2022

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Received: 24 July 2022 | Revised: 24 October 2022 | Accepted: 11 November 2022

DOI: 10.1002/hbm.26159

RESEARCH ARTICLE

WILEY

The relevance of rich club regions for functional outcome post-stroke is enhanced in women

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Funding information
MGH ECOR Fund for Medical Discovery (FMD) Clinical Research Fellowship; NIH-NINDS, Grant/Award Numbers: R01NS082285, R01NS086905, U19NS115388; Société Française de Neuroradiologie, Société Française de Radiologie, Fondation ISITE-ULNE; Swedish

Abstract

This study aimed to investigate the influence of stroke lesions in predefined highly interconnected (rich-club) brain regions on functional outcome post-stroke, determine their spatial specificity and explore the effects of biological sex on their relevance. We analyzed MRI data recorded at index stroke and ~3-months modified Rankin Scale (mRS) data from patients with acute ischemic stroke enrolled in the multisite MRI-GENIE study. Spatially normalized structural stroke lesions were parcellated into 108 atlas-defined bilateral (sub)cortical brain regions. Unfavorable outcome (mRS > 2) was modeled in a Bayesian logistic regression framework. Effects of individual brain regions were captured as two compound effects for (i) six bilateral

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Research Council, Grant/Award Numbers: 2019-01757, 2021-01114; Swedish Heart and Lung Foundation, Grant/Award Number: 20190203; The Swedish Government; The Swedish Heart and Lung Foundation; Swedish Stroke Association

rich club and (ii) all further non-rich club regions. In spatial specificity analyses, we randomized the split into "rich club" and "non-rich club" regions and compared the effect of the actual rich club regions to the distribution of effects from 1000 combinations of six random regions. In sex-specific analyses, we introduced an additional hierarchical level in our model structure to compare male and female-specific rich club effects. A total of 822 patients (age: 64.7[15.0], 39% women) were analyzed. Rich club regions had substantial relevance in explaining unfavorable functional outcome (mean of posterior distribution: 0.08, area under the curve: 0.8). In particular, the rich club-combination had a higher relevance than 98.4% of random constellations. Rich club regions were substantially more important in explaining long-term outcome in women than in men. All in all, lesions in rich club regions were associated with increased odds of unfavorable outcome. These effects were spatially specific and more pronounced in women.

KEYWORDS
Bayesian hierarchical modeling, functional outcome, lesion-symptom mapping, rich club, sex differences

1 | INTRODUCTION

Stroke is the most burdensome neurological disorder in the US, surpassing both Alzheimer disease and migraine with respect to absolute Disease-Adjusted Life Years (DALYs) (Feigin et al., 2021). Enhancing our understanding of underlying factors of severe disease is a stepping stone in designing tailored acute and rehabilitative stroke therapies and improving stroke outcome in the longer term (Bonkhoff, Rehme, et al., 2021; Boyd et al., 2017).

One particularly promising avenue when aiming to understand the neurobiological effects of ischemic stroke lesions, is to build upon our current understanding of physiological brain organization—with its network structure as a core element (Mesulam, 1990; Sporns et al., 2005). Specific to this network conceptualization is the assumption of a hub structure, that is, highly interconnected brain regions constituting the so-called rich club (Van Den Heuvel & Sporns, 2011). These rich club brain regions are assumed to form the backbone for functional integration of diverse brain networks and, hence, large-scale, inter-regional communication (Van Den Heuvel et al., 2012). In their seminal study involving healthy participants, van den Heuvel and Sporns identified six bilateral regions central to this rich club: Superior parietal and frontal lobules, precuneus, thalamus, putamen, and hippocampus (Van Den Heuvel & Sporns, 2011). Subsequent studies suggest joint genetic underpinnings (Arnatkeviciute et al., 2021), higher metabolic needs (Bullmore & Sporns, 2012), and critical implications in cognition of these rich club regions (Crossley et al., 2013). What is more, neuropsychiatric diseases, such as Alzheimer's dementia (Buckner et al., 2009), schizophrenia (Van Den Heuvel et al., 2013), and epilepsy (Larivière et al., 2020), show a tendency to affect these rich club regions primarily. This later observation constitutes the "nodal stress hypothesis" (Buckner et al., 2009; Fornito et al., 2015).

Recent work in the stroke field has also adopted the notion of stroke as a network disease (Grefkes & Fink, 2011) and started to integrate connectome-derived information in stroke outcome models. In particular, these approaches successfully established links between stroke lesions in highly central brain regions and functional outcomes (Ktena et al., 2019; Schirmer, Ktena, et al., 2019), cognitive functions (Aben et al., 2019; Reber et al., 2021), aphasia (Gleichgerrcht et al., 2015) and motor recovery post-stroke (Egger et al., 2021). However, it is important to appreciate that these studies primarily tested whether brain regions central to the network structure, that is, a priori defined brain regions, had the capacity to explain outcome. In most cases, these studies did not assess any spatial specificity aspects, that is, whether their a priori chosen constellations of brain regions were indeed more informative than random constellations of brain regions.

The current study aimed to complement previous approaches by scrutinizing the spatial specificity of classically assumed rich club regions in their relevance for functional stroke outcome in a broad, unselected multi-center stroke sample. To this end, we designed a probabilistic lesion-symptom mapping framework and employed permutation analyses to probe the rich club constellation against 1000 random constellations of brain regions. Leveraging our Bayesian models' flexibility, we also examined whether there were any sex-related differences in the relevance of rich club regions. We hypothesized that rich club regions would have a disproportionately important role in explaining stroke outcome and recovery. In view of our previous findings of enhanced effects of left-hemispherical posterior circulation lesions in women (Bonkhoff et al., 2021; Bonkhoff, Bretzner, et al., 2022), with many of these posterior regions being part of the rich club, we furthermore hypothesized that we would find more augmented rich club effects in women compared to men.

