GLM results for both WM and GM were reported at $p < 0.01$, family-wise error corrected.

To mitigate possible confounds due to regional atrophy, we included GM cortical thickness or WM volume as additional covariates in vertex/voxel-based statistical models. To control for the influence of vascular-related factors, we included the 8 vascular-related covariates (hypertension, hyperlipidemia, diabetes mellitus, a history of heart disease, a history of stroke, antiplatelet therapy, smoking history, and BMI) as nuisance variables. Last, to minimize potential confounds due to WM hyperintensity (WMH), we derived FW in normal-appearing WM after excluding regions with WMH and repeated the association analyses. We also compared the participant characteristics across the 3 cognitive groups (see eMethods, links.lww.com/WNL/C813 and Table 1).

Associations Between Cardiovascular Biomarker Levels and Cognition

Based on the previous evidence that memory and executive dysfunctions are most prevalent in dementia with concomitant AD and CeVD,[1,4,28,34] we conducted correlation analyses between logarithmically transformed cardiovascular biomarker levels and cognition decline over time in all patients (CIND + dementia), with a priori interest in global cognition, memory, and executive function. Linear regression was calculated between the baseline cognitive scores/longitudinal rate of changes and cardiovascular biomarker levels across all patients. The main model adjusted for age, sex, years of education, ethnicity, TIV, cognitive stage, and CeVD status. We also validated the results in crude model (no covariates adjusted) and a model with further adjusted vascular-related covariates. The threshold was set at $p < 0.05$ (2-tailed).

Figure 1 Study Design Schematic



A total of 308 participants with either NCI, CIND or dementia were studied. GLMs were performed to identify region-specific associations between brain FW and the 3 blood cardiovascular biomarkers within the CIND + dementia group or NCI at baseline (step 1). Path analyses were used to evaluate whether and how FW in the gray and white matter mediated the effects of higher blood marker levels on baseline global cognitive deficits and longitudinal decline (step 2). Furthermore, the influences of network-specific GM FW on the association of higher blood marker levels with individual cognitive domains were also evaluated. CIND = cognitive impairment with no dementia; FW = free-water; GLM = general linear model; GM = gray matter; NCI = no cognitive impairment; WM = white matter.

To calculate the annual rate of change in cognitive outcomes over time (mean = 3.81, SD = 1.52 years), linear mixed models were conducted (see eMethods, links.lww.com/WNL/C813).

