



Hyperintense vessels on imaging account for neurological function independent of lesion volume in acute ischemic stroke

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ABSTRACT

In acute ischemic stroke, reported relationships between lesion metrics and behavior have largely focused on lesion volume and location. However, hypoperfusion has been shown to correlate with deficits in the acute stage. Hypoperfusion is typically identified using perfusion imaging in clinical settings, which requires contrast. Unfortunately, contrast is contraindicated for some individuals. An alternative method has been proposed to identify hypoperfusion using hyperintense vessels on fluid-attenuated inversion recovery (FLAIR) imaging. This study aimed to validate the clinical importance of considering hypoperfusion when accounting for behavior in acute stroke and demonstrate the clinical utility of scoring the presence of hyperintense vessels to quantify it.

One hundred and fifty-three participants with acute ischemic stroke completed a battery of commonly-used neurological and behavioral measures. Clinical MRIs were used to determine lesion volume and to score the presence of hyperintense vessels seen on FLAIR images to estimate severity of hypoperfusion in six different vascular regions. National Institutes of Health Stroke Scale (NIHSS) scores, naming accuracy (left hemisphere strokes), and language content produced during picture description were examined in relation to lesion volume, hypoperfusion, and demographic variables using correlational analyses and multivariable linear regression.

Results showed that lesion volume and hypoperfusion, in addition to demographic variables, were independently associated with performance on NIHSS, naming, and content production. Specifically, hypoperfusion in the frontal lobe independently correlated with NIHSS scores, while hypoperfusion in parietal areas independently correlated with naming accuracy and content production.

These results correspond to previous reports associating hypoperfusion with function, confirming that hypoperfusion is an important consideration—beyond lesion volume—when accounting for behavior in acute ischemic stroke. Quantifying hypoperfusion using FLAIR hyperintense vessels can be an essential clinical tool when other methods of identifying hypoperfusion are unavailable or time prohibitive.

1. Introduction

MRI and CT imaging have become standard components of routine clinical care in acute ischemic stroke. Different protocols and scan sequences are helpful to identify various characteristics of stroke etiology and pathology. While diffusion weighted imaging (DWI) is preferred to

identify acute lesions, perfusion weighted imaging (PWI) and CT perfusion imaging are typically used to identify severe hypoperfusion surrounding the infarct (i.e., the ischemic penumbra). However, complications and/or nephrotoxicity of contrast agents, such as gadolinium or iodinated contrast, limit the application of PWI/CT perfusion when patients have renal insufficiency (Ramalho et al., 2016; Hasebroock and

Abbreviations: ACA, anterior cerebral artery; BNT, Boston Naming Test; cc, cubic centimeters; CU, content unit; DWI, diffusion weighted imaging; FHV, FLAIR hyperintense vessel(s); FLAIR, fluid-attenuated inversion recovery; LH, left hemisphere; MCA, middle cerebral artery; NIHSS, National Institutes of Health Stroke Scale; PCA, posterior cerebral artery; PWI, perfusion weighted imaging; RH, right hemisphere; rTPA, recombinant tissue plasminogen; SD, standard deviation; TIA, transient ischemic attack.

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Serkova, 2009) or after repeated administration (McDonald et al., 2015; Kanda et al., 2015; Kanda et al., 2014). Alternative methods of identifying hypoperfusion are needed when PWI/CT perfusion application is contraindicated. Arterial spin labeling perfusion is useful but time consuming and highly sensitive to motion artifact, making it often difficult to interpret.

Hyperintense vessels on fluid-attenuated inversion recovery (FLAIR) MRI sequences are another possible alternative to PWI/CT perfusion for identifying hypoperfusion (Legrand et al., 2015; Toyoda et al., 2001; Reyes et al., 2017). FLAIR hyperintense vessels (FHV) are bright serpentine-like structures and/or isolated bright spots near or within the sulci (see Fig. 1). Typically, blood vessels appear dark on FLAIR sequences as signal intensity is lost when the blood flows out of the imaging slice prior to the next pulse. This phenomenon is described as a ‘flow void.’ Hyperintense vessels reflect the absence of the flow void because blood is not moving fast enough during image acquisition.

While the exact underlying cause of FHV is unclear (i.e., as an indication of slow antegrade flow, collateral retrograde flow, and/or new thrombus), it is generally accepted that FHV reflect abnormal hemodynamic function. A relationship between the presence of FHV and vessel occlusion/stenosis and/or hypoperfused tissue has been demonstrated in numerous studies for both stroke (Legrand et al., 2015; Toyoda et al., 2001; Noguchi et al., 1997; Maeda et al., 1999; Maeda et al., 2001; Legrand et al., 2016; Cosnard et al., 1999; Huang et al., 2012; Olindo et al., 2012; Cheng et al., 2012; Kamran et al., 2000; Gawlitza et al., 2014; Hohenhaus et al., 2012; Azizyan et al., 2011; Iancu-Gontard et al., 2003; Schellinger et al., 2005; Sanossian et al., 2009; Lee et al., 2009), and transient ischemic attack (TIA) (Kobayashi et al., 2013; Sanossian et al., 2007). The association of FHV with lesion size, stroke severity, and clinical outcomes/prognosis is not yet fully understood. For example, some studies report presence of FHV to be predictive of clinical outcomes (Iancu-Gontard et al., 2003), while others do not (Schellinger et al., 2005; Lee et al., 2009). Thus, some practitioners remain unconvinced of the clinical utility of FHV in managing acute ischemic stroke/TIA, possibly because of the conflicting diagnostic/prognostic relationship reported across the literature.

Recently, Reyes and colleagues proposed a method to estimate the amount/severity of hypoperfusion by quantifying the presence of FHV (Reyes et al., 2017). They found that the FHV scores correlated strongly with volume of hypoperfusion on PWI. Previous work using PWI has shown that the volume and location of hypoperfusion often contributes additional information, beyond DWI lesion volume, in accounting for deficits in acute stroke (Hillis et al., 2002; Hillis et al., 2004; Hillis et al., 2004; Shirani et al., 2009; Hillis et al., 2001; Hillis et al., 2005; Hillis,

2007; Hillis et al., 2002; Philipose et al., 2007; Hillis et al., 2006; Fridriksson et al., 2002), but similar demonstrations are needed using FHV to establish validity for use in clinical and/or research settings. The purpose of this study is to evaluate the clinical utility of estimating volume and site of hypoperfusion with FHV in explaining neurological deficits in a large cohort of both right- and left-hemisphere acute ischemic stroke patients. We hypothesized that neurological impairment measured with the National Institutes of Health Stroke Scale (NIHSS) (National Institute of Neurological Disorders and Stroke, 2011) would be better explained by estimated volume of hypoperfusion by FHV than with volume of DWI lesion alone. Furthermore, we hypothesized that both NIHSS score and performance on some simple language tests would be best accounted for by a combination of DWI lesion volume, location of hypoperfusion, age, and education.

2. Materials and methods

2.1. Participants

Participants were retrospectively selected from a larger, prospective observational study examining various aspects of behavioral performance following acute ischemic stroke in the cerebral hemispheres (i.e., strokes in anterior/middle/posterior cerebral artery territories). Strokes that were primary hemorrhages or restricted to the brainstem/cerebellum were excluded. Additional inclusion/exclusion criteria were that participants be at least 18 years of age, have pre-morbid proficiency in English, normal or corrected to normal vision/hearing, no prior history of neurological disease affecting the brain other than stroke, no contraindications for MRI, and were not intubated (thus precluding participation in the behavioral measures). Medical records for those with prior stroke were reviewed, and only those without residual deficits (i.e., modified Rankin Score [mRS] = 0) before the new stroke were retained in the sample. Potential participants were further excluded if clinical MRI was not obtained within 48 h of hospital admission or if reperfusion therapies such as recombinant tissue plasminogen (rtPA) or mechanical thrombectomy occurred after the MRI but before behavioral assessments. For those with bilateral or chronic lesions, diffusion weighted images (DWI) were carefully reviewed by the first two and last authors. Only those with small (e.g., lacunar) chronic or contralateral lesions were retained in the sample. Chronic lesions were confirmed asymptomatic using medical records. Participants were administered the right or left hemisphere testing battery (described in subsequent sections), depending on [primary] lesion location. All participants, or legally authorized representatives, provided informed consent in accordance with the Declaration of Helsinki and as approved by the Internal Review Board of Johns Hopkins Medicine.