2 | METHODS

2.1 | Ischemic stroke patient cohort

This complete case study utilized data originating from the international MRI–Genetics Interface Exploration (MRI-GENIE) collaboration (Giese et al., 2017). MRI-GENIE had the main aim of facilitating neuroimaging genetic analyses in acute ischemic stroke and hence assembled individual patient data comprising sociodemographic/clinical, neuroimaging, and genotypic information from 12 primary studies; it relied on the infrastructure of the Stroke Genetics Network (SiGN) (Meschia et al., 2013; NINDS Stroke Genetics Network, International Stroke Genetics Consortium, 2016). We here included all those MRI-GENIE patients that had readily available, high-quality DWI-derived lesion segmentations (Wu et al., 2019), clinical information on sociodemographic/clinical characteristics (age, sex, comorbidities), and follow-up modified Rankin Scale (mRS) data (c.f., Supporting Information for a sample size calculation and information on individual studies). The resulting sample was the same as investigated in some of our prior work (Bonkhoff, Bretzner, et al., 2022). It is important to note that the research questions and analytical approaches of our previous and this current work differ substantially as outlined below. The results presented here are hence novel. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The study protocol was approved by Massachusetts General Hospital's Institutional Review Board (Protocol #: 2001P001186 and 2003P000836) and Review Boards of individual sites.

2.2 | Sociodemographic, clinical, and neuroimaging data

We considered age, sex, available cardiovascular risk factors (hypertension (HTN), coronary artery disease (CAD), diabetes mellitus (DM), atrial fibrillation (AF), history of smoking and prior stroke), and the mRS-derived functional outcome (7-point score: 0 = no detectable symptoms, 2 = slight disability, 3 = moderate disability, 6 = death). Data on age, sex, and comorbidities were acquired during hospitalization, and functional outcome was recorded between day 60 and day 190 post-stroke. Neuroimaging scans, more specifically diffusion-weighted images (DWI), were collected during the acute hospital stay (in the majority of cases in the first 48 h, c.f., Supporting Information for a description of imaging parameters). DWI-derived stroke lesion segmentations were generated via a previously validated ensemble of 3-dimensional convolutional neural networks (Wu et al., 2019). We nonlinearly normalized DWI images and respective DWI-lesion segmentations to Montreal Neurological Institute (MNI)-space. We employed nearest neighbor interpolation for coregistration to MNI-space, an additional thresholding step for binary lesion masks was hence not necessary (Winzeck et al., 2019). Results underwent careful quality control by two experienced raters (A.K.B., M.B.) to ensure a high quality of lesion segmentation and spatial normalization. We then calculated the number of stroke lesion-affected voxels per atlas-defined area in 94 cortical and 14 subcortical bilateral brain regions (the unilateral brainstem parcel was excluded, as nonhemisphere-specific region) (Desikan et al., 2006). These 108 brain regions were divided into "rich club" and "non-rich club" regions according to previous work by van den Heuvel and Sporns (Van Den Heuvel & Sporns, 2011). The rich club here consisted of bilateral cortical precuneus, superior frontal, and superior parietal cortex parcels, as well as subcortical bilateral hippocampus, putamen, and thalamus parcels (Figure 1). The definition and structural extent of rich club regions did not differ between men and women.

2.3 | Modeling unfavorable functional outcomes

We employed Bayesian logistic regression to model unfavorable outcome (mRS > 2) (Regenhardt et al., 2022). Brain region-specific lesion effects were captured separately for "rich club" and "non-rich club" brain regions within a hierarchical model structure, that is, we designed two hyperparameters on the higher level that summarized

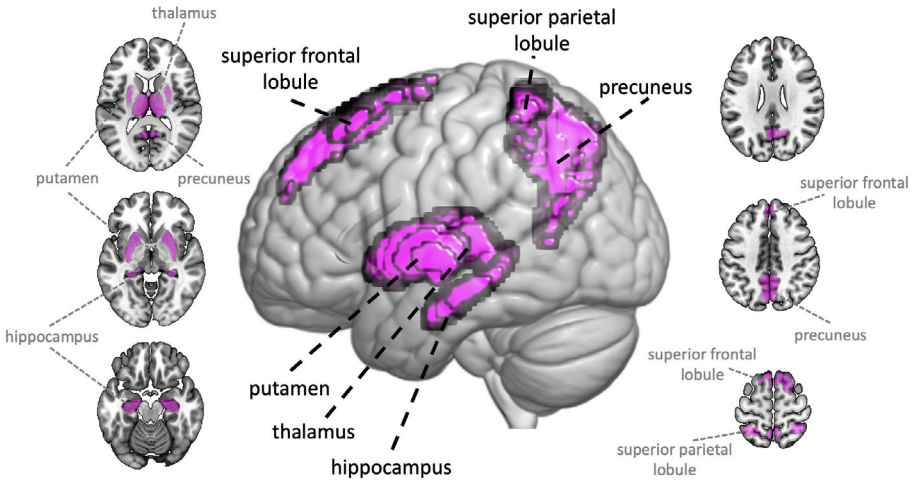

FIGURE 1 Brain renderings of rich club regions, as defined in work by Van Den Heuvel and Sporns (2011). In the present study, we focused on six bilateral brain regions: The superior parietal and frontale lobules, the precuneus, the thalamus, the putamen and the hippocampus.

the effects of the six bilateral "rich club" and 48 bilateral "non-rich club" regions. In addition to the lesion information, we accounted for (mean-centered) age, age (Boyd et al., 2017), sex, total lesion volume, and the presence of following known cardiovascular risk factors: hypertension, diabetes mellitus type 2, atrial fibrillation, coronary artery disease, prior stroke, and smoking. Covariates were chosen line with previous work (Bonkhoff et al., 2021; Bonkhoff, Bretzner, et al., 2022). Both age and age (Boyd et al., 2017) were included to correct for linear, as well as nonlinear U-shaped age effects (e.g., if the outcome is affected the same way in both younger and older, but not middle-aged patients). As in previous work (Bonkhoff, Bretzner, et al., 2022), we refrained from including initial stroke severity as a covariate, as it conceivably represents the extent and location of brain injury. The full model specifications are stated in our Supporting Information.