Path Analyses

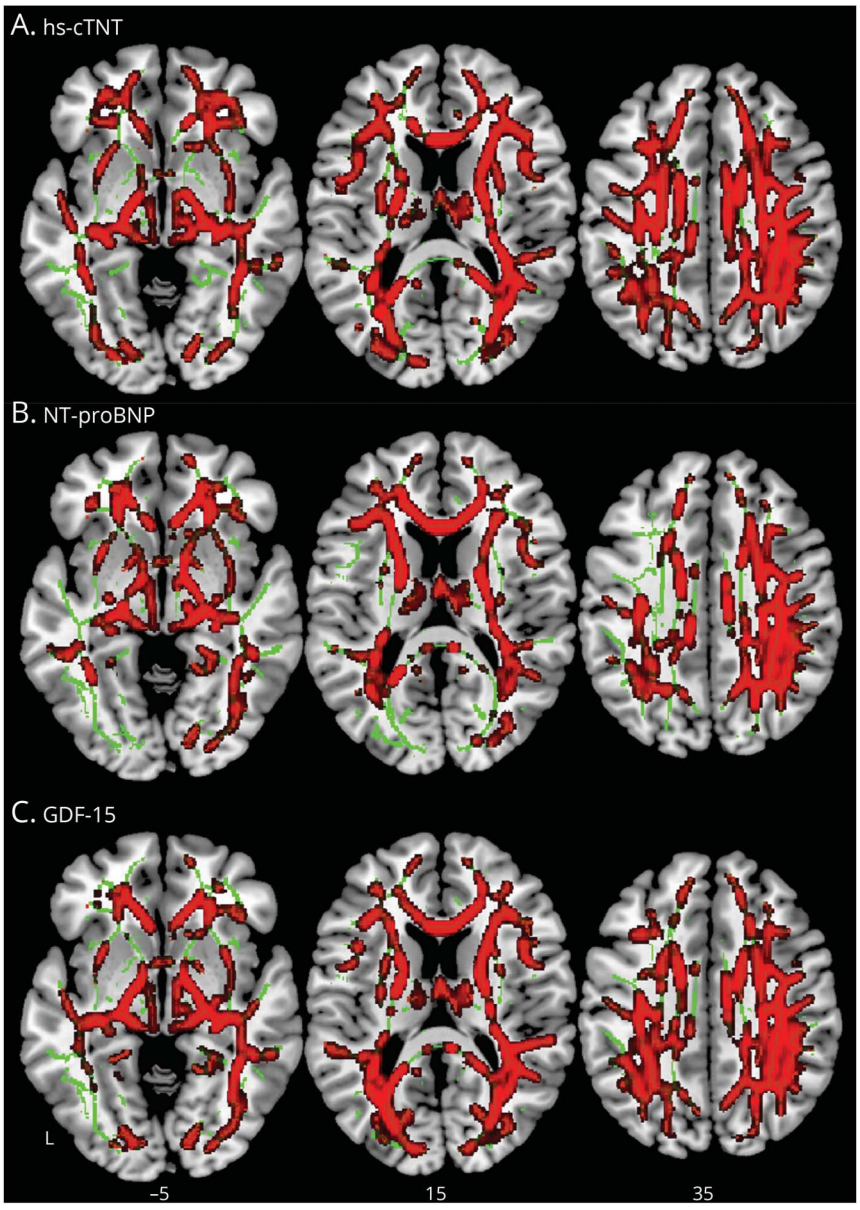
To evaluate whether and how FW in the GM and WM mediates the effects of higher blood marker levels on baseline global cognitive deficits and longitudinal decline, we first performed path analyses by including each blood biomarker (NT-proBNP, hs-cTnT, or GDF-15) as a predictor, both WM and GM matter FW as mediators, and baseline global cognitive scores or longitudinal global cognitive rate of changes as outcomes (Figure 1, step 2). We used structural equation modeling method (R [version 3.3.1] packages Lavaan [version 0.5–20]) controlling for age, sex, years of education, ethnicity, TIV, cognitive stage, and CeVD status following our previous work.[33] We built 1 model for each of the 3 blood biomarkers and each of the 2 outcome (baseline or longitudinal cognition) variables (i.e., in total, 6 models). For each model, to represent GM and WM FW, we created brain masks containing only the regions that were significantly correlated with each blood cardiovascular biomarker. Path analyses were used to simultaneously consider the direct effect (blood biomarker on cognition) and the indirect effect (each blood marker on cognition through mediators).

Second, we further evaluated how FW influenced the association of higher blood marker levels on individual cognitive domains (executive function and memory) using path models. Based on the work from our group and others,[15,17,28,35,36] we expected that the role of FW in WM would be widespread while the contribution from GM would be specific to cognitive networks. Therefore, we parcellated blood biomarker-related GM regions (from the previous step) into regions of interests according to the existing cortical functional parcellation.[37] This parcellation used clustering approach to identify and replicate 7 networks of functionally coupled regions across the cerebral cortex, which have been shown corresponding to individual cognitive performance.[37] In these models, blood biomarker was the predictor; the mean GM FW of each network and mean WM FW values derived from previous significant regions were the mediators, and baseline memory and executive function scores or longitudinal rate of changes were the outcomes. Age, sex, years of education, TIV, cognitive stages, and CeVD status were also included in the models. To mitigate possible confounds due to regional atrophy, we also repeated the same path analyses using the ratio of mean WM FW divided by WM volume and network-specific GM FW divided by network-specific cortical thickness as mediators. We built the path model, evaluated the model fits, and reported direct and indirect effects following the criteria in the previous work[33] (see eMethods, links.lww.com/WNL/C813).

Standard Protocol Approvals, Registrations, and Patient Consents

Ethical approval was obtained from National Healthcare Group Domain-Specific Review Board (2015/00406-AMD0012). Participants gave informed consent according to the Declaration of Helsinki.

