

1 Functional MRI brain state 2 occupancy in the presence of 3 cerebral small vessel disease – 4 pre-registration for a replication 5 analysis of the Hamburg City Health 6 Study

✉ For correspondence:
e.schlemm@uke.de

Present address:
Dr. Dr. Eckhard Schlemm,
Klinik und Poliklinik für
Neurologie,
Universitätsklinikum
Hamburg-Eppendorf,
Martinistr. 52,
D-20251 Hamburg

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Preprocessed data will be
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7 **Eckhard Schlemm, MBBS PhD^①✉ and Thies Ingwersen, MD¹**

8 ¹Department of Neurology, University Medical Center
9 Hamburg-Eppendorf

11 **Abstract**

12 **Objective:** To replicate recent findings about the association between the extent of
13 cerebral small vessel disease (cSVD), functional brain network dedifferentiation and
14 cognitive impairment.
15 **Methods:** We will analyze demographic, imaging and behavioral data from the
16 prospective population-based Hamburg City Health Study. Using a fully prespecified
17 analysis pipeline, we will estimate discrete brain states from structural and resting-state
18 functional magnetic resonance imaging (MRI). In a multiverse analysis we will vary brain
19 parcellations and functional MRI confound regression strategies. Severity of cSVD will
20 be operationalised as the volume of white matter hyperintensities of presumed
21 vascular origin. Processing speed and executive dysfunction are quantified by the trail
22 making test (TMT).
23 **Hypotheses:** We hypothesize a) that greater volume of supratentorial white matter

²⁴ hyperintensities is associated with less time spent in functional MRI-derived brain
²⁵ states of high fractional occupancy; and b) that less time spent in these high-occupancy
²⁶ brain states is associated with longer time to completion in part B of the TMT.

²⁷

²⁸ Introduction

²⁹ Cerebral small vessel disease (cSVD) is an arteriolopathy of the brain, associated with
³⁰ age and common cardiovascular risk factors (Wardlaw, C. Smith, and Dichgans, 2013).
³¹ cSVD predisposes to ischemic, in particular lacunar, stroke and may lead to cognitive im-
³² pairment and dementia (Cannistraro et al., 2019). Neuroimaging findings in cSVD reflect
³³ its underlying pathology (Wardlaw, Valdés Hernández, and Muñoz-Maniega, 2015) and
³⁴ include white matter hyperintensities (WMH) and lacunes of presumed vascular origin,
³⁵ small subcortical infarcts and microbleeds, enlarged perivascular spaces as well as brain
³⁶ atrophy (Wardlaw, E. E. Smith, et al., 2013). However, the extent of visible cSVD features
³⁷ on magnetic resonance imaging (MRI) is an imperfect predictor of the severity of clini-
³⁸ cal sequelae (Das et al., 2019), and our understanding of the causal mechanisms linking
³⁹ cSVD-associated brain damage to clinical deficits remains limited (Bos et al., 2018).

⁴⁰ Recent efforts have concentrated on exploiting network aspects of the structural (Tu-
⁴¹ ladhar, Dijk, et al., 2016; Tuladhar, Tay, et al., 2020; Lawrence, Zeestraten, et al., 2018) and
⁴² functional (Dey et al., 2016; Schulz et al., 2021) organization of the brain to understand
⁴³ the relation between cSVD and clinical deficits in cognition and other domains reliant
⁴⁴ on distributed processing. Reduced structural network efficiency has repeatedly been
⁴⁵ described as a causal factor in the development of cognitive impairment, in particular
⁴⁶ executive dysfunction and reduced processing speed, in cSVD (Lawrence, Chung, et al.,
⁴⁷ 2014; Shen et al., 2020; Reijmer et al., 2016; Prins et al., 2005). Findings with respect to
⁴⁸ functional connectivity (FC), on the other hand, are more heterogeneous than their SC
⁴⁹ counterparts, perhaps because FC measurements are prone to be affected by hemody-
⁵⁰ namic factors and noise, resulting in relatively low reliability, especially with resting-state
⁵¹ scans of short duration (Laumann, Gordon, et al., 2015). This problem is exacerbated
⁵² in the presence of cSVD and made worse by the arbitrary processing choices (Lawrence,
⁵³ Tozer, et al., 2018; Gesierich et al., 2020).