Samples were drawn from the Bayesian posterior parameter distributions via the No U-Turn Sampler (NUTS), a type of Monte Carlo Markov Chain algorithm (setting: draws = 2500) (Hoffman & Gelman, 2014). The model performance was evaluated as the area under the curve (AUC). While we refrained from interpreting individual region-wise effects in view of the higher dimensional input space, we focused on interpreting collapsed rich club and non-rich club effects.

2.4 | Comparison to the baseline model

To ensure that information on lesion location, as captured in our atlas-defined ROIs, substantially augmented outcome prediction performance, we first conducted a Bayesian model comparison with a baseline model. This baseline model considered clinical characteristics and total DWI stroke lesion volume only.

2.5 | Permutation analysis

Our main aim was to estimate the overall effect of lesions to rich club regions on unfavorable outcome post-stroke. Accordingly, the model parameter of interest was the hyperprior $mu\_\beta_{rich\ club}$ summarizing all individual rich club region effects. We evaluated the sampled Bayesian posterior distribution of $mu\_\beta_{rich\ club}$ in several ways. First, we compared the overall rich club region effect to the overall non-rich club region effect by subtracting both of their posterior distributions, similar to our previous work (Bonkhoff et al., 2021; Bonkhoff, Bretzner, et al., 2022; Bonkhoff, Hong, et al., 2022; Bonkhoff, Lim, et al., 2021). We defined substantial differences as 90% highest probability density intervals (HDPIs) of difference distributions not overlapping with zero. Furthermore, we conducted permutation analyses: In these analyses, we randomly selected six bilateral brain regions and combined them as competing "rich club" regions. The non-selected brain regions were subsequently designated "non-rich club" regions. We then ran the same logistic regression model, as described for the main analyses. This step was repeated 1000 times.

We computed the mean values of all 1000 sampled posterior distributions for random "rich club" combinations and compared the resulting distribution of mean values to the mean value determined for the original "real" rich club combination. In particular, we determined the number of mean values higher or equal to the real rich club regions' mean value. We counted how often each region was selected to gain insights into which brain regions contributed to constellations resulting in comparably high or higher mean values than for the "real" rich club constellation.

2.6 | Sex-specific rich club effects

Further analyses centered on sex-specific effects of lesions to the rich club. As in previous analyses (Bonkhoff et al., 2021), we integrated hyperpriors that were capable of capturing overall rich club and non-rich club effects separately for men and women. We then evaluated differences between hierarchically estimated female and male-specific rich club and non-rich club effects via contrasting of the corresponding posterior parameter distributions. Lastly, we tested whether there were any significant sex differences in either the total or parcel-wise lesion volumes and the frequencies with which each parcel was affected ($p < .05$, FWE-corrected).

2.7 | Ancillary analyses

To gain insights into the effects of further potentially modifying factors and some of our modeling decisions, we repeatedly conducted our main rich club region analyses after (1) including a measure of chronic vascular injury, that is, white matter hyperintensities (WMH), as covariate into our model (continuous WMH burden was available for $n = 698$ patients) (Schirmer, Dalca, et al., 2019), (2) adjusting for scan site (i.e., inclusion of indicator variables to represent the five included centers), (3) changing the cut-off between favorable and unfavorable outcome from mRS > 2 to mRS > 1 and (4) taking hemisphere-specific effects into account.

2.8 | Data and code availability

The authors agree to make the data available to any researcher for the express purposes of reproducing the here presented results and with the explicit permission for data sharing by individual sites' institutional review boards. The Harvard-Oxford atlas can be downloaded here: https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Atlases. Bayesian analyses were implemented in Python 3.7 (predominantly relying on packages: nilearn [Abraham et al., 2014] and pymc3 [Salvatier et al., 2016]).

3 | RESULTS

This study relied on a total of 822 patients with AIS (mean age: 64.7 [15.0], 39.2% women). A favorable 3-months outcome (mRS < 3) was achieved by 72.3% of all patients, the median score on the modified

TABLE 1 Patient characteristics. Mean values and standard deviation, unless otherwise noted. Characteristics of men and women were compared either via two-sample *t*-tests or two-sided Fisher's exact tests as appropriate.

		All participants ($n = 822$)	Male participants ($n = 500$)	Female participants ($n = 332$)	Statistical comparison of male and female participants
Age		64.7 (15.0)	63.9 (14.2)	65.8 (16.2)	$p = .07$
Female sex		39.2%	-	-	-
Acute stroke severity (median, interquartile range)		4 (5)	4 (5)	4 (6)	$p = .07$
3-Months mRS (median, interquartile range)		1 (22)	1 (1)	2 (2)	$p < .001$
Normalized DWI-derived stroke lesion volume (ml, median, interquartile range)		3.3 (19.0)	2.9 (16.6)	3.8 (28.1)	$p = .28$
Comorbidities	Hypertension	64.1%	63.0%	65.8%	$p = .41$
	Diabetes mellitus type 2	21.8%	23.0%	19.9%	$p = .30$
	Atrial fibrillation	16.8%	14.6%	2.2%	$p = .04$
	Coronary artery disease	18.4%	21.8%	13.0%	$p = .002$
	Smoking	55.0%	61.0%	45.7%	$p < .001$
	Prior stroke	9.7%	9.4%	1.2%	$p = .72$
Stroke etiology (based on the causative classification of stroke system [CCS])	Cardio-aortic embolism	16.9%	14.4%	2.8%	$p = .02$
	Large artery atherosclerosis	21.8%	24.2%	18.0%	$p = .04$
	Small artery occlusion	13.9%	13.8%	13.9%	$p = 1.00$
	Other etiology	7.4%	7.2%	7.8%	$p = .79$
	Undetermined etiology	40.0%	40.4%	39.4%	$p = .83$

Rankin Scale was 1 (interquartile range [IQR]: 3). The cohort was furthermore characterized by 64.1% patients with HT, 21.8% with DM, 16.8% with AF, 18.4% with CAD, 9.7% with prior stroke, and 55.0% with smoking as cardiovascular risk factors. An exhaustive display of patients' characteristics, differentiating between men and women, is shown in Table 1 (c.f., Table S1 for characteristics specific to patients with favorable and unfavorable outcomes). The maximum overlay of structural stroke lesions was found to be subcortically, surrounding the lateral ventricles. Lesions were equally distributed between the left and right hemispheres and showed similar spatial distributions for men and women (Figure 2).

