Equalization of Brain State Occupancy Accompanies Cognitive Impairment in Cerebral Small Vessel Disease

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ABSTRACT

BACKGROUND: Cognitive impairment is a hallmark of cerebral small vessel disease (cSVD). Functional magnetic resonance imaging has highlighted connections between patterns of brain activity and variability in behavior. We aimed to characterize the associations between imaging markers of cSVD, dynamic connectivity, and cognitive impairment.

METHODS: We obtained magnetic resonance imaging and clinical data from the population-based Hamburg City Health Study. cSVD was quantified by white matter hyperintensities and peak-width of skeletonized mean diffusivity (PSMD). Resting-state blood oxygen level–dependent signals were clustered into discrete brain states, for which fractional occupancies (%) and dwell times (seconds) were computed. Cognition in multiple domains was assessed using validated tests. Regression analysis was used to quantify associations between white matter damage, spatial coactivation patterns, and cognitive function.

RESULTS: Data were available for 979 participants (ages 45–74 years, median white matter hyperintensity volume 0.96 mL). Clustering identified five brain states with the most time spent in states characterized by activation (+) or suppression (−) of the default mode network (DMN) (fractional occupancy: DMN+ = 25.1 ± 7.2%, DMN− = 25.5 ± 7.2%). Every 4.7-fold increase in white matter hyperintensity volume was associated with a 0.95-times reduction of the odds of occupying DMN+ or DMN−. Time spent in DMN-related brain states was associated with executive function.

CONCLUSIONS: Associations between white matter damage, whole-brain spatial coactivation patterns, and cognition suggest equalization of time spent in different brain states as a marker for cSVD-associated cognitive decline. Reduced gradients between brain states in association with brain damage and cognitive impairment reflect the dedifferentiation hypothesis of neurocognitive aging in a network-theoretical context.

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The clinical manifestations of cerebral small vessel disease (cSVD) include stroke, depression, and cognitive impairment (1). On structural magnetic resonance imaging (MRI), cSVD may manifest as white matter hyperintensities (WMHs), which can be quantified in an automated fashion (2) and might appear earlier in the course of the disease than other markers (3–5). WMHs are specifically associated with deficits in information processing and executive function (6,7).

Network neuroscience studies the organizational principles underlying the interplay between remote, yet connected, brain areas in normal neurologic functioning and the mechanisms by which network disruptions interact with pathobiology and clinical illness (6). As a step toward understanding the link between cSVD and cognitive deficits, several studies have investigated the effect of WMHs on the structural connectome (9–13). A parallel line of investigation has focused on disruption of functional connectivity (FC), culminating in a network disintegration model of vascular cognitive impairment (14,15).

Dynamic FC (dFC) studies have revealed spatiotemporal organizational principles that cannot be assessed using static FC methods (16). These include brain states, characterized by distinct temporally separated patterns of synchronous brain activity (17–19). While their number is still under debate, evidence for their scientific and clinical utility is accumulating (20–26). Understanding of cognitive processes has further benefited from dFC approaches in terms of the detection of different behaviorally relevant timescales of brain dynamics (27) and an appreciation of the discrete event structure underlying FC (28,29).

Spatial coactivation patterns in the presence of cSVD pathology and their relationship to cognitive impairment, however, are unknown. Using data from a population-based cohort study, we have investigated the association of cSVD pathology, spatiotemporal organization of brain activity measured by resting-state functional MRI, and cognitive performance. Based on results of reduced dFC speed associated with aging...
(30) and cognitive impairment in multiple sclerosis (31), we hypothesized that the extent of WM damage would be associated with a reduction in the complexity of spatiotemporal patterns. Moreover, we hypothesized that such changes would be associated with measures of subcortical cognitive impairment.

**METHODS AND MATERIALS**

A high-level overview of the imaging and behavioral data, processing, and analysis steps is shown in Figure S1. MRI sequence parameters, imaging preprocessing steps, and details on the avoidance of false positive WMH segmentations are detailed in the Supplemental Methods.