A total of 153 participants were included: 79 with right hemisphere (RH) stroke (35 female, mean [SD] age = 64.3 [14.4]), and 74 with left hemisphere (LH) stroke (39 female, mean [SD] age = 61.4 [11.7]). Years of education for the whole group averaged 13.8 ($SD = 3.0$, range = 7–20 years), with the LH group averaging 14.0 years ($SD = 2.9$, range = 8–20) and the RH group averaging 13.7 years ($SD = 3.2$, range = 7–20). Additional demographic information is reported in Table 1. A total of seven participants with bilateral lesions were included, with four being assigned to the RH group and three to the LH group (stroke in the opposite hemisphere was <1 cc). Three participants with chronic asymptomatic infarcts (mRS = 0) were retained, all of whom were in the LH group (i.e., the acute stroke was in the LH). Two of the chronic lesions were ipsilateral lacunar infarcts and one was a contralateral ACA infarct. Note that numbers reported for education and hand dominance do not sum to 153 as this information was not available for some participants. There were no statistically significant differences between LH and RH groups in age, sex, education, race, or handedness.

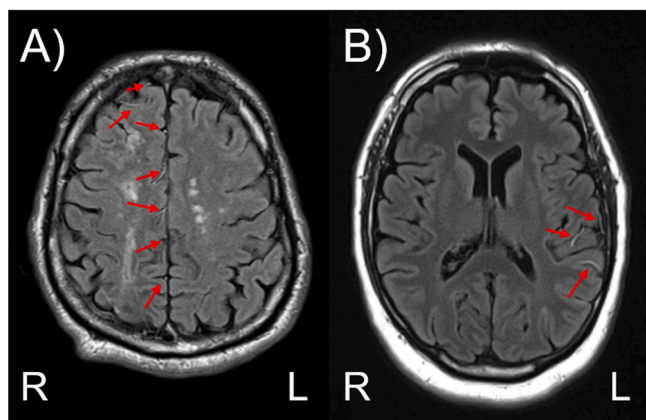


Fig. 1. Examples of hyperintense vessels on FLAIR. Panel (a) demonstrates hyperintense vessels in the right ACA territory. Panel (b) demonstrates hyperintense vessels in the temporal region of the left MCA territory. Note that these images are in radiological convention with the right hemisphere on the left side of the image.

Table 1
Participant demographics.

	Age Mean (SD) Range	Sex	Years of Education* Mean (SD) Range	Race [†]	Handedness [‡]	Testing Interval Mean (SD) Range
LH (n = 74)	61.4(11.7) 39–91	39F 35M	14.0 (2.9) 8–20	W/C = 37 B/AA = 33 Asian = 1 Other = 3	R = 61 L = 7 Amb. = 2	1.2 (0.7)
RH (n = 79)	64.3(14.4) 28–88	35F 44M	13.7 (3.2) 7–20	W/C = 41 B/AA = 35 Asian = 2 Other = 1	R = 64 L = 7 Amb. = 0	1.0 (0.7)
Total Sample (n = 153)	62.9(13.2) 28–91	74F 79M	13.8 (3.0) 7–20	W/C = 78 B/AA = 68 Asian = 3 Other = 4	R = 125 L = 14 Amb. = 2	1.12 (0.7)

Note. R = right, L = left, LH = Left hemisphere stroke, RH = Right hemisphere stroke, F = female, M = male, Amb. = ambidextrous, W/C = White/Caucasian; B/AA = Black/African American; Testing Interval = time between MRI and behavioural assessments.

*Years of education only available for n = 137.

†No participants identified as Native American or Pacific Islander.

‡Premorbid hand dominance only available for n = 141.

2.2. Neuroimaging

Clinical MRI scans (1.5 or 3T) were completed within 48 h of hospital admission (Johns Hopkins Hospital or Johns Hopkins Bayview Medical Center). Data were collected between 2003 and 2020; exam parameters and device specifications/manufacturers have changed during this period and are thus not specified here. Participants completed axial DWI and FLAIR scans as part of their routine clinical management, which were used for this investigation. Trained study team members manually traced lesions slice by slice on DWI scans using MRIcron or MRICroGL (available at nitric.org); tracings were verified by experienced researchers. We used routines from SPM12 (Statistical Parameter Mapping; <https://www.fil.ion.ucl.ac.uk/spm/software/spm12/>) to warp each patient's DWI b0 image to a healthy older adult template (Rorden et al., 2012) and subsequently applied the normalization parameters to the lesion map. We calculated the volume of the normalized lesion map (in mm³) using NiiStat (<https://www.nitrc.org/projects/niiostat/>). DWI scans were also used to determine general lesion location prior to viewing/rating presence of FHV.

2.3. FLAIR hyperintense vessel ratings

The first two authors—blinded to behavioral and NIHSS score—scored presence of FHV using the method developed by Reyes et al.

(2017) FLAIR scans were viewed in native space, slice by slice in conjunction with an atlas of vascular territories corresponding to the individual's brain shape (Damasio and Damasio, 1989). Across all available slices, presence of FHV was scored on a 3-point scale (i.e., 0–2) in six different vascular regions— anterior cerebral artery (ACA) territory, posterior cerebral artery (PCA) territory, and the middle cerebral artery (MCA) territory divided into frontal (MCA-frontal), temporal (MCA-temporal), insular (MCA-insular), and parietal regions (MCA-parietal; see Fig. 2). The vascular region was scored 0 if no hyperintense vessels were visible in that area on any slice. A score of 1 was given if there were 1–2 hyperintense vessels on one or two different slices. A score of 2 was given for three or more vessels on one slice or three or more slices with hyperintense vessels. Scores for each region were summed for a total of 12 possible points for the hemisphere.

2.4. Hypoperfusion on FLAIR and PWI

Although the primary aim of this study was to examine the relationship between FHVs and function, we did also examine the relationship between FHV and hypoperfusion on PWI for a subset of participants (n = 73; 43 LH and 30 RH) who had PWI as part of their clinical MRI. Although underpowered for strong conclusions, we examined the volume and location of hypoperfused tissue on PWI compared to ratings and location of FHVs for 69 of these individuals

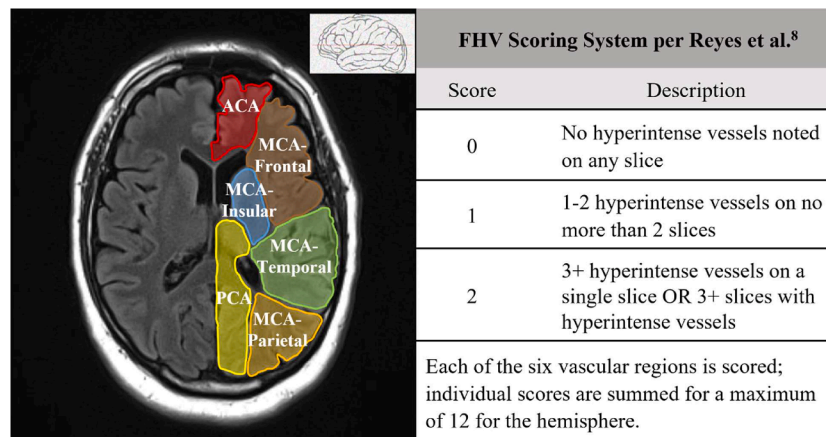


Fig. 2. FLAIR hyperintense vessel (FHV) scoring system and example of vascular areas. Presence of FHV was rated in six different regions—ACA territory (red), PCA territory (yellow), MCA frontal region (brown), MCA insular region (blue), MCA temporal region (green), and MCA parietal region (orange)—as demonstrated in this sample slice. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

(four had inadequate data quality to be included) as a preliminary examination of the agreement between the two methods. That is, did the location of FHV correspond with hypoperfusion measured on PWI? Volumes and location of hypoperfusion were calculated by a stroke neurologist (senior author) per methods described previously, without knowledge of clinical scores or FHV ratings (Hillis et al., 2006).

2.5. Neurological & behavioral assessments

NIHSS scores for all participants were collected from routine neurological examinations administered on the same day as the MRI or as close as possible to the scan time.

Participants completed different batteries of behavioral tasks depending on the location of their stroke (i.e., RH vs. LH) within 48 h of the MRI (*mean [SD]* interval was 1.2 [0.7] days for LH and 1.0 [0.7] days for RH, calculated from the absolute difference). For this study, we examined only two of these batteries' language production tasks—picture naming (LH only) and content production (LH and RH)—that are highly reliable, frequently completed, and representative of left or right hemisphere cortical dysfunction, described subsequently. As not all participants were able to complete all behavioral assessments, the number of data points for each assessment task varies and is reported with the description of each task.