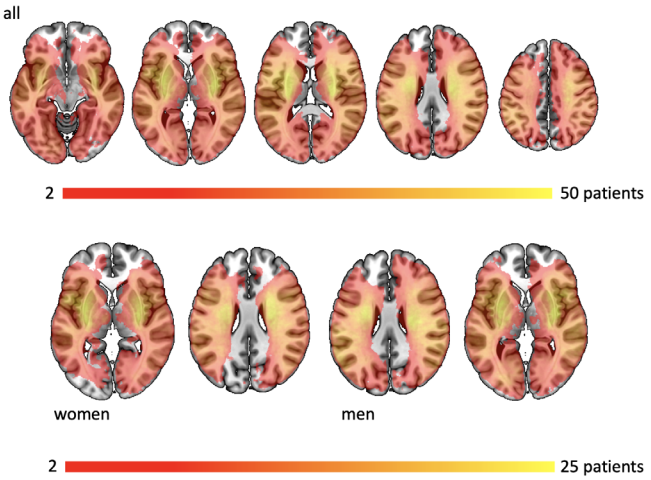

FIGURE 2 Lesion overlaps of all patients (upper row) and specifically for all female and male patients (bottom row)

3.1 | Prediction of unfavorable functional outcomes

We employed Bayesian hierarchical logistic regression to model unfavorable outcome (mRS > 2) (Regenhardt et al., 2022). Our main model relied on clinical information, such as age, sex, and cardiovascular risk factors, as well as information on brain region-wise lesion information, as derived from individual lesion segmentations. Due to the hierarchical structure of our model, we could integrate information originating from "rich club" and "non-rich club" brain regions separately (c.f., Supporting Information for full model specifications).

The AUC for modeling unfavorable outcome (mRS > 2) by relying on our main rich club model was 0.80. As demonstrated by a leave-one-out cross validation-based Bayesian model comparison, this rich club model noticeably outperformed a baseline model that considered information on total stroke lesion volume, but not individual brain-region-wise lesion location. Consequently, the rich club model was regarded as superior (model weights assigned during model comparison: rich club model: 0.96; baseline: 0.04, Figure S1).

The overall rich club region hyperprior effect indicated increased odds of unfavorable outcome in case of rich club region lesion (posterior mean: 0.08, 90%-HPDI: 0.04–0.13, Figure 3, *upper left*). In particular, this overall rich club region effect was substantially larger than the

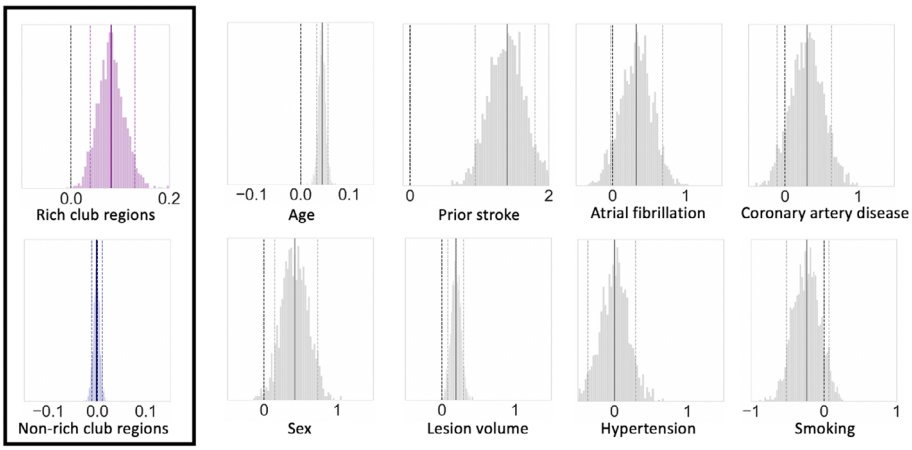

FIGURE 3 Bayesian posterior distributions of the non-sex-specific rich club region model. We considered effects to be substantially relevant, if the 90% highest probability density intervals, as marked by the dashed lines, did not overlap with zero. Correspondingly, lesions in rich club regions, as well as the covariates age, female sex, DM, prior stroke and total DWI lesion volume were all positively associated with increased odds of unfavorable ~3-months outcome. Additionally, the rich club region effect emerged as substantially more pronounced than the non-rich club region effect in direct comparisons of posterior distributions.

respective one for all other non-rich club brain regions combined (difference in posterior mean: −0.08, 90%-HDPI: −0.13 to −0.03). The covariates age, female sex, DM, prior stroke, and total DWI lesion volume all independently increased the odds of unfavorable outcomes (age: posterior mean: 0.04, 90%-HPDI: 0.03–0.06; female sex: posterior mean: 0.42, 90%-HPDI: 0.15–0.74; DM: posterior mean: 0.645, 90%%-HPDI: 0.29–0.99; prior stroke: posterior mean: 1.4, 90%-HPDI: 0.94–1.8; lesion volume: posterior mean: 0.19, 90%-HPDI: 0.08–0.3). Further covariates (HTN, CAD, AF, smoking) were not associated (Figure 3). What is more, our ancillary analyses indicated that the rich club effect, as apparent in the main analyses, could predominantly be traced back to women: The compound rich club effect was substantially more pronounced in women compared to men, as suggested by the difference in Bayesian posterior distributions that did not overlap with zero (difference in posterior distributions: mean: −0.107, 90%-HDPI: −0.193 to −0.0124). At the same time, we did not observe any statistically significant differences in total or parcel-wise lesion volumes or parcel-wise lesion status frequency (all $p > .05$, FWE-corrected).