**Study Population**

The Hamburg City Health Study (HCHS) is a prospective, population-based cohort study that aims to include a cross-sectional sample of 45,000 participants between 45 and 74 years (32). Bias is minimized by random selection from official registries. We used all available data at the time of planning the analysis, when 4253 participants had been included in the HCHS, 1000 of which were documented as having received brain imaging. The first and last patients were examined in June 2016 and February 2017, respectively. HCHS was approved by the local ethics committee of the Landesärztekammer Hamburg (State of Hamburg Chamber of Medical Practitioners, PV5131), and all participants provided written informed consent.

**Clinical Characterization**

Arterial hypertension was operationalized as a previous diagnosis of hypertension, prescription of antihypertensive medication, or blood pressure exceeding 140 mm Hg (systolic) or 90 mm Hg (diastolic) during the study clinic visit. Diabetes mellitus was defined as the disjunction of previously diagnosed diabetes mellitus, prescription of anti-diabetic medication, or a serum glucose level exceeding 126 mg/dL (fasting) or 200 mg/dL (nonfasting).

Cognitive functions were assessed by neuropsychological tests during participants’ visits at the study center. The Mini-Mental State Examination was used to screen for global impairment of cognitive function (33). The Animal Naming and Word List Learning/Recall tests from the Consortium to Establish a Registry for Alzheimer Disease neuropsychology battery (34) were used to assess verbal fluency and working memory; the Trail Making Test (TMT) was used to quantify cognitive processing speed and executive function (35). The multiple choice vocabulary test (Mehrfach-Wortschatz test) was used to estimate semantic memory (36). Here, participants selected an item from lists of five potential words containing four phonetically related neologisms. The score is the number of correctly identified items, with a maximum score of 37.

**WMH Segmentation**

WMHs were segmented in subject space using k-nearest neighbors classification as implemented in FSL’s Brain Intensity Abnormality Classification Algorithm (37). FLAIR and T1w intensities and Montreal Neurological Institute coordinates were used as features. The classifier was trained on manually segmented WMHs from 98 randomly selected subjects (13). For cross-modal registration, images were brain-extracted using HD-BET (38) and linearly aligned using FLIRT with 6 degrees of freedom (39-41).

**Postprocessing of Lesion Probability Maps**

Binary lesion maps were created from the BIANCA (Brain Intensity Abnormality Classification Algorithm) output using the recent LOCATE (Locally Adaptive Threshold Estimation) approach (42). LOCATE was trained on the same 98 subjects as BIANCA. After binarization, clusters containing fewer than 30 lesioned voxels were discarded. For supplemental analyses, lesioned voxels were classified as either periventricular (distance to the ventricles <10 mm) or deep (≥10 mm) (43,44).

**Dynamic Connectivity Quantification**

Denoised voxel-level data were parcellated by averaging the blood oxygen level–dependent (BOLD) signal in 400 regions of the Schaefer atlas (45). This choice was motivated by prior work showing that parcellations of this scale replicate voxel-wise clustering results more closely than coarser scales (46).

We chose to quantify dFC using a coactivation pattern approach (47,48). This method was chosen because it provides the maximal temporal resolution of 1 repetition time (TR), is robust, and does not require the a priori selection of additional parameters, such as shapes and lengths in sliding window approaches (49-51). To map synchronous brain activation to discrete brain space, we used unsupervised clustering as described previously (52,53); after concatenating the parcellated BOLD data from all participants into a \( n_{\text{subjects}} \times n_{\text{time points}} \times 400 \) feature matrix, we performed k-means clustering in 400-dimensional brain activation space with 1 minus the sample Pearson correlation between points as distance measure \( d \). We thus partitioned the set of \( n_{\text{subjects}} \times n_{\text{time points}} \) BOLD observations into k clusters \( C_1, C_2, \ldots, C_k \), with centroids \( \gamma_1, \gamma_2, \ldots, \gamma_k \) such that the within-cluster variance \( D \) was minimized, calculated as

\[
D = \sum_{k=1}^{k} \sum_{p \in C_k} d(p, \gamma_k)
\]