Eighty-five participants (RH = 37, LH = 48) participants completed the Cookie Theft picture description task (Goodglass et al., 2001). This task is clinically useful for describing and quantifying abnormal behavior for strokes in either hemisphere (Agis et al., 2016; Trupe and Hillis, 1985; Yorkston and Beukelman, 1980; Mackenzie and Brady, 2004; Brookshire and Nicholas, 1995; Myers and Brookshire, 1978; Myers and Brookshire, 1979). Participants were given general instructions to describe what was happening in the picture. Responses were audio-recorded and transcribed verbatim, including dysfluencies, fillers, nonwords, paraphasic errors, and sound errors per methods described in Nicholas and Brookshire (Nicholas and Brookshire, 1993). Transcripts were scored for mention of specific content units (CUs) produced by normative samples (Yorkston and Beukelman, 1980). If a participant presented with aphasia, they still received credit for any accurate content but did not receive credit for paraphasic errors, semantic jargon, or repeated or confabulatory content. Many individuals with aphasia are able to produce at least some appropriate content in response to this stimulus, but those with severe global impairment may not be able to produce any (receiving a score of zero). In the case of participants with motor-speech disorders, any apraxic or dysarthric errors that were easily recognizable in context were given credit. Various metrics can be collected from this task, but we used only the total number of content units produced as this measure is reduced in *both* RH and LH strokes (allowing for more direct comparison and for the two groups to be combined).

LH stroke participants ($n = 68$) completed a 30-item version of the Boston Naming Test (BNT) (Mack et al., 1992) to quantify naming impairment, as this deficit is a consistent feature across all aphasia types. Administration and scoring followed the instructions published by the test authors (Kaplan et al., 1983).

2.6. Statistical analyses

Due to skewed distributions for some numerical variables (i.e., NIHSS, DWI lesion volume, and BNT accuracy), we used a log transform for DWI lesion volume and recoded BNT scores as an ordinal variable (log transform was not effective to correct the distribution because of floor/ceiling effects). As a log transformation of the NIHSS did not significantly alter results, we opted to retain the raw values for ease of interpretation. BNT scores were coded from 0 to 3 with 0 = "little to no difficulty" as indicated by scoring above the mean for normal controls (Goodglass et al., 2001), 1 = "mild difficulty" indicated by scoring within 1 SD below the mean, 2 = "moderate difficulty" indicated by

scoring between 1 and 2 SD below the mean, and 3 = "significant difficulty" indicated by scoring > 2 SDs below the mean.

We used Pearson's correlations to examine the relationship between our independent (i.e., demographic variables, lesion volume, and hypoperfusion) and dependent variables (i.e., NIHSS, naming accuracy, and content production) and multivariable linear regression to identify variables that were independently associated with an outcome measure (Katz, 2003; Hidalgo and Goodman, 2013). We used Spearman's correlation to examine PWI hypoperfusion volumes and total FHV scores, and Fisher's Exact tests to examine the relationship between location of hypoperfusion on PWI and FHVs for each of the six vascular regions. For Fisher's Exact, PWI hypoperfusion and FHVs were scored as either "present" or "absent."

2.7. Reliability

Approximately 20% of participants were pseudorandomly selected for reliability purposes so that RH and LH strokes were equally represented in the sample. Following training on scoring FHV, the first two authors independently scored the selected participant scans for presence of FHV in each of the six vascular regions. Interrater agreement—calculated using weighted Cohen's kappa—was moderate ($\kappa = 0.78$, $p < 0.000$, 95% CI [66–0.91]) (McHugh, 2012). Weighted kappa was used so that differences of one point in FHV was not as large of a disagreement as differences of two points (e.g., if one rater identified zero FHVs while the other identified three or more). Behavioral measures were not rescored for reliability for this investigation as FHV scores were the focus. Additionally, the participants are part of a larger parent study, and reliability for those measures have been reported, as appropriate, in other publications.

2.8. Data availability

Data are available at score.jhmi.edu.

3. Results

3.1. Imaging data

Summary statistics for imaging and behavioral measures are reported in Table 2. Although RH and LH strokes are often characterized by different features, NIHSS scores were not statistically different for the two different hemisphere groups (two-tailed t -test, $t[151] = 0.45$, $p = .66$). Thus, groups were combined for regression analyses. The two stroke groups were significantly different in terms of total content units produced (two-tailed t -test, $t(83) = -2.89$, $p = .004$), but since both LH and RH strokes demonstrate reduced CUs on Cookie Theft picture description (Agis et al., 2016), and differentiating between LH and RH strokes was not the purpose of this investigation, the two groups were combined for regression analyses on this outcome measure as well. BNT

Table 2
Summary Statistics for Independent and Dependent Variables.

	Mean (SD)	Range	Median
Lesion Volume (mm ³)	20,093 (36,226)	49 – 227,214	6397
LH Group Only	21,704 (41,733)	83 – 227,214	6092
RH Group Only	18,583 (30,373)	49 – 143,934	6563
Total FHV Score (out of 12)	1.39 (1.77)	0 – 8	1
LH Group Only	1.35 (1.51)	0 – 7	1
RH Group Only	1.43 (1.99)	0 – 8	1
NIHSS	4.39 (4.13)	0 – 20	3
BNT Percent Accuracy (%)	62.5 (29.86)	0 – 100	71.5
Total CUs (Cookie Theft)	8.33 (5.48)	0 – 23	11

Note. Lesion Volume = lesion volume on DWI; LH = left hemisphere; RH = right hemisphere; FHV = FLAIR hyperintense vessel; NIHSS = National Institutes of Health Stroke Scale; BNT = Boston Naming Test; CUs = content units.

was only given to LH stroke participants. Since some outcomes were completed by only one group (e.g., LH), lesion metrics (DWI lesion volume and FHV score) are reported for the whole group, and for RH and LH stroke groups individually to aid in interpretation.

3.2. Correlation analyses

Correlations are reported in Table 3. To account for multiple comparisons, we used a Benjamini and Hochberg (Benjamini and Hochberg, 1995) correction at a 5% false discovery rate (FDR, $q = 0.05$). After correction, there was a significant moderate negative correlation between years of education and naming difficulties (i.e., more education correlated with fewer naming difficulties). DWI lesion volume correlated moderately with all four outcome measures (i.e., increased lesion volume corresponded with higher NIHSS scores, fewer CUs on picture description, and greater naming difficulties). The total FHV score had a small positive correlation only with NIHSS scores (see Discussion).

3.3. Regression analyses

Multivariable linear regression models (MLRM) are reported in Tables 4-6 (all model assumptions were met in each case). Participants with missing data were dropped from respective models, thus the observations for each model may differ slightly from numbers reported previously. Based on the correlation results, we initially ran a MLRM examining NIHSS scores with only DWI lesion volume and total FHV score as the independent variables (see Table 4, Model A). Total FHV score was significantly associated with NIHSS score independent of DWI lesion volume. Subsequent models used the FHV scores in the six individual vascular regions rather than the total FHV score so that contributions from specific anatomical areas could be examined (i.e., is hypoperfusion in a particular area(s) independently associated with the variability in the dependent variable?). This was particularly important for the language measures since total FHV scores did not correlate with these outcomes (see Table 3). While age and education correlated with only some outcome measures, both variables were also included in each of our models based on the assumption that these demographic variables contribute to the variance in confrontational naming (Neils et al., 1995; Zec et al., 2007; Tsang and Lee, 2003; Henderson et al., 1998; Welch et al., 1996), content production (Yorkston and Beukelman, 1980; Cooper, 1990; Ardila and Rosselli, 1996; Pistono et al., 2017; Mackenzie, 2000), and stroke severity—in terms of the effect of premonitory neurological function on stroke outcomes (Umarova et al., 2021; Umarova et al., 2019; Habeck et al., 2017). The MLRM for NIHSS is reported in Table 4 (Model B), in Table 5 for picture naming, and in Table 6 for content production on Cookie Theft picture description.

Overall models for each outcome were statistically significant. The model for NIHSS scores with total FHV scores accounted for 17% of the variance (Model A, Table 4), whereas the addition of age and education and the breakdown of FHV by region accounted for 23% of the variance (Model B, Table 4). Models for naming accuracy (Table 5), and content

Table 3
Pearson's Correlations.