3.2 | Spatial specificity analyses

Permutation analyses indicated that the overall effect of rich club regions was greater than the effects of 98.4% of the random brain region combinations. In absolute numbers, only 15 out of the 1000 random constellations exceeded the effect of the original rich club combination. The combination of regions achieving the highest effect comprised the superior parietal lobule, the subcallosal cortex, the occipital fusiform gyrus, the superior temporal gyrus (anterior division), and the inferior temporal gyrus (anterior and posterior division; Figure 4). The inferior temporal gyrus (posterior division), the putamen

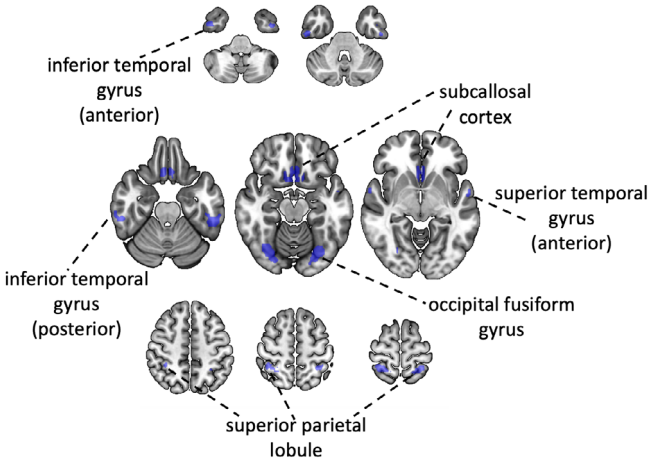

FIGURE 4 Visualization of bilateral brain regions constituting the combination of random "rich club" regions with the highest overall effect on ~3-months functional outcomes post-stroke. The superior parietal lobule was the only region being part of both the real rich club constellation, as well as random combination. While there was no contribution from subcortical regions in this best performing random combination, further regions were distributed all across the cortical surface, that is, featuring frontal, temporal, parietal and occipital regions. Temporal regions were the most frequently represented ones.

(both in 8 out of the 15 constellations), the cingulate gyrus (7/15), and the superior parietal lobule (6/15) were the most frequently involved parcels in these 15 constellations. Altogether, the majority (13) of these 15 constellations included at least one rich club region. The remaining two constellations interestingly overlapped in encompassing parcels relating to the cingulate gyrus, the inferior temporal gyrus, and the fusiform gyrus, suggesting their potential importance in functional outcome modeling.

3.3 | Ancillary analyses

Results remained essentially the same when adjusting for WMH burden and scan center: The overall rich club region hyperprior effect was substantially larger than the one for non-rich club regions (WMH burden analysis: difference in posterior mean between rich club and non-rich club regions: −0.07, 90%-HDPI: −0.12 to −0.02; scan center analysis: difference in posterior mean between rich club and non-rich club regions: −0.09, 90%-HDPI: −0.14 to −0.04). In sex-specific analyses, this rich club region-specific effect was, once again, observable for female patients in particular (WMH burden analysis: difference in posterior mean for rich club region effects between female and male patients: −0.12, 90%-HDPI: −0.22 to −0.04; scan center analysis: difference in posterior mean for rich club region effects between female and male patients: −0.10, 90%-HDPI: −0.20 to −0.02). Moreover, a higher WMH burden increased the odds of unfavorable outcome (posterior mean: 0.41, 90%-HDPI: 0.20–0.60). The prediction performance slightly dropped when employing a cut-off of mRS > 1 to differentiate between favorable and unfavorable outcomes (49.0% patients with an unfavorable outcome, $n = 403$). Qualitatively, we could however observe the same substantially larger rich club region effect when comparing to the non-rich club region effect. This difference was, once again, more pronounced in female patients (difference in posterior mean between rich club and non-rich club regions: −0.07, 90%-HDPI: −0.12 to −0.02; difference in posterior mean for rich club region effects between female and male patients: −0.09, 90%-HDPI: −0.16 to −0.02). Lastly, we will summarize the results of hemispheric evaluations: Rich club region effects in the left and right hemisphere did not differ substantially (difference in posterior mean for rich club regions in the right versus left hemisphere: 0.04, 90%-HPDI: −0.04 to 0.13). However, when comparing rich club und non-rich club effects in either the left, or the right hemisphere, only the right-hemispheric difference in posterior means did not overlap with zero. This finding thus indicated a more substantial effect of rich club regions specifically in the right hemisphere (left: difference in posterior mean for rich club and non-rich club regions: −0.06, 90%-HPDI: −0.12 to 0.02; right: difference in posterior mean for rich club and non-rich club regions: −0.11, 90%-HPDI: −0.18 to −0.03). In sex-specific analyses, we determined a substantially more pronounced left-hemispheric rich club effect in female compared to male patients (difference in posterior mean for left rich club regions in male compared to female patients: −0.13, 90%-HPDI: −0.24 to −0.03). Both female, and male patients showed comparable right-hemispheric rich club effects; the difference of their posterior mean distributions overlapped with zero (difference in posterior mean for right rich club regions in male compared to female patients: −0.08, 90%-HPDI: −0.18 to 0.05). These sex- and hemisphere-specific results may however be viewed as exploratory and warrant further confirmation in additional large data sets.

4 | DISCUSSION

Rich club regions represent critical nodes for cerebral information transfer (Van Den Heuvel & Sporns, 2011). Capitalizing on a large, multi-site international sample of patients with AIS, we show that this combination of structurally defined rich club regions has a prime effect on outcome in the subacute phase post-stroke. Permutation analyses exemplified that the rich club combination exceeded the effects on outcomes of 98.4% of random brain region combinations. In sex-specific analyses, biological female sex emerged as a potential key driver of this rich club effect.