To this end, we started from some initial centroids and used the iterative expectation-maximization algorithm \( \text{kmeans}^+ \) implemented in MATLAB R2021a (The MathWorks, Inc.) to assign, at each step, individual observations to their closest centroid and to update centroid locations to the mean of z-transformed observations thus assigned until convergence occurred. The number of clusters was varied between \( k = 2 \) and \( k = 12 \), and 20 repetitions were performed for each \( k \) with random initial conditions. The optimal number of clusters was determined by assessing the incremental variance explained by the lowest error solution at each value of \( k \). Clusters were identified as brain states and named based on the cosine similarity of the positive and negative activations of their centroid with seven a priori–defined functional networks (54). To quantify dynamic aspects of spatial coactivation patterns, we estimated subject- and state-specific fractional occupancies and dwell times. The former is defined as the proportion of BOLD volumes assigned to each brain state, and the
latter is the average number of contiguous volumes thus assigned (55,56).

**Statistical Analysis**

Multiple imputation analysis and generalized regression modeling with a gamma response distribution was used to describe the association between cardiovascular risk factors and cSVD markers (57). Generalized linear and beta regression models were used to quantify the association between logarithmically transformed WMH volume and peak-width of skeletonized mean diffusivity (PSMD), and spatial coactivation patterns. For cognitive scores, we used generalized linear modeling with gamma and binomial response distributions to assess associations with cSVD markers and brain dynamics. The statistical significance of deviations from the null hypothesis of an absent association was quantified using Wald t tests and adjusted for multiplicity across cognitive measures and brain states using the Bonferroni-Holm method (58). No multiple testing correction was applied across different operationalizations of ischemic WM disease burden (WMH volume, PSMD) and brain dynamics (fractional occupancy, dwell time). Statistical analysis were performed in R version 4.0.5 (59).

**RESULTS**

**Sample Characteristics**

Overall, 1000 MRI session data points were collected from HCHS, corresponding to 986 subjects with usable imaging data. Segmentation of WMHs is exemplified in Figure 1A. The spatial distribution of WMHs is shown in Figure 2B. In 4 subjects, no WMHs were identified and these participants were excluded from further analysis. The numerical distribution of the remaining WMH volumes was skewed to the right with a median of 0.96 mL (interquartile range 0.46–2.2 mL) (Figure 2C). PSMD could be computed for 924 subjects (58 patients did not undergo diffusion-weighted imaging). Median PSMD was 0.000217 (interquartile range 0.000194–0.000245).

For 3 subjects, clinical data were not available, leaving n = 979 subjects (441 females, 45%) for joint analysis of imaging, cardiovascular risk factors, and cognitive function. The mean age was 62.5 years (SD = 8.2 years). Of the patients included in the sample, 666 had hypertension (71.5%; 47 missing), 156 were active smokers (17.5%; 87 missing), and 82 had a diagnosis of diabetes (9.1%; 80 missing); the average body mass index was 26.7 kg/m² (SD = 4.5 kg/m²; 57 missing). A total of 292 participants had a Framingham risk score exceeding 7.

Full sets of cognitive scores were available in 673 of 979 (68.7%) subjects. Summary statistics and associations with age are presented in Table 1. Higher age was associated with poorer cognitive performance in most domains. However, older subjects performed better on the multiple choice vocabulary test.

**Associations Between Cardiovascular Risk Factors, WMH Volume, and Cognition**

Greater WMH volumes were associated with higher age, diabetes, obesity, and smoking. There was no significant association between WMH volume and hypertension. PSMD was associated with higher age, female sex, hypertension,
diabetes, and smoking. Multiplicative effect sizes are reported in Table 2.

Associations between WMH volume and cognitive scores obtained from generalized linear regression modeling are shown in Figure 3. Adjusted for age and sex, extent of WM disease was associated with impaired executive function. For every 4.7-fold increase in WMH volume (corresponding to the interquartile ratio $Q_1^{\text{WMH}}/Q_3^{\text{WMH}}$), the model predicted a 1.06-fold (95% CI = 1.01–1.10) longer completion time in part B of the TMT ($p = .0075$, $p_{\text{Holm}} = .0448$), where the Bonferroni-Holm correction is performed over six tests corresponding to different cognitive scores. There was a trend toward an association between WMH volume and reduced short-term memory with an estimated interquartile odds ratio of recalling an item in the delayed recall test of 0.93 (95% CI = 0.87–1.01, $p = .0778$).