	Age	Yrs. Edu.	Lesion Vol.	Total FHV
NIHSS	0.08 (n = 153)	-0.04 (n = 137)	0.37*** (n = 153)	0.26* (n = 153)
CUs on Cookie Theft picture	-0.16 (n = 85)	0.26 (n = 75)	-0.37** (n = 85)	-0.16 (n = 85)
BNT Accuracy (i.e., 0-3 difficulty rating)	0.13 (n = 68)	-0.32 (n = 66)	0.42** (n = 68)	0.13 (n = 68)

Note. LH = left hemisphere; RH = right hemisphere; Yrs. Edu. = years of education; Vol. = volume; FHV = FLAIR hyperintense vessel score; NIHSS = National Institutes of Health Stroke Scale; CUs = content units; BNT = Boston Naming Test. All p -values adjusted for multiple comparisons (FDR, $q = 0.05$). *significant at $p < 0.05$; **significant at $p < 0.01$; ***significant at $p < 0.001$.

Table 4
Multivariable linear regression models for NIHSS.

Model A				
Overall Model (n = 153):	F [2, 150] = 15.38			
	$r^2 = 0.170$	Adj. $r^2 = 0.159$		$p < .000$ ***
	Coefficient	Std. Error	t	p-value
Lesion Volume	0.70	0.16	4.36	0.000***
Total FHV score	0.42	0.18	2.39	0.018**
Constant	-2.11	1.36	-1.55	0.123
Model B				
Overall Model (n = 137):	F [9, 127] = 4.17			
	$r^2 = 0.228$	Adj. $r^2 = 0.173$		$p < .000$ ***
	Coefficient	Std. Error	t	p-value
Age	-0.03	.003	-0.93	0.357
Yrs. Educ.	-0.02	0.11	-0.21	0.838
Lesion Volume	0.76	0.18	4.30	0.000***
FHV – ACA	0.85	0.90	0.94	0.348
FHV – PCA	-0.79	1.01	-0.78	0.438
FHV – MCA-frontal	2.10	0.75	2.81	0.006**
FHV – MCA-temporal	-0.46	0.58	-0.79	0.431
FHV – MCA-parietal	0.20	0.58	0.34	0.731
FHV – MCA-insular	.033	0.98	0.34	0.735
Constant	-0.35	2.53	-0.14	0.889

Note. NIHSS = National Institutes of Health Stroke Scale; Lesion Volume = lesion volume on DWI (lesion volume is log transformed); Adj. = adjusted; Yrs. Educ. = years of education; FHV = FLAIR hyperintense vessel score; ACA = anterior cerebral artery; PCA = posterior cerebral artery; MCA = middle cerebral artery. *significant at $p < .05$; **significant at $p < .01$; ***significant at $p < .001$.

Table 5
Multivariable Linear Regression Model for Picture Naming on BNT.

Overall Model (n = 66):	F [9, 56] = 4.23			
	$r^2 = 0.404$	Adj. $r^2 = 0.309$		$p < .001$ ***
	Coefficient	Std. Error	t	p-value
Age	0.002	0.01	0.13	0.894
Yrs. Educ.	-0.13	0.04	-3.03	0.004**
Lesion Volume	0.24	0.07	3.61	0.001***
FHV – ACA	0.69	0.66	1.04	0.302
FHV – PCA	0.07	0.32	0.21	0.837
FHV – MCA-frontal	0.10	0.25	0.39	0.699
FHV – MCA-temporal	-0.18	0.19	-0.92	0.361
FHV – MCA-parietal	0.58	0.23	2.52	0.015*
FHV – MCA-insular	-0.73	0.51	-1.44	0.155
Constant	1.84	1.02	1.79	0.078

Notes. BNT = Boston Naming Test (scored as 0-3, 0 = "little to no difficulty" up to 3 = "significant difficulty"); Adj. = adjusted; Yrs. Educ. = years of education; Lesion Volume = lesion volume on DWI (lesion volume is log transformed); FHV = FLAIR hyperintense vessel score; ACA = anterior cerebral artery; PCA = posterior cerebral artery; MCA = middle cerebral artery. *significant at $p < .05$; **significant at $p < .01$; ***significant at $p \leq 0.001$.

production (Table 6) accounted for 40% and 31% of the variance, respectively.

In each model, DWI lesion volume was significantly associated with performance ($p \leq 0.001$ in each case) independent of the other variables. Age was not independently associated with outcomes in any model, but years of education independently correlated with naming accuracy and content production on picture description. With more education, performance on picture naming improved. For every two years of education, an additional content unit, approximately, was produced on the picture description task.

In terms of area(s) of hypoperfusion associated with performance, NIHSS scores were independently related to hypoperfusion in the frontal region of the MCA territory. A 1-point increase in FHV score

Table 6

Multivariable regression model for content units on cookie theft picture description.

	Overall Model ($n = 75$):			
	F [9, 65] = 3.21			
	$r^2 = 0.308$	Adj. $r^2 = 0.212$		$p = .003^{**}$
Coefficient	Std. Error	t	p -value	
Age	-0.007	0.05	-0.13	0.897
Yrs. Educ.	0.45	0.19	2.34	0.023*
Lesion Volume	-1.53	0.37	-4.07	0.000***
FHV – ACA	0.82	1.54	0.54	0.594
FHV – PCA	-1.05	2.51	-0.42	0.677
FHV – MCA-frontal	0.09	1.39	0.06	0.950
FHV – MCA-temporal	0.12	1.26	0.09	0.925
FHV – MCA-parietal	-2.63	1.14	-2.32	0.024*
FHV – MCA-insular	2.48	1.76	1.41	0.164
Constant	17.57	5.10	3.45	0.001

Notes. Adj. = adjusted; Yrs. Educ. = years of education; Lesion Volume = lesion volume on DWI (lesion volume is log transformed); FHV = FLAIR hyperintense vessel score; ACA = anterior cerebral artery; PCA = posterior cerebral artery; MCA = middle cerebral artery.

*significant at $p < .05$; **significant at $p < .01$; ***significant at $p < .001$.

corresponded to just over a 2-point increase in NIHSS score. Hypoperfusion in the parietal region of the MCA territory was significantly associated with naming performance, with a 1-point increase in FHV score in the parietal region corresponding to almost a full point on the BNT categorical score (e.g., a decrease from 0 “little to no difficulties” to 1 “mild difficulties”).

Content production on the Cookie Theft picture description task was associated with hypoperfusion in the parietal region of the MCA territory. A 1-point increase in FHV score corresponded to a decrease of 2–3 CUs. The constant in this model was significant, possibly suggesting that there may be other important variables not accounted for, but this can be difficult to interpret.

3.4. Hypoperfusion on PWI & FHV

Total FHV scores and volume of hypoperfusion on PWI were strongly positively correlated ($r = 0.79$, $p < .0001$). Presence of FHVs and hypoperfusion on PWI was significantly associated in the PCA (Fisher's Exact = 69.0, $p < .001$), MCA-frontal (Fisher's Exact = 13.7, $p < .001$), MCA-temporal (Fisher's Exact = 31.2, $p < .001$), MCA-parietal (Fisher's Exact = 26.9, $p < .001$), and MCA-insular areas (Fisher's Exact = 29.5, $p < .001$). There was no significant relationship in the ACA territory (Fisher's Exact = 10.3, $p < .086$), but very few of our participants (i.e., $n = 3$) demonstrated FHVs in the ACA region.

4. Discussion

The purpose of this study was to present a clinical application of FHVs, as an estimation of hypoperfusion, by accounting for variability on various clinical measures. Using MLRMs, we were able to demonstrate that performance on several widely-used clinical measures can be accounted for by the presence of hypoperfusion—as indicated by FHV scores—in specific vascular regions, independent of other significant relationships (i.e., after controlling for the other variables). The primary motivation behind running MLRMs was not to identify the model of independent variables that accounted for the most variance, but rather show that the addition of hypoperfusion—as indicated by FHVs—can provide important clinical information, which may subsequently be used in diagnosis, management, and, potentially, prognosis. Specifically, when individuals are unable to receive perfusion imaging—either because of contraindications or lack of access/feasibility—estimating hypoperfusion using FLAIR imaging could be a useful alternative. Significance of specific clinically-meaningful relationships are discussed in the following sections.

4.1. Correlational relationships

As expected, DWI lesion volume correlated with each clinical outcome. Total FHV scores (i.e., the summed score for the whole hemisphere) correlated with NIHSS scores, which was unsurprising since the NIHSS captures global deficits. Thus, dysfunction caused by hypoperfusion in any of the six scored regions would be expected to be captured in the NIHSS scores. The total FHV score did not correlate with any other behavioral measures, but this is not surprising for essentially the same reason. Picture naming and verbal language production are specific language and cognitive processes, which are somewhat more localized in general, so deficits on these measures would not necessarily be explained by hypoperfusion across all six regions (as opposed to the range of domains captured by the NIHSS).