Figure 2 Higher White Matter FW Correlated With Circulating Cardiovascular Marker Levels



The whole-brain voxel-wise linear regression indicated that higher FW values in widespread brain white matter regions were associated with increased levels of (A) hs-cTNT, (B) NTpro-BNP, and (C) GDF-15. Results are TFCE enhanced, reported at $p < 0.01$, FWE corrected. FW = free water; FWE = family-wise error; GDF-15 = growth/differentiation factor 15; hs-cTnT = high-sensitivity cardiac troponin-T; NT-proBNP = N-terminal pro hormone B-type natriuretic peptide; TFCE = threshold-free cluster enhancement.

Data Availability

Data are available on reasonable request. Datasets generated for this study are available on request to the senior author for noncommercial academic studies but may be subject to some restrictions according to consent and confidentiality.

Results

Group Differences in Blood Cardiovascular Markers and Brain FW

Blood cardiovascular markers levels were higher in those with CIND and patients with dementia compared with those with NCI. Patients with dementia had greater blood cardiovascular marker levels than the CIND group (Table 1). Within the same cognitive stage, participants with CeVD had higher cardiovascular markers levels than the non-CeVD participants (see eMethods and eTable 4, links.lww.com/WNL/C813). FW averaged across all the WM regions was greater in those with CIND with and without CeVD compared with their NCI counterparts (eFigure 2A). Furthermore, patients with dementia had greater WM FW than those with CIND. Participants with CeVD had greater WM FW compared with non-CeVD participants among NCI, CIND, and dementia groups. Similarly, FW averaged across all the GM regions was increased along the dementia continuum. However, participants with CeVD did not show higher GM FW than their non-CeVD counterparties (eFigure 2B). These results remained in an age-matched, sex-matched, and education-matched subcohort (see eResults and eFigure 3).

Associations of WM FW With Circulating Cardiovascular Biomarker Levels

The voxel-wise analysis on the WM FW metrics showed that greater cardiovascular biomarker levels (NT-proBNP, hs-cTnT, and GDF-15) were associated with higher FW in multiple WM regions (including projection, association, commissural, limbic, and brainstem fibers) in all patients with CIND and dementia at baseline (Figure 2, eTable 5, links.lww.com/WNL/C813). There was no interaction effect of cognitive stage or CeVD status on such association. There was no region showing association of WM FW with blood biomarkers in NCI regardless of the CeVD status.

The results remained when (1) controlling for regional WM volume (eFigure 4A, links.lww.com/WNL/C813), (2) controlling for vascular-related covariates (eFigure 4B), and (3) using FW in normal-appearing WM after excluding regions with WMH (eResults). In addition, there was no association of blood cardiovascular biomarker levels with WM tissue compartment FAt. GDF-15, but not NT-proBNP and hs-cTNT, was associated with total WMH volume ($r = 0.19$, 95% confidence interval 0.07–0.31, $p < 0.05$).