Similar associations between PSMD and cognitive function are shown in Figure S3. Adjusted for age and sex, every 1.26-fold increase in PSMD (interquartile ratio $Q_1^{\text{PSMD}}/Q_3^{\text{PSMD}}$) was associated with a 1.06-fold (95% CI = 1.02–1.12, $p = .0032$, $p_{\text{Holm}} = .0161$) longer completion time in TMT-B and 1.10-fold increased odds of correctly identifying a word from the lexicon in the Mehrfach-Wortschatz test (95% CI = 1.04–1.16, $p = .0022$, $p_{\text{Holm}} = .0130$).

Table 1. Association of Measures of Small Vessel Disease With Demographic and Cardiovascular Risk Factors

| Predictor         | Total WMH, $N = 979$, $n_{\text{complete}} = 758$ | PSMD, $n = 924$, $n_{\text{complete}} = 710$ |
|-------------------|------------------------------------------------|-----------------------------------------------|
| Age (per 10 Years)| 2.11 (1.88–2.36)                                | 1.11 (1.10–1.12)                              |
| Sex, Male         | 0.98 (0.82–1.17)                                | 0.96 (0.94–0.97)                              |
| Hypertension      | 0.96 (0.78–1.19)                                | 1.02 (0.99–1.04)                              |
| Diabetes          | 1.41 (1.03–1.92)                                | 1.04 (1.00–1.07)                              |
| BMI (per 1 kg/m²) | 1.05 (1.02–1.07)                                | 1.00 (1.00–1.00)                              |
| Active Smoking    | 1.23 (0.97–1.55)                                | 1.03 (1.00–1.05)                              |

Values are presented as effect size (95% CI).

Individual models are fitted for WMH volume and PSMD (multiple imputation analysis, $m = 10$). Estimates of effect sizes are obtained from a multivariable generalized linear regression model with gamma response distribution and logarithmic link function and are thus multiplicative on the response scale.

BMI, body mass index; PSMD, peak-width of skeletonized mean diffusivity; WMH, white matter hyperintensity.

Coactivation Patterns as Discrete Brain States

The variance explained by clustering concatenated BOLD signals into $k$ discrete clusters in 400-dimensional Euclidean space, for $k$ ranging from 2 to 12, and the incremental $R^2$ gain associated with each additional cluster are shown in Figure 4A. Less than 1% additional variance was explained by

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**Networks and Cognition in cSVD**

**Figure 2.** Associations between white matter lesion volume and cognitive performance scores (total $N = 979$ independent subjects). Opacity of hexagons indicates number of individual patient data falling within each cell. Solid lines represent estimated population means from simple unadjusted generalized linear models (top row: Mini-Mental State Examination, Vocabulary, Word List Recall: binomial with logit link; bottom row: Animal Naming, Trail Making Test [TMT] A/B: gamma with log link). Shaded ribbons indicate pointwise 95% confidence bands. Insets report effect sizes and $p$ values both with (adjusted [Adj]) and without (Raw) adjustment for the nuisance variables age and sex. Effect sizes are quantified as odds ratios (ORs) (top) or response scale multipliers ($\exp(b)$) (bottom) and correspond to a 4.7-fold increase in white matter hyperintensity volume. $p(H)$ indicates Bonferroni-Holm–corrected $p$ values across cognitive scores (six tests).
incrementing the number of clusters beyond \( k = 5 \). Moreover, the number of subjects who failed to visit each state at least once markedly increased at this value (Figure 4B), and \( k = 5 \) was therefore chosen for further analyses. The identified clusters of recurrent spatial coactivation patterns are shown in Figure 4C. According to their similarity with the DMN, visual network (VIS), and frontoparietal control network (FPCN), we named these states DMN\(^+\), DMN\(^-\), FPCN\(^+\), FPCN\(^-\), VIS\(^+\), and VIS\(^-\) (Figure 4D).