4.1 | Rich club-focused lesion studies now and then

The critical prime role of rich club regions as determined here is well in line with previous studies: These studies carved out hub region involvement in a manifold of neuropsychiatric diseases (Fornito et al., 2015), such as Alzheimer's dementia (Buckner et al., 2009), schizophrenia (Van Den Heuvel et al., 2013), epilepsy (Larivière et al., 2020), and, as pivotally relevant in our context, focal brain lesions in general and stroke in particular. In fact, the importance of hub regions in stroke has been investigated in various ways: Variations related to the studied outcome or stroke-induced impairment, that is, for example global functional outcome (Ktena et al., 2019; Schirmer, Ktena, et al., 2019) or more specific language impairment (Gleichgerrcht et al., 2015). Furthermore, timepoints were varied, that is, from acute to chronic ones (Reber et al., 2021; Warren et al., 2014), and definitions of "hubness" differed, that is, different measures decided about whether a brain region was considered central or not (Aben et al., 2019; Egger et al., 2021; Gleichgerrcht et al., 2015; Ktena et al., 2019; Reber et al., 2021; Schirmer, Ktena, et al., 2019). Altogether, all of these innovations in qualitative and quantitative approaches in previous stroke studies generated valuable insights. They collectively point to the importance of hub regions for stroke outcome. However, most of these studies investigated the relevance of connectomic information in very circumscribed frameworks, heavily built upon a priori chosen hub regions. They only tested small sets of hypotheses in small to medium-sized data sets, on occasion resulting in conflicting results. Warren and colleagues, for example, explicitly tested whether hubs identified based on *two* specific resting-state fMRI, and hence grey matter-focused, measures explained severe and widespread cognitive deficits after cerebral lesions (i.e., high system density/participation coefficients versus high degree centrality) (Warren et al., 2014). In contrast, Reber and colleagues compared the associations of *two* grey and white matter-based measures with cognitive impairment after focal brain lesions (i.e., high participation coefficient versus high edge density) (Reber et al., 2021). Taken together, our novel methodological framework complements these previous approaches by alleviating the necessity of defining a narrow, specific alternative hypothesis. Rather, our framework allows testing of the rich club solution against a great variety of random brain region constellations, independent of any a priori formulated connectomic measures. This more agnostic approach enhances the validity and reliability of rich club involvement further, especially given our comparably large sample size. This sample size

aspect allows good whole-brain coverage (Figure 2) and grants the possibility that the rich club combination, as well as other kinds of constellations can be tested in a meaningful way (c.f., Table S2 for an explicit count of how often each rich club brain region was affected).

4.2 | Clinical implications of lesions in rich club regions and the question *why*?

Our analyses indeed confirmed a predominant and spatially unique role of rich club regions in explaining modified Rankin Scale (mRS)-based unfavorable outcome. In the following, we will break down the specifics, implications and potential explanatory factors of this finding. The modified Rankin Scale represents a very global assessment of stroke sequelae (0: no symptoms, 2: slight disability, 3: moderate disability, 6: death) (Erler et al., 2022; Van Swieten et al., 1988). With an mRS > 2 as cut-off, our distinction between favorable and unfavorable outcome reflected the change from slight to moderate disability and the ability to look after daily activities independently versus requiring some help. Hence, while being coarse-grained, this favorable versus unfavorable distinction captured appreciable clinical, subjectively meaningful effects on patients' lives. Essentially, the combination of this ascertained real-world value and the ease of its collection has motivated the widespread reliance on the mRS as primary, FDA-(Hicks et al., 2018) and NINDS-endorsed (Grinnon et al., 2012) endpoint in the majority of acute stroke treatment trials (Berkhemer et al., 2015; Braun et al., 2021; National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group, 1995).

Altogether, the relevance of our chosen outcome underscores the salience of our findings: Given the detrimental effect of stroke lesions specifically affecting rich club regions, there is, at the same time, the promise that rescuing rich club region tissue could enhance outcomes in clinically significant ways. More concretely, our findings raise the testable hypothesis that acute thrombolytic treatment or endovascular thrombectomy could be more impactful in case of lesions to rich club regions.

Our study also motivates the investigation of several new follow-up questions to render treatment recommendations even more specific. We have here started to explore the role of lesioned hemisphere: We ascertained that rich club region effects themselves were comparable in the left and right hemisphere. However, there was a more pronounced difference between rich club and non-rich club region effects in the right hemisphere that was not detectable in the left hemisphere. This finding contrasts with our prior assumption to find more pronounced left-hemispheric effects, given that left-hemispheric lesions could conceivably entail more language-related functional impairment. In fact, we had observed a more wide-spread involvement of left-hemispheric brain regions for functional outcomes in some of our previous work (Bonkhoff, Bretzner, et al., 2022; Regenhardt et al., 2022). Upon second thought, however, the links between lesions to rich club and non-rich club regions, language impairments and eventually functional outcomes could be more complex and result in this less distinct difference between rich club and non-rich club regions in the left hemisphere. Given that we did not have any access to specific information on language impairments, these links may have to be examined in future studies. Future studies will also be necessary to increase the level of detail further, both with respect to behavioral, as well as brain measures.

In addition to investigating hemispheric effects with further scrutiny, it will be crucial to carve out the importance of *individual* rich club regions: Do all regions affect the outcome equally or to varying degrees? Do several of them have to be affected for noticeable sequelae or is one region sufficient? In addition, is it only the direct injury to rich club regions that is detrimental to outcomes, or also indirect ties to the lesions? Such evaluations of indirect effects will be possible thanks to more recently developed techniques to estimate structural (Foulon et al., 2018; Horn & Kühn, 2015) and functional lesion connectivity (Boes et al., 2015; Fox, 2018). In sum, these additional pieces of information will be of particular relevance, as the rate of affection and therapeutic accessibility differ for the individual rich club regions. In view of the anatomy of the human vasculature and classic locations of vessel occlusions, there are naturally more patients experiencing a stroke that affects the putamen or thalamus than superior frontal or precuneous cortices (Bonkhoff, Xu, et al., 2021). For example, in our sample ~200 and ~300 patients had lesions affecting the thalamus or putamen, respectively, and only ~30 and ~50 for the superior frontal or precuneous cortex (c.f., Table S2 for an overview). Hence, the clinical actionability critically hinges upon the importance of individual rich club regions, especially given the amenability of more proximal vessel occlusions to endovascular thrombectomy. Optimally, all of these analyses will be conducted in combination with methodological approaches ensuring spatial specificity, as showcased here. In addition, it will be promising to continue exploring the specifics of rich club lesion links to acute and chronic impairments in individual domains, such as sensory, motor, visual, cognitive, their combination (e.g., cognitive and motor impairments (Lin et al., 2021)) and domain-specific *recovery* trajectories (Braun et al., 2021). In an ideal scenario, various behavioral domains would be evaluated in the same stroke sample to allow for direct comparisons. Are lesions in rich club regions linked to differing domains with equal or varying strength? Are they particularly crucial for the actual recovery, independent of the initial impairment?