Associations of GM FW With Circulating Cardiovascular Biomarker Levels

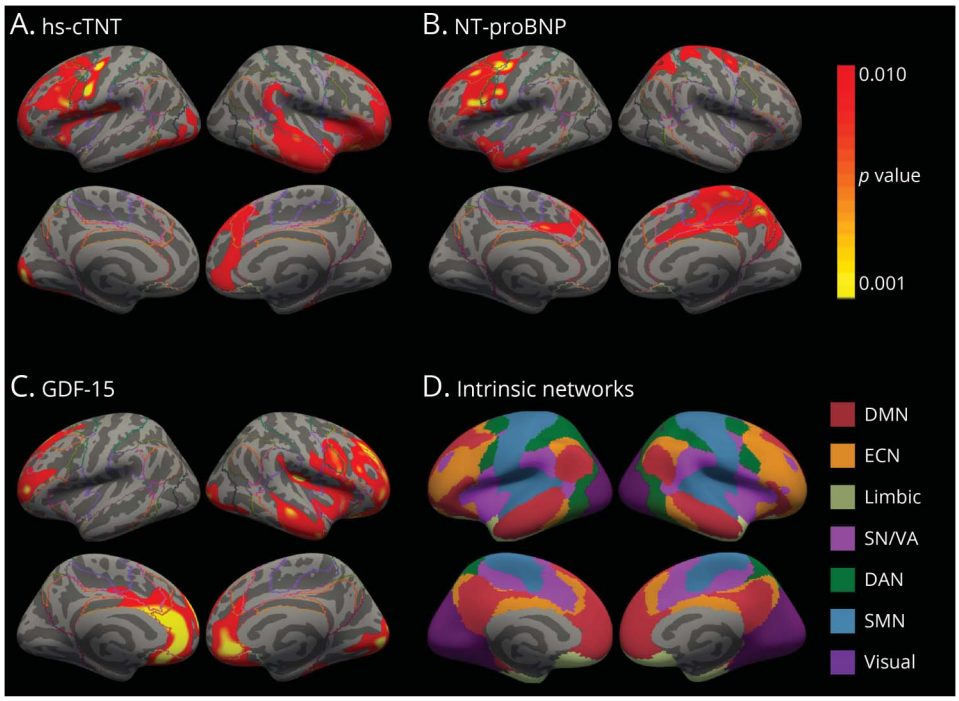
All 3 cardiovascular biomarkers were related to higher FW in GM at baseline, primarily in the ECN, DMN, and SMN. Specifically, higher hs-cTnT was associated with greater FW in bilateral middle frontal and temporal regions, mainly within the DMN, ECN, SMN, and parts of dorsal/ventral attention and limbic networks (Figure 3A, eTable 6, links.lww.com/WNL/C813). Similarly, greater NT-proBNP was associated with higher FW in bilateral frontal-parietal and left temporal regions, within the ECN, DMN, SMN, and attention networks (Figure 3B, eTable 6). Higher GDF-15 levels were associated with higher FW in the bilateral superior frontal and anterior cingulate regions and right temporal-occipital regions, which contain bilateral DMN, ECN, attention networks, and right limbic and visual networks (Figure 3C, eTable 6). There was no interaction effect of cognitive stage or CeVD status on this relationship. For NCI with and without CeVD, no association was found between GM FW and blood biomarkers.

The results remained when controlling for (1) the regional cortical thickness (eFigure 5A, links.lww.com/WNL/C813) and (2) vascular-related covariates (eFigure 5B). Besides, we did not find any associations between cardiovascular biomarker levels and cortical thickness.

Brain FW Mediated the Association of Cardiovascular Biomarkers With Cognition

We found that baseline cardiovascular biomarker levels were associated with baseline global cognition, executive functioning, and memory impairment and longitudinal cognitive decline (Table 2). The results remained after further adjusting for vascular-related covariates and in the crude model (no covariates adjusted) (eTable 7, links.lww.com/WNL/C813).

Figure 3 Higher Gray Matter FW Correlated With Circulating Cardiovascular Marker Levels



The whole-brain vortex-wise linear regression indicated that higher FW values in middle frontal and temporal lobes and cingulate regions were associated with increased levels of (A) hs-cTNT, (B) NTpro-BNP, and (C) GDF-15. (D) Yeo's functional intrinsic networks parcellation.[37] Results are reported at $p < 0.01$, FWE corrected. DAN = dorsal attention network; DMN = default mode network; ECN = executive control network; FW = free water; GDF-15 = growth/differentiation factor 15; hs-cTnT = high-sensitivity cardiac troponin-T; NT-proBNP = N-terminal pro hormone B-type natriuretic peptide; SMN = somatomotor network; SN/VA = ventral attention network.

Table 2 Associations of Cardiovascular Biomarker Levels With Baseline and Longitudinal Cognitive Scores

	hs-cTnT (*r*, 95% CI)	NT-proBNP (*r*, 95% CI)	GDF 15 (*r*, 95% CI)
Baseline			
Sample size	173	173	232
Global cognition	−0.24 (−0.41 to −0.07)**	−0.26 (−0.45 to −0.07)**	−0.22 (−0.36 to −0.09)**
Executive function	−0.25 (−0.40 to −0.09)**	−0.28 (−0.45 to −0.11)***	−0.21 (−0.35 to −0.06)**
Memory	−0.35 (−0.52 to −0.19)***	−0.25 (−0.40 to −0.11)**	−0.28 (−0.45 to −0.11)***
Longitudinal			
Sample size	155	155	203
Global cognition	−0.22 (−0.37 to −0.07)**	−0.23 (−0.38 to −0.08)**	−0.24 (−0.39 to −0.11)***
Executive function	−0.21 (−0.35 to −0.06)**	−0.22 (−0.37 to −0.07)**	−0.20 (−0.34 to −0.06)**
Memory	−0.30 (−0.45 to −0.16)***	−0.29 (−0.43 to −0.15)***	−0.22 (−0.35 to −0.08)**