Brain states were similar when constructed separately from patients with WMH volume lower than the first or greater than the third quantile of the whole-sample WMH volume distribution. The spatial correlation between cluster centroids varied between 0.956 (FPCN\(^-\)) and 0.999 (DMN\(^+\)).

### Whole-Brain Spatial Coactivation Patterns

Subjects switched brain states roughly once every two frames (median number of transitions = 68, interquartile range = 64–71; average dwell time \([1.85 \pm 0.16]\) \(\times\) TR). Global switching rate and average dwell time were associated with WM damage. For any 4.7-fold increase in WMH volume, an extra 0.64 (95% CI = 0.18–1.10, \( p = 0.0626 \)) state transitions and a dwell time reduction by 0.017 \(\times\) TR (95% CI = [0.004–0.030] \(\times\) TR, \( p = 0.0120 \)) were estimated. Similarly, any 1.26-fold increase in PSMD was associated with an extra 0.55 (95% CI = 0.05–1.06, \( p = 0.0342 \)) state transitions and a dwell time reduction by 0.015 \(\times\) TR (95% CI = [0.001–0.030] \(\times\) TR, \( p = 0.0376 \)).

We observed higher fractional occupancies in DMN\(^+\) (mean ± SD: 25.1 ± 7.2%) and DMN\(^-\) (25.5 ± 7.2%) compared with VIS\(^-\) (15.8 ± 7.0%), VIS\(^+\) (17.6 ± 6.7%), and FPCN\(^-\) (16.0 ± 6.2%). Consistently, the average dwell times in states DMN\(^+\) (1.98 ± 0.40 TR) and DMN\(^-\) (2.01 ± 0.41 TR) were longer than in VIS\(^-\) (1.60 ± 0.36 TR), VIS\(^+\) (1.65 ± 0.36 TR), and FPCN\(^-\) (1.62 ± 0.34 TR).

Associations with WMH volume are depicted in Figure 4. In beta regressions adjusted for age and sex, patients with higher WMH volumes spent less time in the high-occupancy states DMN\(^+\) (0.95-times reduction of the odds of occupying DMN\(^+\) for every 4.7-fold increase in WMH volume, \( p = 0.0108 \), \( \rho_{\text{Holm}} = 0.0325 \), corrected over five tests corresponding to different brain states) and DMN\(^-\) (odds ratio = 0.95, \( p = 0.0036 \), \( \rho_{\text{Holm}} = 0.0144 \)) and more time in the low-occupancy state FPCN\(^-\) (odds ratio = 1.07, \( p = 0.0010 \), \( \rho_{\text{Holm}} = 0.0050 \)). On a linear scale, these figures correspond to reductions in fractional occupancy of 0.75 (DMN\(^+\)) and 0.84 (DMN\(^-\)) percentage points and an increase of 1.0 percentage points (FPCN\(^-\)), respectively. Consistently, higher WMH burden was associated with reduced average dwell times in default mode states (DMN\(^+:\) relative shortening = 0.98, \( p = 0.0776 \), \( \rho_{\text{Holm}} = 0.3100 \); DMN\(^-\): 0.97, \( p = 0.0020 \), \( \rho_{\text{Holm}} = 0.0099 \)), corresponding to absolute reductions on a linear scale of 0.03 \(\times\) TR (DMN\(^+\)) and 0.06 \(\times\) TR (DMN\(^-\)), respectively. Similar effects were seen for PSMD (Figure S5).

There were no significant associations between age and fractional occupancy or dwell time in any brain state.