Previous work suggests that rich club regions might be particularly susceptible to brain disease given their unique properties, such as exceptionally high baseline activities and associated metabolic needs (Liang et al., 2013; Tomasi et al., 2013; Van Den Heuvel et al., 2012), longer-distance connections (Harriger et al., 2012) and a high proportion of shortest paths passing through (Van Den Heuvel et al., 2012) (c.f. Fornito et al., 2015, for an excellent overview). In fact, empirical evaluations emphasize the rich club region involvement in neuropsychiatric disease, with schizophrenia and Alzheimer's disease exhibiting the most pronounced associations (Crossley et al., 2014). In case of Alzheimer's disease, it has been hypothesized that it is precisely their higher baseline activity that may underlie the observable preferential accumulation of amyloid-beta in hub regions (Buckner et al., 2009). Rich club region lesion status was shown to be informative about the

acute symptom burden post-stroke (Ktena et al., 2019; Schirmer, Ktena, et al., 2019). The apparent link of hub region affection and global cognitive decline in Alzheimer's disease however raises the question whether stroke ischemia-induced disturbances of hub region integrity could reduce the capability to *recover* in general. Independent of the acute degree of impairment and specifically affected domain, patients may have a greater potential to recover any kind of function in the case of unaffected rich club regions.

4.3 | Sex-specific aspects of rich club relevance

Furthermore, our data are indicative of a female-pronounced rich club effect on functional outcomes. If lesioned in a female brain, rich club regions increased the likelihood of unfavorable outcomes substantially more than if lesioned in a male brain.

Sex differences in the human brain represent a delicate and highly debated topic. A recent comprehensive review on neuroimaging-based cerebral sex differences concluded that the human brain was "not 'sexually dimorphic'": According to the author's evaluation, sex/gender explained only 1% in total variance of structural differences once brain size was taken into account (brain size, in turn, is consistently found to be ~12% higher in males (Ruigrok et al., 2014)) (Eliot et al., 2021). In response, others (Hirnstein & Hausmann, 2021) have argued that sex differences with small effect sizes, while not representing "sexual dimorphisms," may still entail meaningful behavioral consequences, for example, if affecting repeated events (Funder & Ozer, 2019). Furthermore, it may be worth considering that, even if men and women categorically only differed in their brain sizes, it might be a difference of high clinical relevance: Previous research suggests that outcomes are more favorable in case of larger brain volumes (Schirmer et al., 2020).

More fine-grained analyses of structural connectivity in healthy participants have demonstrated enhanced within-hemisphere connectivity and modularity in men, in contrast to higher between-hemisphere connectivity and cross-module participation in women (Ingalhalikar et al., 2014). With respect to functional connectivity, a large-scale study in ~5000 UK Biobank participants detailed stronger functional connectivity in unimodal sensorimotor areas in men, while women were characterized by stronger connectivity in the default mode network (DMN) (Ritchie et al., 2018). Given the large overlap of brain regions thought to be part of the rich club on the one hand and the DMN on the other hand, this female-specific enhanced DMN connectivity could contribute to explain the greater vulnerability to rich club lesions in women. Lesions in a female brain could conceivably lead to a more far-reaching impairment of whole-brain processing. Initial sex-specific lesion network mapping-based explorations of lesion pattern effects also point in the direction of more far-reaching disruptions of functional connectivity underlying the more pronounced lesion pattern effects in women (Bonkhoff, Bretzner, et al., 2022).

Altogether, our findings suggest pronounced sex differences in the relevance of injury to rich club regions. It is important to realize that those cerebral sex differences were apparent in relation to behavior, that is, we investigated the interaction between rich club effects and biological sex on the functional outcome. Our stroke patients were also on average ~30 years older than most subjects in studies of healthy participants. Such an age difference has dramatic effects on hormonal levels of both estrogen in women, as well as testosterone in men (Salminen et al., 2022) and may alter cerebral functioning via activational effects (Koellhoffer & McCullough, 2013). Therefore, these two key differences could already explain why comparable rich club region effects were not observed in previous studies comparing rich club regions in male and female brains without any links to behavior or age (Wang et al., 2019; Zhao et al., 2021). Future studies interrogating sex differences could generate novel insights by more frequently embracing some of this additional complexity. In particular, sex differences may be modified by additional factors, such as socioeconomic status, education, sexual orientation, and sex hormones (Hirnstein & Hausmann, 2021), which need to be explicitly incorporated in analytical approaches. Stroke and further neuropsychiatric diseases, with Alzheimer's disease being a primary example, may be promising model diseases, given their intricate links to age and significantly impacted behavior.

4.4 | Strength and limitations

The current work has several strengths and limitations: First, we had access to a large stroke database, that, due to its multicenter character, may be representative of a common stroke patient population. In combination with our comprehensive Bayesian modeling and cross-validation scheme, these factors may lay the foundation for a successful subsequent generalization to new stroke samples and individual patients. However, patients were relatively mildly affected by their strokes (~73% with favorable outcomes) and had overall fairly small stroke lesions. One might hypothesize that this small average stroke lesion volume could be due to a high fraction of patients experiencing strokes due to small artery occlusion. However, only 13.9% of our patient sample were categorized as small artery occlusion strokes, which is lower than for example reported in registry-based studies (e.g., 20.5% for a German cohort of ~150,000 patients with ischemic stroke) (Bonkhoff, Rübsamen, et al., 2022). Altogether, future studies are needed to conduct additional analyses in samples of more severely affected participants experiencing larger lesions on average. Plausibly, findings could be even more pronounced than reported here. Information on the pre-stroke functional status or any acute treatment was furthermore not available for our data sample. Patients contributing to MRI-GENIE were recruited prior to 2012, which renders the administration of any acute treatment, both thrombolysis and even more so endovascular thrombectomy, generally less likely, as the number of treated patients was generally still low at that point (Bonkhoff, Karch, et al., 2021). Future studies are hence warranted to scrutinize interactions between treatment effects and lesions to rich club and non-rich club lesions further. As recommended in the literature (Toba et al., 2020), we computed continuous values for region-wise lesion status (i.e., we calculated how many voxels were damaged per region),