Abbreviations: GDF-15 = growth/differentiation factor 15; hs-cTnT = high-sensitivity cardiac troponin-T; NT-proBNP = N-terminal pro hormone B-type natriuretic peptide.
**$p < 0.01$ and ***$p < 0.001$.

The baseline mean FW levels in both GM and WM mediated the association of hs-cTNT with baseline global cognitive impairment (Figure 4A, eTable 8, links.lww.com/WNL/C813) and the rate of global cognitive decline over time (Figure 4B, eTable 9). Given the significant indirect effects (eTables 5 and 6) of hs-cTNT on global cognition through GM FW and WM, and nonsignificant direct paths from blood markers levels to global cognition, we observed a complete mediation effect of both GM and WM FW. Similar mediation effects of brain FW on the association of NT-proBNP and GDF-15 levels with both baseline global cognition and rate of change in global cognition over time were observed (eResults, eFigure 6, eTables 8 and 9).

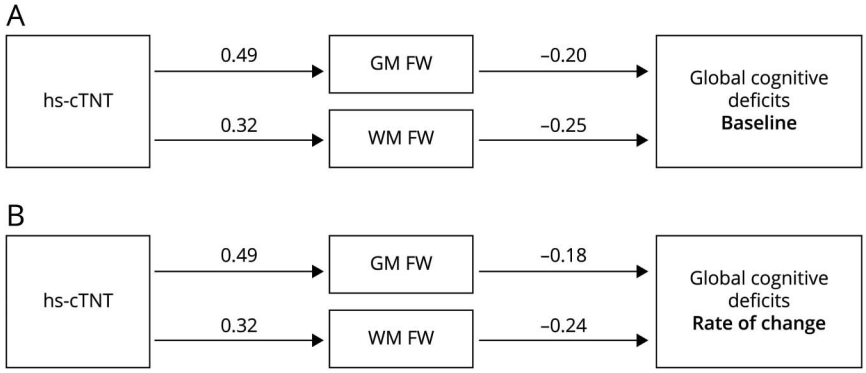
For the cognitive domain–specific (executive function and memory) path analysis, FW in the ECN mediated the effect of hs-cTnT levels on baseline (eFigure 7, eTable 10, links.lww.com/WNL/C813) and the rate of executive function decline (Figure 5, eTable 11). ECN FW had no effect on memory. By contrast, FW in the DMN mediated the effect of hs-cTnT levels on baseline and longitudinal memory decline but did not influence executive function. Last, the mean WM FW was the mediator of both pathways (executive function and memory).

Notably, the direct paths between hs-cTnT and cognition were not significant during the model pruning stage. All mediators exerted a full mediation effect because the indirect effects of hs-cTnT on cognition through all FW measures were significant. Similar findings were observed in the path analysis of NT-proBNP and CDF-15 (eResults, eTables 10 and 11, links.lww.com/WNL/C813). All results remained after controlling for WM volume and network-specific cortical thickness (eTables 12 and 13).