### Association Between Measures of Brain Dynamics and Cognitive Performance

There was no association between switch rate or average dwell time and cognitive function. Regression modeling adjusted for age, sex, years of education, and severity of WM disease (WMH volume) revealed that deficits in executive functioning, as measured by longer completion times in part B of the TMT, were associated with less time spent in state DMN\(^+\) (0.94-fold reduction for each additional TR; 95% CI = 0.92–0.96, \( p = 0.0001 \), \( \rho_{\text{Holm}} = 0.0050 \)), corresponding to 0.043 seconds less time spent in states aligned with the DMN. Similarly, increased WMH burden was associated with reduced average dwell times in default mode states (DMN\(^+\): relative shortening = 0.98, \( p = 0.0776 \), \( \rho_{\text{Holm}} = 0.3100 \); DMN\(^-\): 0.97, \( p = 0.0020 \), \( \rho_{\text{Holm}} = 0.0099 \)), corresponding to absolute reductions on a linear scale of 0.03 \(\times\) TR (DMN\(^+\)) and 0.06 \(\times\) TR (DMN\(^-\)), respectively. Similar effects were seen for PSMD (Figure S5).

There were no significant associations between age and fractional occupancy or dwell time in any brain state.

The results for each measure are provided in Table 2. The summary of cognitive performance scores is as follows:

| Cognitive Performance Measure | No. Missing | Mean (SD) | Median [Interquartile Range] | Association With Age |
|------------------------------|-------------|-----------|----------------------------|---------------------|
| MMSE (Max. 30)              | 53          | –         | 28 [27–29]                 | OR 0.80 per item and 10 years, 0.73–0.85 |
| Word Recall (Max. 10)       | 58          | –         | 8 [7–9]                    | OR 0.63 per word and 10 years, 0.59–0.67 |
| Vocabulary (MWT-B) (Max. 37) | 259        | 30.8 (3.9) | 32 [29–34]                | OR 1.20 per word and 10 years, 1.15–1.25 |
| Animal Naming               | 46          | 24.9 (7.1) | 24 [20–30]                 | 0.94-fold decrease per 10 years, 0.92–0.96 |
| TMT-A, seconds              | 148         | 39.3 (14.7)| 36 [29–46]                | 1.19-fold increase per 10 years, 1.16–1.23 |
| TMT-B, seconds              | 156         | 86.2 (36.9)| 78 [63–99]                 | 1.20-fold increase per 10 years, 1.17–1.24 |

Table 2. Summary of Cognitive Performance Scores

Descriptive data for \( N = 979 \) subjects and association with increasing age, assessed by multivariable generalized linear regression analysis adjusted for sex and years of formal education. MMSE, word recall, and MWT-B scores are modeled with a binomial response distribution and logit link function; animal naming and TMT scores are modeled with a gamma response distribution and logarithmic link function.

Max., maximum; MMSE Mini-Mental State Examination; MWT, Mehrfach-Wortschatz test; OR, odds ratio; TMT, Trail Making Test.

**DISCUSSION**

Our analysis yielded two main results. First, after identifying discrete brain states as clusters of recurrent activity and reproducing their characteristic occupancy pattern (51), we showed that increased WMH burden is associated with a reduction of time spent in high-occupancy states and an increase of time spent in low-occupancy states. Second, time spent in states aligned with the DMN was an independent predictor for poor performance in the executive function task.

We analyzed a risk-enhanced subgroup of HCHS. Our sample was mildly affected by cSVD pathology with a median WMH volume of 0.9 mL, explained by a low median age of 62.5 years and our anatomy-informed segmentation approach with an emphasis on avoiding false positives.
Of the different cognitive domains, only executive function as measured by the TMT-B was associated with WMH volume after adjusting for age. The effect size estimate of 6% increase in completion time for every 4.7-fold increase in WMH load is consistent with previous reports from the UK Biobank, where a 2.7-fold increase in WMH volume was associated with a 4.5% increase in reaction times in a variant of the Snap card game (60). The observed pattern of neuropsychological deficits with greatest impairments in executive functions and relative sparing of cortical functions, such as episodic memory, is typical for vascular cognitive impairment (61–63), confirming ischemic WM disease as a predominantly subcortical pathology (64,65). Supplemental analyses (Figures S5 and S6) suggest that the association between WMH and executive dysfunction might be driven in large part by periventricular lesions, supporting the recent notion that these might differ in pathophysiology and clinical sequelae from lesions in the deep white WM (43,66–69).