4.2. Multivariable linear regression models

NIHSS. Our initial model for NIHSS demonstrated that overall amount/severity of hypoperfusion accounts for differences in scores, independent of lesion volume. This corroborates other studies that have shown relationships between NIHSS scores and hypoperfusion on PWI, both in the NIHSS' ability to account for behavior or not (Hillis et al., 2004; Hillis et al., 2003). When demographic variables and individual regions of hypoperfusion were added to the model, the specific region of hypoperfusion contributing most to the variance in the scores was the MCA-frontal region. The fact that hypoperfusion in this region was associated with NIHSS scores corresponds nicely with previous studies showing NIHSS bias toward motor and language functions (Hillis et al., 2003; Lee et al., 2012; Sato et al., 2008; Woo et al., 1999; Fink et al., 2002).

Naming performance on the BNT. Education, lesion volume, and hypoperfusion in the MCA-parietal region were significantly associated with naming performance, independent of other variables. The relationship between naming and education has been well documented (as discussed previously). Likewise, the ability for lesion volume to account for naming performance was expected as well (Døli et al., 2021; Thye and Mirman, 2018; Hertrich et al., 2020). Hypoperfusion on PWI and CT in the left MCA territory has been associated with aphasia, in general, in multiple studies (Hillis et al., 2002; Hillis et al., 2004; Fridriksson et al., 2002; Hillis et al., 2000; Croqueolois et al., 2003; Olsen et al., 1986). Specific regions of the temporoparietal cortex have also been identified as important for naming in both lesion analyses (Baldo et al., 2013; Fridriksson et al., 2018; Yourganov et al., 2015; Butler et al., 2014) and studies of hypoperfusion (Hillis et al., 2002; Hillis et al., 2006). Our findings are in line with these results, indicating that presence of FHV in the parietal region could correspond with naming difficulties observed clinically. Of course, disruption to oral naming can be related to breakdown in various processing stages that are associated with distinct neuroanatomical regions, so these results are not to say that impaired naming could not be associated with hypoperfusion in other areas instead of or in addition to the parietal lobe. Indeed, some studies have identified multiple specific regions of hypoperfusion—on CT or PWI—associated with naming (Hillis et al., 2002; Hillis et al., 2006), while others have not (Croqueolois et al., 2003). Additional study of FHV in a specific cohort of individuals with acute stroke naming deficits may identify other areas of hypoperfusion contributing to observed behaviors.

Content production on picture description. Our MLRM for language content produced on the Cookie Theft picture description task also identified education, lesion volume, and hypoperfusion in the MCA-parietal region to be independently associated with content production (see Table 6). The parietal region could account for reduced content production for both LH and RH strokes, albeit for different reasons. Dysfunction in LH parietal regions (e.g., supramarginal gyrus and angular gyrus) (Fridriksson et al., 2018) likely impair lexical-semantic processing and thus word retrieval reflected in decreased

content production; whereas dysfunction in RH parietal regions could affect visuospatial attention and processing again reflected as decreased content production. Hypoperfused RH parietal regions, as part of the central executive network, may also play a role in disinhibition that might result in production of irrelevant, rather than relevant, content, potentially contributing to reduced content units as well. The relationship between content production on the Cookie Theft picture description and lesion location has been documented (Agis et al., 2016), but, to our knowledge, there have not been examinations of this specific outcome in relation to hypoperfusion on PWI (although it has been used diagnostically for inclusion/exclusion purposes, see Hillis et al., 2002). However, as noted in the previous section, numerous studies have found hypoperfusion on PWI or CT to associate with aphasia in general, often quantified using the same or similar measures intended to capture the amount of accurate/appropriate content provided during language production tasks.

4.3. Limitations

There are several limitations of this study that need to be addressed. First, although we provided preliminary evidence correlating the suspected regions of hypoperfusion using FHV and actual hypoperfusion measured on PWI, additional evidence is still needed to confirm that FHV in a particular area correspond with hypoperfusion in the same area, as corroborated by hypoperfusion on PWI. Second, while imaging and clinical/behavioral assessments were completed within 48 h of each other, and we specifically excluded individuals with reperfusion treatments between the MRI and testing, some spontaneous reperfusion could still have occurred during the interval. Imaging and clinical/behavioral assessments would ideally be completed on the same day, but it was not always feasible. Thus, relationships between hypoperfusion and performance on outcome measures may have been underappreciated. An anonymous reviewer pointed out that the potential for recanalization could have been confirmed on MR angiogram (MRA) prior to inclusion. However, it is possible that participants could have recanalized after the MRA. Additionally, some individuals with chronic occlusion may still have normal perfusion due to collateral circulation—thus, MRA is not always useful. We cannot be certain that some results are not erroneous due to reperfusion, but we attempted to control for this factor as much as was feasible.

Another limitation is that over the course of data collection, clinical MRI specifications changed. Slice thickness for FLAIR scans decreased from 5 mm to 4 mm, resulting in an overall different number of slices spanning the whole brain (i.e., 28 vs. 40). As higher FHV scores were given when hyperintense vessels were seen on multiple slices, those with fewer slices had fewer opportunities to demonstrate hyperintense vessels. This may have resulted in underestimated hypoperfusion for some participants.

Several variables in our study were not normally distributed; rather, they were skewed toward smaller and less severe strokes (as reflected in the descriptive statistics of each variable, Table 2). For example, although NIHSS scores ranged from 0 to 20, the average severity score was about 4.4. Likewise, total FHV scores ranged from 0 to 8 for the whole group, but the average score was less than two. Understandably, individuals with more severe acute ischemic stroke were less likely to be able to participate in most study tasks due to sequelae of severe stroke (e.g., somnolence) or medical interventions (e.g., intubation secondary to respiratory complications or post-surgical care). Subsequently, these individuals were not included considering our study parameters. We did attempt to address the issue of skewed distribution, as noted in the methodologies, but the fact remains that our sample, overall, tended toward small, mild strokes and/or mild behavioral impairment.

Some might also consider it a limitation that our sample did not exclude individuals without hypoperfusion (as indicated by FHV scores). If asking the specific question of whether FHV scores in a particular region account for behavior on an outcome, it may have been useful to

examine only participants with the presence of FHV. However, the absence of hypoperfusion can be just as important to explain behavioral differences as the presence of hypoperfusion. Thus, we felt it important not to limit our sample to the presence of FHV. Doing this would have also created other challenges regarding sample size for some regression models. Since we did not control for the number of participants contributing FHV scores, in general, or for the number of participants demonstrating FHV in each vascular region, it is possible that there were insufficient sample sizes in each subgroup to identify some relationships between hypoperfusion in a particular area and performance on a behavioral measure. Subsequent studies could more critically examine the ability of FHV in a specific region to account for variability in outcomes.

5. Conclusions

Despite the potential limitations of our study, we are confident in the preliminary findings that hypoperfusion, as estimated using FLAIR imaging, can contribute meaningful information toward brain-behavior relationships in acute stroke. The FHV scoring method used in this study is a relatively quick and easy method to estimate hypoperfusion from FLAIR imaging if/when other imaging options are unavailable. While the amount and location of hypoperfusion indicated by FHV scores can only be approximated, we did provide some preliminary evidence suggesting that location of FHV does correspond to PWI. Furthermore, the relationships between FHV and outcomes that we identified correspond to those previously identified in a number of different studies using PWI or CT perfusion. For example, identified relationships between hypoperfusion in the MCA-frontal region and NIHSS scores and hypoperfusion in the MCA-parietal region and naming accuracy/content production on the Cookie Theft picture description task were expected. Our study is an initial step for validating the clinical application of FHV ratings of hypoperfusion, and additional investigation is still needed to determine the clinical utility of estimating hypoperfusion using FLAIR scans. However, this investigation is an important step in demonstrating ecological and construct validity for FHV scores in management of acute ischemic stroke. Also, these preliminary data could be used in future studies including clinical applications of machine learning (to identify predictor variables that could be applied to individual cases), examinations of the sensitivity/specificity of FHV ratings, or correlating FHV on MRI with hypoperfusion on CT and PWI.