rather than applying a binarizing damage threshold. Nonetheless, we focused on a binary outcome—favorable versus unfavorable outcomes—and ensured consistency of results for two commonly used cut-offs only (i.e., mRS > 1 and mRS > 2 to define unfavorable outcomes). Continuous, more granular and domain-specific outcome measures may facilitate even more detailed insights, as outlined above. We here adopted the definition of rich club regions based on white matter-focused and hence structural diffusion tensor imaging (DTI)-derived measures, such as the node-specific degree or strength, as put forward in the fundamental work by Van Den Heuvel and Sporns (2011). Alternative definitions exist, and it would have been equally valid to define "hubness" based on grey matter-focused and functional resting state fMRI data-defined measures, such as the participation coefficient (Reber et al., 2021). Similarly, future work could evaluate different numbers of rich club regions, as we here strictly relied on the number six, as established and employed in prior work (Schirmer, Ktena, et al., 2019; Van Den Heuvel & Sporns, 2011).

5 | CONCLUSIONS

Employing comprehensive Bayesian modeling techniques and permutation analyses, we here demonstrate the spatial specificity of rich club regions in their relevance for long-term stroke outcomes. Notably, this rich club effect on outcomes post-stroke was substantially more pronounced in female as compared to male patients. More research is needed to determine further intricacies of these rich club effects. Nevertheless, our findings suggest that taking lesions to rich club regions into account when deciding about patient-centered, individualized acute stroke treatments allows greater understanding of longer-term outcomes after stroke. Our findings underscore the relevance of rich club regions for neuropsychiatric diseases and hold promise to explain cerebral sex differences beyond acute ischemic stroke.

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ACKNOWLEDGMENTS

We are grateful to our colleagues at the J. Philip Kistler Stroke Research Center for valuable support and discussions. Furthermore, we are grateful to our research participants without whom this work would not have been possible.

FUNDING INFORMATION

A.K.B. is supported by a MGH ECOR Fund for Medical Discovery (FMD) Clinical Research Fellowship Award. M.B. acknowledges support from the Société Française de Neuroradiologie, Société Française de Radiologie, Fondation ISITE-ULNE. A.V. is in part supported by NIH-NINDS (R01 NS103824, RF1 NS117643, R01 NS100417, U01NS100699, U01NS110772). C.J. acknowledges support from the Swedish Research Council (2021-01114), the Swedish state under the agreement between the Swedish government and the county councils, the "Avtal om Läkarutbildning och Medicinsk Forskning" (ALF) agreement (ALFGBG-965328); the Swedish Heart and Lung Foundation (20190203). A.G.L. is funded by: The Swedish Research Council (2019-01757), The Swedish Government (under the "Avtal om Läkarutbildning och Medicinsk Forskning, ALF"), The Swedish Heart and Lung Foundation, The Swedish Stroke Association, Region Skåne, Lund University, Skåne University Hospital, Sparbanksstiftelsen Färs och Frosta, Fremasons Lodge of Instruction Eos in Lund. N.S.R. is in part supported by NIH-NINDS (R01NS082285, R01NS086905, U19NS115388).

CONFLICT OF INTEREST

M.E. has received personal fees for consulting from Astra Zeneca and WorldCare Clinical Group. C.G. has received consulting honoraria from Microvention and Strykere and research funding from Medtronic and Penumbra. A.V. has received research funding from Cerenovus. A.G.L. reports personal fees from Bayer, NovoNordisk, Astra Zeneca, and BMS Pfizer outside this work. T.T. has served/serves on scientific advisory boards for Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Inventiva, Portola Pharm, and PHRI; has/has had research contracts with Bayer, Boehringer Ingelheim, and Bristol Myers Squibb. N.S.R. has received compensation as scientific advisory consultant from Omniox, Sanofi Genzyme and AbbVie Inc.

DATA AVAILABILITY STATEMENT

The authors agree to make the data available to any researcher for the express purposes of reproducing the here presented results and with the explicit permission for data sharing by individual sites' institutional review boards. The Harvard-Oxford atlas can be downloaded here: https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Atlases. Bayesian analyses were implemented in Python 3.7 (predominantly relying on packages: nilearn and pymc3).

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SUPPORTING INFORMATION

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How to cite this article: Bonkhoff, A. K., Schirmer, M. D., Bretzner, M., Hong, S., Regenhardt, R. W., Donahue, K. L., Nardin, M. J., Dalca, A. V., Giese, A.-K., Etherton, M. R., Hancock, B. L., Mocking, S. J. T., McIntosh, E. C., Attia, J., Cole, J. W., Donatti, A., Griessenauer, C. J., Heitsch, L., Holmegaard, L., Jood, K., Jimenez-Conde, J., Kittner, S. J., Lemmens, R., Levi, C. R., McDonough, C. W., Meschia, J. F., Phuah, C.-L., Ropele, S., Rosand, J., Roquer, J., Rundek, T., Sacco, R. L., Schmidt, R., Sharma, P., Slowik, A., Sousa, A., Stanne, T. M., Strbian, D., Tatlisumak, T., Thijs, V., Vagal, A., Wasselius, J., Woo, D., Zand, R., McArdle, P. F., Worrall, B. B., Jern, C., Lindgren, A. G., Maguire, J., Wu, O., Rost, N. S., & on behalf of the MRI-GENIE and GISCOME Investigators and the International Stroke Genetics Consortium (2023). The relevance of rich club regions for functional outcome post-stroke is enhanced in women. *Human Brain Mapping*, *44*(4), 1579–1592. https://doi.org/10.1002/hbm.26159