Clustering BOLD signals in regional activity space identified five discrete brain states. Consistent with previous reports, dwell times and fractional occupancies were greater in brain states characterized by activation or suppression of the DMN (+/−) compared with states orthogonal to the DMN (51).

Our first main finding contributes to the search for structural determinants of spatiotemporal brain dynamics. In an
analysis of the Human Connectome Project, the global geometry and topology of the spatially embedded brain network were implicated as important factors modulating temporal fluctuations of brain activity (70). Focusing on discrete brain states, an application of network control theory to the Philadelphia Neurodevelopment Cohort showed that the transition probabilities between states are constrained by linear spread of activity along the structural connectome (51). It would therefore be conceivable that WMH, preferentially damaging long-range fibers (13), would lead to impaired communications in brain networks such as the DMN, which relies on distributed processing within anterior and posterior brain regions. While the effect of ischemic WMH on static FC has been described extensively elsewhere (15), dFC has only recently been investigated in the context of ischemic vascular disease; in a small study of 19 patients with subcortical ischemic vascular disease, an increase in time spent in a high-occupancy weakly connected brain state was found compared with healthy control subjects (71). More recently, a study of 101 patients with subcortical ischemic vascular disease found no consistent pattern of altered brain state occupancy along a clinical spectrum from asymptomatic to amnestic and nonamnestic mild cognitive impairment (72). Due to differences in inclusion criteria and severity of WM pathology, comparability with the present work is limited.

Our results are also broadly consistent with the disturbances of spatiotemporal brain dynamics associated with focal lesions. In patients with ischemic stroke, a sliding window analysis revealed altered preferences for cortical, subcortical, and cerebellar subdomains of a brain network related to motor function that were modulated by the severity of clinical deficits (73). In a separate cohort, patients severely affected by stroke preferentially occupied a brain state characterized by high dynamic segregation, reflecting important aspects of the structural connectome after stroke (74–76). At a descriptive level, the observed decrease in time spent in high-occupancy states related to the DMN and simultaneous increase in time spent in low-occupancy states orthogonal to the DMN, in association with increasing WMH load, may be described as a dedifferentiation of brain state preference, although this must not be confused with similar notions from cell or developmental biology.

The association between WMH volume and dedifferentiation of brain state preference was expected to be confounded by age. Increasing age is a risk factor for cSVD (7), and structural attributes of WM are recognized as important imaging markers of biological brain age (77). Changes in spatiotemporal brain activation patterns across the life span, on the other hand, are less well understood. By interpreting dFC as a random walk, reduced complexity has been identified as a hallmark of age-related changes in spatiotemporal

Figure 4. Associations between white matter lesion volume and fractional occupancy/mean dwell time (DT) as state-specific metrics of spatial coactivation patterns.Opacity of hexagons indicates number of individual patient data falling within each cell. Solid lines represent estimated population means from fixed-dispersion beta regressions with logit link function in the case of fractional occupancies (top row) and from simple generalized linear regressions with gamma response function and log link function in the case of DTs (bottom row). Shaded ribbons indicate pointwise 95% confidence bands. DT is given in units of repetition time (TR) (2.5 seconds). Insets report effect sizes and p values both with (adjusted [Adj.]) and without (Raw) adjustment for the nuisance variables age and sex. Effect sizes are quantified as odds ratios (OR) (top) or response scale multipliers [exp(b)] (bottom) and correspond to a 4.7-fold increase in white matter hyperintensity volume. P(H) indicates Bonferroni-Holm-corrected p values across brain states (five tests, separately for fractional occupancy and DT). DMN, default mode network; FPCN, frontoparietal control network; TR, repetition time; VIS, visual network.
dynamics (78). Contrasting results have been obtained in younger people, suggesting an inverted U-shaped relationship between age and state fluidity similar to static FC (79–83); in 879 healthy participants between 8 and 22 years, more time spent in high-occupancy DMN-related brain states was associated with increasing age, reflecting an increase in differentiation during development. In 780 adolescents, increasing age was associated with higher state transition flexibility (84). Similar results of more variable connectivity patterns in association with increasing age manifesting as gradients in mean dwell time and fractional state occupancy were observed in a cross-sectional analysis of 51 children and young adults (85). In our sample, neither fractional occupancy nor dwell time in any state were associated with age. This would still be compatible with an inverted U-shaped relationship, given that the median age of 62.5 years in our sample is relatively close to the apex of the age-FC relationship described in (79). The fact that, in contrast, an association between WMH pathology and brain state metric does exist might point toward a complex relationship between chronological age and brain age, in which WMH pathology anticipates functional changes that are otherwise only seen in older subjects.