CRedit authorship contribution statement

Lisa D. Bunker: Investigation, Formal analysis, Validation, Visualization, Writing – original draft, Writing – review & editing, Project administration. **Alexandra Walker:** Investigation, Validation, Visualization, Writing – review & editing, Project administration. **Erin Meier:** Investigation, Writing – review & editing. **Emily Goldberg:** Investigation, Writing – review & editing. **Richard Leigh:** Methodology, Writing – review & editing. **Argye E. Hillis:** Conceptualization, Formal analysis, Investigation, Resources, Writing – review & editing, Funding acquisition.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

- Agis, D., Goggins, M.B., Oishi, K., Oishi, K., Davis, C., Wright, A., Kim, E.H., Sebastian, R., Tippett, D.C., Faria, A., Hillis, A.E., 2016. Picturing the size and site of stroke with an expanded National Institutes of Health Stroke Scale. *Stroke* 47 (6), 1459–1465. <https://doi.org/10.1161/STROKEAHA.115.012324>.
- Ardila, A., Rosselli, M., 1996. Spontaneous language production and aging: Sex and educational effects. *Int. J. Neurosci.* 87 (1–2), 71–78. <https://doi.org/10.3109/00207459608990754>.
- Azizyan, A., Sanossian, N., Mogensen, M.A., Liebeskind, D.S., 2011. Fluid-attenuated inversion recovery vascular hyperintensities: An important imaging marker for cerebrovascular disease. *Am. J. Neuroradiol.* 32 (10), 1771–1775. <https://doi.org/10.3174/ajnr.A2265>.
- Baldo, J.V., Arévalo, A., Patterson, J.P., Dronkers, N.F., 2013. Grey and white matter correlates of picture naming: Evidence from a voxel-based lesion analysis of the Boston Naming Test. *Cortex* 49 (3), 658–667. <https://doi.org/10.1016/j.cortex.2012.03.001>.
- Benjamini, Y., Hochberg, Y., 1995. Controlling the false discovery rate: A practical and powerful approach to multiple testing. *J. R. Stat. Soc. Series B Stat. Methodol.* 57 (1), 289–300.
- Brookshire, R.H., Nicholas, L.E., 1995. Performance deviations in the connected speech of adults with no brain damage and adults with aphasia. *Am. J. Speech Lang. Pathol.* 4 (4), 118–123. <https://doi.org/10.1044/1058-0360.0404.118>.
- Butler, R.A., Ralph, M.A.L., Woollams, A.M., 2014. Capturing multidimensionality in stroke aphasia: Mapping principal behavioural components to neural structures. *Brain* 137 (12), 3248–3266. <https://doi.org/10.1093/brain/awu286>.
- Cheng, B., Ebinger, M., Kufner, A., Köhrmann, M., Wu, O., Kang, D.-W., Liebeskind, D., Tourdias, T., Singer, O.C., Christensen, S., Warach, S., Luby, M., Fiebach, J.B., Fiehler, J., Gerloff, C., Thomalla, G., 2012. Hyperintense vessels on acute stroke fluid-attenuated inversion recovery imaging: Associations with clinical and other MRI findings. *Stroke* 43 (11), 2957–2961. <https://doi.org/10.1161/STROKEAHA.112.658906>.
- Cooper, P.V., 1990. Discourse production and normal aging: Performance on oral picture description tasks. *J. Gerontol. Psychol. Sci.* 45 (5), 210–212. <https://academic.oup.com/geronj/article/45/5/P210/651647>.
- Cosnard, G., Duprez, T., Grandin, C., Smith, A.M., Munier, T., Peeters, A., 1999. Fast FLAIR sequence for detecting major vascular abnormalities during the hyperacute phase of stroke: a comparison with MR angiography. *Neuroradiology* 41 (5), 342–346.
- Croquelois, A., Wintermark, M., Reichhart, M., Meuli, R., Bogousslavsky, J., 2003. Aphasia in hyperacute stroke: Language follows brain penumbra dynamics. *Ann. Neurol.* 54 (3), 321–329.
- Damasio, H., Damasio, A.R., 1989. *Lesion analysis in neuropsychology*. Oxford University Press.
- Døll, H., Andersen Helland, W., Helland, T., Specht, K., 2021. Associations between lesion size, lesion location and aphasia in acute stroke. *Aphasiology* 35 (6), 745–763. <https://doi.org/10.1080/02687038.2020.1727838>.
- Fink, J.N., Selim, M.H., Kumar, S., Silver, B., Linfante, L., Caplan, L.R., Schlaug, G., 2002. Is the association of National Institutes of Health Stroke Scale scores and acute magnetic resonance imaging stroke volume equal for patients with right- and left-hemisphere ischemic stroke? *Stroke* 33 (4), 954–958.
- Fridriksson J., den Ouden D. B., Hillis A. E., et al. 2018. Anatomy of aphasia revisited. *Brain*. 141(3):848-862. doi:10.1093/brain/awx363.
- Fridriksson, J., Holland, A.L., Coull, B.M., Plante, E., Trouard, T.P., Beeson, P., 2002. Aphasia severity: Association with cerebral perfusion and diffusion. *Aphasiology* 16 (9), 859–871. <https://doi.org/10.1080/02687030244000347>.
- Gawlitza, M., Gragert, J., Quäschling, U., Hoffmann, K.T., 2014. FLAIR-hyperintense vessel sign, diffusion-perfusion mismatch and infarct growth in acute ischemic stroke without vascular recanalisation therapy. *J. Neuroradiol.* 41 (4), 227–233. <https://doi.org/10.1016/j.neurad.2013.10.004>.
- Goodglass, H., Kaplan, E., Barresi, B., 2001. *BDAE-3: Boston Diagnostic Aphasia Examination-Third Edition*. Lippincott Williams & Wilkins, Philadelphia, PA.
- Habeck, C., Razlighi, Q., Gazes, Y., Barulli, D., Steffener, J., Stern, Y., 2017. Cognitive reserve and brain maintenance: Orthogonal concepts in theory and practice. *Cereb. Cortex* 27 (8), 3962–3969. <https://doi.org/10.1093/cercor/bhw208>.
- Hasebroeck, K.M., Serkova, N.J., 2009. Toxicity of MRI and CT contrast agents. *Expert. Opin. Drug Metab. Toxicol.* 5 (4), 403–416. <https://doi.org/10.1517/1742525090287396>.
- Henderson, L.W., Frank, E.M., Pigatt, T., Abramson, R.K., Houston, M., 1998. Race, gender, and educational level effects on Boston Naming Test scores. *Aphasiology* 12 (10), 901–911. <https://doi.org/10.1080/02687039808249458>.
- Herrlich, I., Dietrich, S., Ackermann, H., 2020. The margins of the language network in the brain. *Front. Commun.* 5, 1–26. <https://doi.org/10.3389/fcomm.2020.519955>.
- Hidalgo, B., Goodman, M., 2013. Multivariate or multivariable regression? *Am. J. Public Health* 103 (1), 39–40. <https://doi.org/10.2105/AJPH.2012.300897>.
- Hillis, A.E., 2007. Magnetic resonance perfusion imaging in the study of language. *Brain Lang.* 102 (2), 165–175. <https://doi.org/10.1016/j.bandl.2006.04.016>.
- Hillis, A.E., Barker, P.B., Beauchamp, N.J., Gordon, B., Wityk, R.J., 2000. MR perfusion imaging reveals regions of hypoperfusion associated with aphasia and neglect. *Neurology* 55 (6), 782–788.