Discussion

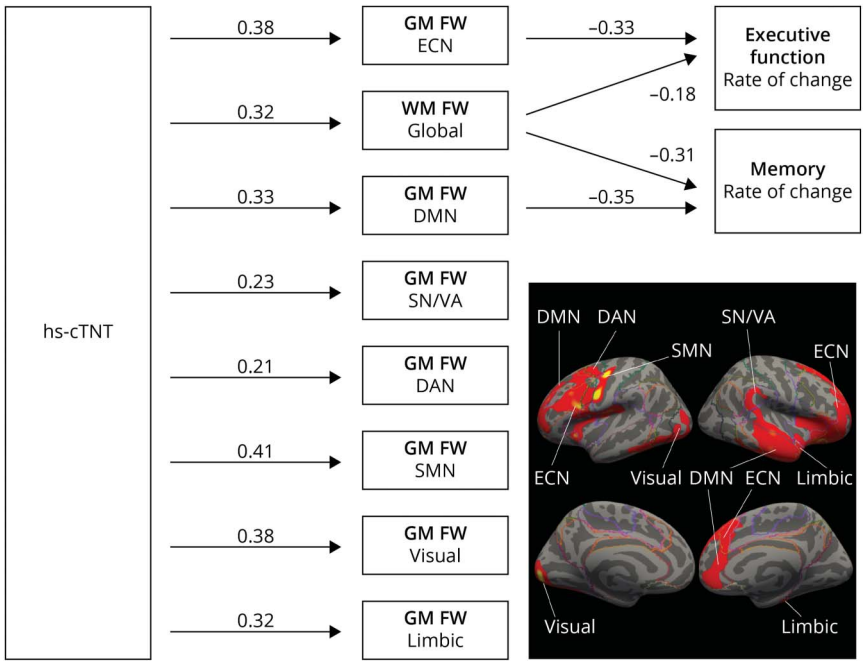
This study demonstrates that baseline circulating cardiovascular biomarker levels were associated with higher baseline FW in multiple WM regions and in the DMN, ECN, and

Figure 4 Effects of Circulating Cardiovascular Biomarker Levels on Global Cognition Through Mediators



Schematic diagram of the path analyses for hs-cTNT. hs-cTNT was entered as a predictor in each model. The mean WM FW and mean GM FW were added as mediators. (A) Global cognition baseline impairment and (B) rate of decline over time (5 years) were treated as the outcome. Numbers on the paths indicate standardized coefficients that were statistically significant. FW = free water; GM = gray matter; hs-cTnT = high-sensitivity cardiac troponin-T; WM = white matter.

Figure 5 Effects of Circulating Cardiovascular Biomarker Levels on Longitudinal Executive Function and Memory Decline Through Mediators



Schematic diagram of the path analyses. hs-cTNT was inputted as a predictor. The mean WM FW and mean GM FW derived from 7 Yeo's intrinsic networks were added as mediators (see parcellations with colored boundary in the right bottom). Rates of changes in executive and memory domains over time (5 years) were treated as outcomes. Numbers on the paths indicate standardized coefficients that were statistically significant. DAN = dorsal attention network; DMN = default mode network; ECN = executive control network; FW = free water; GM = gray matter; hs-cTnT = high-sensitivity cardiac troponin-T; SMN = somatomotor network; SN/VA = ventral attention network; WM = white matter.

somatomotor GM networks. Moreover, we found that the associations of circulating cardiovascular marker levels with baseline and longitudinal cognitive decline were fully mediated by both higher WM and GM FW. Specifically, in GM, the association of cardiovascular markers with executive function was mediated by higher FW in the ECN, while the association of blood markers with memory was mediated by greater FW in the DMN, both at baseline and longitudinally. Widespread higher WM FW mediated the same association for both domains. Our findings provided new evidence supporting increased brain FW as a proxy of cerebrovascular integrity, largely accounting for the linkage between cardiovascular dysfunction and cognitive impairment.

Our study demonstrates that FW measures in the brain are associated with circulating cardiovascular biomarkers. Recently, FW alterations have gained increasing attention because of their capability of detecting early brain abnormalities in neurodegenerative disease and vascular cognitive impairments.[14,38] The findings suggest a substantial increase of FW, which is most likely originating from extracellular water characteristics,[13] but independent of regional atrophy. However, the precise factors leading to the observed increase of extracellular water and hence increased FW signal in vascular-related cognitive impairment are not yet clear. One possible explanation is cerebrovascular-related damage.[16,17,38] Our study thus provided an important support for this hypothesis by uncovering the associations between brain FW and circulating cardiovascular biomarkers. In dementia, concomitant cardiovascular dysfunction may lead to ischemia (reduced blood supply to the brain) and cardioembolic stroke (thrombus from the heart dislodging went into the cerebral vasculature).[4] These processes in turn lead to vascular inflammation and endothelial and blood-brain barrier (BBB) dysfunction,[5,39,40] which may cause FW increases. Moreover, these cerebrovascular dysfunctions may further lead to circulating inflammatory cytokines and other blood-borne mediators of neurotoxicity infiltrating remote brain areas, causing global inflammation, widespread microvascular burden, and brain tissue damage,[6,41,42] and thus further increase brain FW.[16] However, future work is needed to determine the temporal causality between these processes.