Our data suggest that dedifferentiation of brain state preference is associated with executive function deficits. This effect occurred primarily in functional brain states critical to attention-related cognitive tasks, such as the DMN. Previous static FC analyses have shown an age-dependent effect of lower DMN integrity on TMT-B (86). Our findings add evidence to the hypothesis that normal cognitive function is contingent on well-regulated brain dynamics characterized by flexibility and complexity in the transitions between latent states (21,78,84,87,88). The dedifferentiation hypothesis of aging maintains that cortical activity in response to behavioral demands becomes less selective across the life span (89). This loss of selectivity may indicate cognitive disruption and explain age-related variability in executive function and processing speed (61). Changes in the organization of FC in the brain might be responsible for age-related dedifferentiation of cognitive function (90). Our results imply that dedifferentiation also occurs at the dynamic network level, manifesting as the equalization of time spent in different brain states. In a potential alternative explanation of our findings, dedifferentiation might occur as a compensatory mechanism. The observed association between dedifferentiation and executive impairment, however, suggests that this compensation would be unsuccessful (91).

We quantified severity of cSVD mainly by the total volume of WMHs. PSMD was explored as a marker of microstructural WM disease (92). Robustness of reported associations was demonstrated by being reproducible in the context of both imaging markers capturing complementary aspects of cSVD pathology.

Our results are constrained by limitations. On average, study participants were only mildly affected by cSVD. This allowed the application of established processing algorithms for structural and functional MRI and reduced the risk of significant alterations in neurovascular coupling; small WMH volumes, however, limit generalizability of conclusions to more severely affected populations. We cannot rule out that spatially heterogeneous effects of aging and WM disease on neurovascular coupling, even in a mildly affected population, could explain part of the observed associations. Second, due to the cross-sectional observational design of the study, no causal relationships can be asserted. In particular, we were unable to test the hypothesis that altered spatiotemporal patterns of brain activation estimated by BOLD signal intensity causally mediate the effect of ischemic WM disease on cognitive impairment. Even in a longitudinal study design, the lack of controlled interventions would make such an analysis very difficult. Further, no Alzheimer’s disease–specific biomarkers, such as positron emission tomography–computed tomography or cerebrospinal fluid analysis, were available in this HCHS sample. We are therefore unable to quantify the effect of nonvascular pathology of cognitive function or spatial coactivation patterns, in particular with regards to a putative brain state related to the limbic system, which was not identified in our decomposition of brain activation space.

The paper provides the first characterization of whole-brain temporospatial coactivation patterns in the presence of cSVD and their relevance for associated cognitive deficits. We showed that imaging markers of ischemic WM disease are related to an equalization of time spent in different brain states and that, even conditional on structural brain damage, this dedifferentiation is associated with deficits in executive function as the hallmark of subcortical cognitive impairment.

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ES conceived of the project, analyzed the data, and wrote the manuscript. BMF contributed to structural image processing. CM and MP performed manual white matter lesion segmentations. JF and UH oversaw image acquisition and quality assurance. ES, BMF, CM, MP, CG, GT, BC, and SK, RT, JG, and CG administrated the study and acquired funding. GT and BC supervised the project. All authors critically reviewed and edited the manuscript.

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Processed summary data and code used for the analyses that support the findings of this study are openly available at https://github.com/csi-hamburg/dFC-COG-HCHS. Raw data including MRI are not publicly available because they contain information that could compromise the privacy of research participants.

The authors report no biomedical financial interests or potential conflicts of interest.

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