- Hillis, A.E., Kane, A., Tuffiash, E., Ulatowski, J.A., Barker, P.B., Beauchamp, N.J., Wityk, R.J., 2001. Reperfusion of specific brain regions by raising blood pressure restores selective language functions in subacute stroke. *Brain Lang.* 79 (3), 495–510. <https://doi.org/10.1006/brln.2001.2563>.
- Hillis, A.E., Wityk, R.J., Barker, P.B., et al., 2002. Subcortical aphasia and neglect in acute stroke: the role of cortical hypoperfusion. *Brain* 125, 1094–1104.
- Hillis, A.E., Tuffiash, E., Wityk, R.J., Barker, P.B., 2002. Regions of neural dysfunction associated with impaired naming of actions and objects in acute stroke. *Cogn. Neuropsychol.* 19 (6), 523–534. <https://doi.org/10.1080/02643290244000077>.
- Hillis, A.E., Wityk, R.J., Barker, P.B., Ulatowski, J.A., Jacobs, M.A., 2003. Change in perfusion in acute nondominant hemisphere stroke may be better estimated by tests of hemispatial neglect than by the national institutes of health stroke scale. *Stroke* 34 (10), 2392–2396. <https://doi.org/10.1161/01.STR.0000089681.84041.69>.
- Hillis, A.E., Work, M., Barker, P.B., Jacobs, M.A., Breese, E.L., Maurer, K., 2004. Re-examining the brain regions crucial for orchestrating speech articulation. *Brain* 127 (7), 1479–1487. <https://doi.org/10.1093/brain/awh172>.
- Hillis, A.E., Wityk, R.J., Beauchamp, N.J., Ulatowski, J.A., Jacobs, M.A., Barker, P.B., 2004. Perfusion-weighted MRI as a marker of response to treatment in acute and subacute stroke. *Neuroradiology* 46 (1), 31–39. <https://doi.org/10.1007/s00234-002-0918-4>.
- Hillis, A.E., Barker, P.B., Wityk, R.J., Aldrich, E.M., Restrepo, L., Breese, E.L., Work, M., 2004. Variability in subcortical aphasia is due to variable sites of cortical hypoperfusion. *Brain Lang.* 89 (3), 524–530. <https://doi.org/10.1016/j.bandl.2004.01.007>.
- Hillis, A.E., Newhart, M., Heidler, J., Barker, P.B., Herskovits, E.H., Degaonkar, M., 2005. Anatomy of spatial attention: Insights from perfusion imaging and hemispatial neglect in acute stroke. *J. Neurosci.* 25 (12), 3161–3167. <https://doi.org/10.1523/JNEUROSCI.4468-04.2005>.
- Hillis, A.E., Kleinman, J.T., Newhart, M., Heidler-Gary, J., Gottesman, R., Barker, P.B., Aldrich, E., Linas, R., Wityk, R., Chaudhry, P., 2006. Restoring cerebral blood flow reveals neural regions critical for naming. *J. Neurosci.* 26 (31), 8069–8073. <https://doi.org/10.1523/JNEUROSCI.2088-06.2006>.
- Hohenhaus, M., Schmidt, W.U., Brunecker, P., Xu, C., Hotter, B., Rozanski, M., Fiebach, J.B., Jungheutling, G.J., 2012. FLAIR vascular hyperintensities in acute ICA and MCA infarction: A marker for mismatch and stroke severity? *Cerebrovasc. Dis.* 34 (1), 63–69. <https://doi.org/10.1159/000339012>.
- Huang, X., Liu, W., Zhu, W., Ni, G., Sun, W., Ma, M., Zhou, Z., Wang, Q., Xu, G., Liu, X., 2012. Distal hyperintense vessels on flair: A prognostic indicator of acute ischemic stroke. *Eur. Neurol.* 68 (4), 214–220. <https://doi.org/10.1159/000340021>.
- Iancu-Gontard, D., Oppenheim, C., Touzé, E., Méary, E., Zuber, M., Mas, J.-L., Frédy, D., Meder, J.-F., 2003. Evaluation of hyperintense vessels on FLAIR MRI for the diagnosis of multiple intracerebral arterial stenoses. *Stroke* 34 (8), 1886–1891. <https://doi.org/10.1161/01.STR.0000080382.61984.FE>.
- Kamran, S., Bates, V., Bakshi, R., Wright, P., Kinkel, W., Miletic, R., 2000. Significance of hyperintense vessels on FLAIR MRI in acute stroke. *Neurology* 55 (2), 265–269.
- Kanda, T., Ishii, K., Kawaguchi, H., Kitajima, K., Takenaka, D., 2014. High signal intensity in the dentate nucleus and globus pallidus on unenhanced T1-weighted MR images: Relationship with increasing cumulative dose of a gadolinium-based contrast material. *Radiology* 270 (3), 834–841. <https://doi.org/10.1148/radiol.13131669>.
- Kanda, T., Fukusato, T., Matsuda, M., Toyoda, K., Oba, H., Kotoku, J., Haruyama, T., Kitajima, K., Furui, S., 2015. Gadolinium-based contrast agent accumulates in the brain even in subjects without severe renal dysfunction: Evaluation of autopsy brain specimens with inductively coupled plasma mass spectroscopy. *Radiology* 276 (1), 228–232. <https://doi.org/10.1148/radiol.2015142690>.
- Kaplan, E., Goodglass, H., Weintraub, S., 1983. *Boston Naming Test*. Lea & Febiger, Philadelphia, PA.
- Katz, M.H., 2003. Multivariable analysis: A primer for readers of medical research. *Ann. Intern. Med.* 138 (8), 644. <https://doi.org/10.7326/0003-4819-138-8-200304150-00012>.
- Kobayashi, J., Uehara, T., Toyoda, K., Endo, K., Ohara, T., Fujinami, J., Nagatsuka, K., Minematsu, K., 2013. Clinical significance of fluid-attenuated inversion recovery vascular hyperintensities in transient ischemic attack. *Stroke* 44 (6), 1635–1640. <https://doi.org/10.1161/STROKEAHA.111.000787>.
- Lee, K.Y., Latour, L.L., Luby, M., Hsia, A.W., Merino, J.G., Warach, S., 2009. Distal hyperintense vessels on FLAIR An MRI marker for collateral circulation in acute stroke? *Neurology* 72 (13), 1134–1139.
- Lee, M., Saver, J.L., Alger, J.R., Hao, Q., Salamon, N., Starkman, S., Ali, L.K., Ovbiagele, B., Kim, D., Villablanca, J.P., Froehler, M.T., Tenser, M.S., Liebeskind, D. S., 2012. Association of laterality and size of perfusion lesions on neurological deficit in acute supratentorial stroke. *Int. J. Stroke* 7 (4), 293–297. <https://doi.org/10.1111/j.1747-4949.2011.00726.x>.
- Legrand, L., Tisserand, M., Turc, G., Naggara, O., Edjlali, M., Mellerio, C., Mas, J.-L., Méder, J.-F., Baron, J.-C., Oppenheim, C., 2015. Do FLAIR vascular hyperintensities beyond the DWI lesion represent the ischemic penumbra? *Am. J. Neuroradiol.* 36 (2), 269–274. <https://doi.org/10.3174/ajnr.A4088>.
- Legrand, L., Tisserand, M., Turc, G., et al., 2016. Fluid-attenuated inversion recovery vascular hyperintensities—diffusion-weighted imaging mismatch identifies acute stroke patients most likely to benefit from recanalization. *Stroke* 47, 424–427. <https://doi.org/10.1161/STROKEAHA.115.010999>.
- Mack, W.J., Freed, D.M., Williams, B.W., Henderson, V.W., 1992. Boston naming test: Shortened versions for use in Alzheimer's Disease. *J. Gerontol. Psychol. Sci.* 47 (3), P154–P158.
- Mackenzie, C., 2000. Adult spoken discourse: the influences of age and education. *Int. J. Lang. Commun. Disord.* 35 (2), 269–285. <http://www.tandf.co.uk/journals/13682822.html>.