Of interest, we observed that higher cardiovascular biomarker levels were related to higher FW in a region-specific pattern in GM, which was in contrast to the widespread association in WM. These findings are consistent with the previous clinical observation that GM is less vulnerable to CeVD, possibly because GM receives more collateral circulation and has more extensive blood supply than WM.[43] Second, GM regions closely linked with cardiovascular markers included the anterior cingulate and somatosensory cortex, which are known to be heart function–controlling brain regions.[44] We can thus speculate that a vicious circle may occur in CeVD progression, where cardiovascular-derived embolism or ischemia leads to damage in the brain regions of heart controlling center, thus leading to further derangement of cardiovascular function and cognitive function.[45] Future studies using refined cardiac markers (i.e., cardiac imaging markers) could be performed to test this hypothesis and provide further insights into the mechanism of brain-heart interaction. Last, and of importance,

these GM regions overlapped with the canonical cognitive brain networks including DMN, ECN, and SMN. This is aligned with the previous work demonstrating that neurodegenerative disease and CeVD could lead to network-specific dysfunction,[23,25] for example, the DMN in AD while ECN and SMNs in CeVD.[20,21,28,46] Our findings suggested that FW alterations might be one of the early basis of brain network degeneration, which is worth further investigation in combination with other disease pathology.

Previous studies have demonstrated associations of circulating cerebrovascular biomarkers with cerebrovascular burden and cognition.[9] Higher FW were related to cognitive deficits and longitudinal decline in dementia.[14,15,17] Our study put the pieces together by demonstrating that the effects of circulating cardiovascular biomarkers on longitudinal cognitive decline were mediated through higher FW in both WM and GM. Critically, we found brain FW entirely mediated the association of blood cardiovascular biomarkers with cognitive decline, suggesting that FW could be a key brain proxy linking the periphery cardiovascular dysfunction to cognitive decline. According to the 2-hit vascular hypothesis of dementia, concomitant cardiac and peripheral endothelial dysfunction would lead to damage to small arteries, arterioles, and brain capillaries (e.g., hypoperfusion and BBB breakdown) and neurovascular alterations through both vascular and AD pathophysiology pathways (hits).[3] Both pathways interact and converge on these cerebrovascular dysfunction processes and can independently or synergistically lead to neuronal damage, synaptic loss, and neurodegeneration, resulting in dementia and cognitive decline.[47] FW increases in dMRI capture these processes of cerebrovascular dysfunction,[17,38,48] likely leading to the full mediation effect observed in this study. Our results underscore the importance of cerebrovascular function in the connection between heart and cognition. Further longitudinal studies should take into account other dementia-related pathologies such as β-amyloid, tau, or TAR DNA–binding protein-43 to fully understand the intricate interactions among these processes.

Furthermore, we demonstrated ECN FW mediated the influence of cardiovascular biomarkers on executive functioning decline, while DMN FW played a role in memory decline. These findings were supported by prior studies that the DMN is important for episodic memory and DMN dysfunction is widely implicated in AD dementia.[21,23] In parallel, the ECN connectivity alteration was associated with executive function deficits in patients with CeVD.[25] Such dissociable correspondence between cardiovascular-related network-specific GM FW abnormality at baseline and longitudinal decline in cognition suggests that cardiovascular-related cerebrovascular dysfunction may target specific brain networks for specific cognitive domains. Early cardiovascular changes might induce cerebral hypoperfusion, endothelial dysfunction, and ischemic damage in specific brain networks, eventually causing BBB leakage and neuroinflammation, which may manifest as higher GM FW.[38] The reduced blood supply and entry of potentially harmful compounds may cause further injury to axons and neurons resulting in longitudinal cognitive dysfunction in domains supported by the targeted network.[34] Moreover, with reference to the 2-hit vascular hypothesis of dementia, the detected GM pattern might also suggest AD pathophysiology could potentially be more active in the DMN, underlying memory impairment, while the vascular hit might be the leading pathway in the ECN, underlying executive dysfunction. Future investigation could combine blood cardiovascular biomarkers and a neuroimaging scan to identify vascular abnormalities and brain network-specific alterations to predict disease progression and domain-specific cognitive decline.