- Mackenzie, C., Brady, M., 2004. Communication ability in non-right handers following right hemisphere stroke. *J. Neurolinguist.* 17 (4), 301–313. [https://doi.org/10.1016/S0911-6044\(03\)00061-7](https://doi.org/10.1016/S0911-6044(03)00061-7).
- Maeda, M., Abe, H., Yamada, H., Ishii, Y., 1999. Hyperacute infarction: A comparison of CT and MRI, including diffusion-weighted imaging. *Neuroradiology* 41 (3), 175–178.
- Maeda, M., Yamamoto, T., Daimon, S., Sakuma, H., Takeda, K., 2001. Arterial hyperintensity on fast fluid-attenuated inversion recovery images: A subtle finding for hyperacute stroke undetected by diffusion-weighted MR imaging. *Am. J. Neuroradiol.* 22, 632–636.
- McDonald, R.J., McDonald, J.S., Kallmes, D.F., Jentoft, M.E., Murray, D.L., Thielen, K.R., Williamson, E.E., Eckel, L.J., 2015. Intracranial gadolinium deposition after contrast-enhanced MR imaging. *Radiology* 275 (3), 772–782. <https://doi.org/10.1148/radiol.15150025>.
- McHugh, M.L., 2012. Interrater reliability: The kappa statistic. *Biochem. Med.* 22 (3), 276–282.
- Myers, P.S., 1978. Analysis of right hemisphere communication deficits: Implications for speech pathology. In: Brookshire, R. (Ed.), *Clinical Aphasiology*. BRK Publishers, pp. 49–57.
- Myers, P.S., 1979. Profiles of communication deficits in patients with right cerebral hemisphere damage: Implications for diagnosis and treatment. In: Brookshire, R. (Ed.), *Clinical Aphasiology*. BRK Publishers, pp. 38–46.
- National Institute of Neurological Disorders and Stroke, 2011. NIH Stroke Scale. National Institute of Neurological Disorders and Stroke, Dept. of Health and Human Services, USA.
- Neils, J., Baris, J.M., Carter, C., Dell'aira, A.L., Nordloh, S.J., Weiler, E., Weisiger, B., 1995. Effects of age, education, and living environment on Boston Naming Test performance. *J. Speech Hear. Res.* 38 (5), 1143–1149. <https://doi.org/10.1044/jshr.3805.1143>.
- Nicholas, L.E., Brookshire, R.H., 1993. A system for quantifying the informativeness and efficiency of the connected speech of adults with aphasia. *J. Speech Hear. Res.* 36, 338–350. <http://jslhr.asha.org/cgi/content/abstract/36/2/338>.
- Noguchi, K., Ogawa, T., Inugami, A., Fujita, H., Hatazawa, J., Shimosegawa, E., Okudera, T., Uemura, K., Seto, H., 1997. MRI of acute cerebral infarction: A comparison of FLAIR and T2-weighted fast spin-echo imaging. *Neuroradiology* 39 (6), 406–410.
- Olindo, S., Chausson, N., Joux, J., Saint-Vil, M., Signate, A., Edimonana-Kaptue, M., Jeannin, S., Mejdoubi, M., Aveillan, M., Cabre, P., Smadja, D., 2012. Fluid-attenuated inversion recovery vascular hyperintensity: An early predictor of clinical outcome in proximal middle cerebral artery occlusion. *Arch. Neurol.* 69 (11), 1462. <https://doi.org/10.1001/archneurol.2012.1310>.
- Olsen, T.S., Bruhn, P., Öberg, R.G.E., 1986. Cortical hypoperfusion as a possible cause of 'subcortical aphasia'. *Brain* 109 (3), 393–410.
- Philipse, L.E., Gottesman, R.F., Newhart, M., Kleinman, J.T., Herskovits, E.H., Pawlak, M.A., Marsh, E.B., Davis, C., Heidler-Gary, J., Hillis, A.E., 2007. Neural regions essential for reading and spelling of words and pseudowords. *Ann. Neurol.* 62 (5), 481–492. <https://doi.org/10.1002/ana.v62:510.1002/ana.21182>.
- Pistono, A., Pariente, J., Bézy, C., Pastor, J., Tran, T.M., Renard, A., Fossard, M., Nespoulous, J.-L., Jucla, M., 2017. Inter-individual variability in discourse informativeness in elderly populations. *Clin. Linguist. Phon.* 31 (5), 391–408. <https://doi.org/10.1080/02699206.2016.1277390>.
- Ramalho, J., Semelka, R.C., Ramalho, M., Nunes, R.H., AlObaidy, M., Castillo, M., 2016. Gadolinium-based contrast agent accumulation and toxicity: An update. *Am. J. Neuroradiol.* 37 (7), 1192–1198. <https://doi.org/10.3174/ajnr.A4615>.
- Reyes D, Hitomi E, Simpkins A, et al. Detection of perfusion deficits using FLAIR and GRE based vessel signs Poster presented at: International Stroke Conference. February 21–24, 2017. Houston, TX. <https://www.ahajournals.org/doi/abs/10.1161/str.48.suppl.1.tp63>.
- Rorden, C., Bonilha, L., Fridriksson, J., Bender, B., Karnath, H.-O., 2012. Age-specific CT and MRI templates for spatial normalization. *Neuroimage*. 61 (4), 957–965. <https://doi.org/10.1016/j.neuroimage.2012.03.020>.
- Sanossian, N., Ances, B.M., Shah, S.H., Kim, D., Saver, J.L., Liebeskind, D.S., 2007. FLAIR vascular hyperintensity may predict stroke after TIA. *Clin. Neurol. Neurosurg.* 109 (7), 617–619. <https://doi.org/10.1016/j.clineuro.2007.05.004>.
- Sanossian, N., Saver, J.L., Alger, J.R., Kim, D., Duckwiler, G.R., Jahan, R., Vinuela, F., Ovbiagele, B., Liebeskind, D.S., 2009. Angiography reveals that fluid-attenuated inversion recovery vascular hyperintensities are due to slow flow, not thrombus. *Am. J. Neuroradiol.* 30 (3), 564–568. <https://doi.org/10.3174/ajnr.A1388>.
- Sato, S., Toyoda, K., Uehara, T., Toratani, N., Yokota, C., Moriwaki, H., Naritomi, H., Minematsu, K., 2008. Baseline NIH Stroke Scale Score predicting outcome in anterior and posterior circulation strokes. *Neurology* 70 (Issue 24, Part 2), 2371–2377.
- Schellinger, P.D., Chalela, J.A., Kang, D.-W., Latour, L.L., Warach, S., 2005. Diagnostic and prognostic value of early MR imaging vessel signs in hyperacute stroke patients imaged <3 hours and treated with recombinant tissue plasminogen activator. *Am. J. Neuroradiol.* 26, 618–624.
- Shirani, P., Thorn, J., Davis, C., Heidler-Gary, J., Newhart, M., Gottesman, R.F., Hillis, A. E., 2009. Severity of hypoperfusion in distinct brain regions predicts severity of hemispatial neglect in different reference frames. *Stroke* 40 (11), 3563–3566. <https://doi.org/10.1161/STROKEAHA.109.561969>.
- Thye, M., Mirman, D., 2018. Relative contributions of lesion location and lesion size to predictions of varied language deficits in post-stroke aphasia. *Neuroimage Clin.* 20, 1129–1138. <https://doi.org/10.1016/j.nicl.2018.10.017>.
- Toyoda, K., Ida, M., Fukuda, K., 2001. Fluid-attenuated inversion recovery intraarterial signal: An early sign of hyperacute cerebral ischemia. *Am. J. Neuroradiol.* 22, 1021–1029.
- Trupe E. H., Hillis A. Paucity vs. verbosity: Another analysis of right hemisphere communication deficits. In: Brookshire R., ed. *Clinical Aphasiology*. BRK Publishers; 1985:83-96.
- Tsang, H.-L., Lee, T.M.C., 2003. The effect of ageing on confrontational naming ability. *Arch. Clin. Neuropsychol.* 18 (1), 81–89.
- Umarova, R.M., Sperber, C., Kaller, C.P., Schmidt, C.S.M., Urbach, H., Klöppel, S., Weiller, C., Karnath, H.-O., 2019. Cognitive reserve impacts on disability and cognitive deficits in acute stroke. *J. Neurol.* 266 (10), 2495–2504. <https://doi.org/10.1007/s00415-019-09442-6>.
- Umarova, R.M., Schumacher, L.V., Schmidt, C.S.M., Martin, M., Egger, K., Urbach, H., Hennig, J., Klöppel, S., Kaller, C.P., 2021. Interaction between cognitive reserve and age moderates effect of lesion load on stroke outcome. *Sci. Rep.* 11 (1) <https://doi.org/10.1038/s41598-021-83927-1>.
- Welch, L.W., Doineau, D., Johnson, S., King, D., 1996. Educational and gender normative data for the Boston Naming Test in a group of older adults. *Brain Lang.* 53 (2), 260–266.
- Woo, D., Broderick, J.P., Kothari, R.U., Lu, M., Brott, T., Lyden, P.D., Marler, J.R., Grotta, J.C., 1999. Does the National Institutes of Health Stroke Scale favor left hemisphere strokes? *Stroke* 30 (11), 2355–2359.
- Yorkston, K.M., Beukelman, D.R., 1980. An analysis of connected speech samples of aphasic and normal speakers. *J. Speech Hear. Disord.* 45 (1), 27–36. <https://doi.org/10.1044/jshd.4501.27>.
- Yourganov, G., Smith, K.G., Fridriksson, J., Rorden, C., 2015. Predicting aphasia type from brain damage measured with structural MRI. *Cortex* 73, 203–215. <https://doi.org/10.1016/j.cortex.2015.09.005>.
- Zec, R.F., Burkett, N.R., Markwell, S.J., Larsen, D.L., 2007. A cross-sectional study of the effects of age, education, and gender on the Boston Naming Test. *Clin. Neuropsychol.* 21 (4), 587–616. <https://doi.org/10.1080/13854040701220028>.