There are several limitations of this study. First, our results were based on diffusion imaging data obtained with a single shell.[13] More advanced acquisitions including multi b values and FW modeling method could further increase the sensitivity and specificity of the derived measures and potentially tease apart various microstructural and vascular changes.[49] Second, although we performed visual quality control to minimize the possible misalignment between the T1 and dMRI data, partial volume with surrounding CSF cannot be completely ruled out; in other words, brain atrophy may also affect the FW values in the GM. To mitigate these concerns, we performed partial volume correction and controlled for TIV and regional atrophy. Besides, we did not find any association of blood biomarkers with cortical thickness. Moreover, although we accounted for age, sex, and years of education in our analyses, the potential influence of these demographics on brain measures cannot be ruled out. Further investigation in a larger cohort with matching demographics across different groups are necessary. Last, participants were recruited from memory clinics, which might be confounded by selective survival bias. Although we have controlled for a number of vascular risk factors, no physical activity and alcohol consumption information was available for this cohort. More works in other clinical and community cohorts with comprehensive lifestyle evaluation are needed.

There are 3 future directions. First, more advanced diffusion imaging and FW models can be used to potentially tease apart different microstructural and vascular changes. Second, given the 2-hit vascular hypothesis, future work in animal models and human studies is needed to determine the temporal patterns (or even causality) of vascular damage, neurovascular dysfunction, AD pathologies such as amyloid, and neuronal dysfunction.[47] It is also important to combine FW with other biomarkers to determine the relative relevance of vascular pathology to the overall multietiology picture. Third, further developed, the new evidence on brain-heart interactions provided in this study may pave the way for an effective strategy of early detection and prediction of domain-specific cognitive trajectory. Given that brain FW is a sensitive measure for early and mild vascular-related alteration,[50] combining cardiovascular biomarkers with brain FW measurement may help monitor response to pharmacologic and nonpharmacologic therapies in vascular-related treatment of dementia.

In conclusion, we found higher circulating cardiovascular marker levels were associated with higher WM FW in a widespread pattern and higher GM FW in the DMN, ECN, and SMN at baseline. Of importance, baseline FW in both GM and WM fully mediated the association of cardiovascular biomarker levels with cognitive decline over time. The association of blood markers with executive function decline was mediated by higher FW in the ECN, while the same association with memory decline was mediated by the DMN. In other words, the effects of cardiovascular dysfunction proxied by the blood biomarkers on the cognition may be accounted by cerebrovascular pathophysiology detected by higher FW in specific brain networks. Our results suggest that higher FW could underlie the heart-brain interactions. Developed further, assessment of FW in specific brain networks together with circulating cardiovascular assays would be helpful for the prediction and monitoring of cardio/CeVD progression and domain-specific cognitive decline.

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Marcus Ong, BSc	Centre for Sleep and Cognition, Yong Loo Lin School of Medicine, National University of Singapore	Drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data
Arthur Mark Richards, MD	Cardiovascular Research Institute, National University of Singapore; Christchurch Heart Institute, University of Otago, New Zealand	Drafting/revision of the article for content, including medical writing for content
Boon Yeow Tan, MMed	St Luke's Hospital, Singapore	Drafting/revision of the article for content, including medical writing for content
Narayanaswamy Venketasubramanian, FRCP	Memory Aging & Cognition Centre, National University Health System; Raffles Neuroscience Centre, Raffles Hospital, Singapore	Drafting/revision of the article for content, including medical writing for content
Ofer Pasternak, PhD	Departments of Psychiatry and Radiology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA	Drafting/revision of the article for content, including medical writing for content
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Continued

Appendix *(continued)*

Name	Location	Contribution
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