⁵⁴ As a promising new avenue, time-varying, or dynamic, functional connectivity approaches
⁵⁵ have more recently been explored in patients with subcortical ischemic vascular disease

Question	Hypothesis	Sampling plan	Analysis plan	Rationale deciding sensitivity for the test	Interpretation given different outcomes	Theory that could be shown wrong by the outcome
Is severity of cerebral small vessel disease, quantified by the volume of supratentorial white matter hyperintensities of presumed vascular origin (WMH), associated with time spent in high-occupancy brain states, defined by resting-state functional MRI	Higher WMH volume is associated with lower average occupancy of the two highest-occupancy brain states.	Available subjects with clinical and imaging data from the HCHS (Jagodzinski et al., 2020)	Standardized preprocessing of structural and functional MRI data • automatic quantification of WMH • co-activation pattern analysis • multivariable generalised regression analyses	Tradition	$P < 0.05 \rightarrow$ rejection of the null hypothesis of no association between cSVD and fractional occupancy; $P > 0.05 \rightarrow$ insufficient evidence to reject the null hypothesis	Functional brain dynamics are not related to subcortical ischemic vascular disease.

Table 1. Study Design Template

⁵⁶ (Yin et al., 2022; Xu et al., 2021). While the study of dynamic FC measures may not solve
⁵⁷ the problem of limited reliability, especially in small populations or subjects with exten-
⁵⁸ sive structural brain changes, it adds another – temporal – dimension to the study of
⁵⁹ functional brain organisation, which is otherwise overlooked. Importantly, FC dynamics
⁶⁰ do not only reflect moment-to-moment fluctuations in cognitive processes but are also
⁶¹ related to brain plasticity and homeostasis (Laumann and Snyder, 2021; Laumann, Snyder, et al., 2017), which may be impaired in cSVD.

⁶³ In the present paper, we aim to replicate and extend the main results of (Schlemm
⁶⁴ et al., 2022); in this recent study, the authors analyzed MR imaging and clinical data from
⁶⁵ the prospective Hamburg City Health Study (HCHS, (Jagodzinski et al., 2020)) using a coac-
⁶⁶ tivation pattern approach to define discrete brain states and found associations between
⁶⁷ the WMH load, time spent in high-occupancy brain states characterized by activation or
⁶⁸ suppression of the default mode network (DMN) and cognitive impairment.

⁶⁹ The fractional occupancy of a functional MRI-derived discrete brain state is a subject-
⁷⁰ specific measure of brain dynamics defined as the proportion of BOLD volumes assigned
⁷¹ to that state relative to all BOLD volumes acquired during a resting-state scan.

⁷² Our primary hypothesis is that the volume of supratentorial white matter hyperinten-
⁷³ sities is associated with the fractional occupancy of DMN-related brain states in a middle-
⁷⁴ aged to elderly population mildly affected by cSVD. Our second hypothesis is that this
⁷⁵ fractional occupancy is associated with executive dysfunction and reduced processing
⁷⁶ speed, measured as the time to complete part B of the trail making test (TMT).

⁷⁷ Both hypotheses will be tested in an independent subsample of the HCHS study popu-
⁷⁸ lation using the same imaging protocols, examination procedures and analysis pipelines
⁷⁹ as in (Schlemm et al., 2022). The robustness of associations will be explored in a multi-

⁸¹ Methods

⁸² Study population

⁸³ The paper will analyze data from the Hamburg City Health Study (HCHS), which is an
⁸⁴ ongoing prospective, population-based cohort study aiming to recruit a cross-sectional
⁸⁵ sample of 45 000 adult participants from the city of Hamburg, Germany (Jagodzinski et
⁸⁶ al., 2020). From the first 10 000 participants of the HCHS we will aim to include those
⁸⁷ who were documented to have received brain imaging (n=2652) and exclude those who
⁸⁸ were analyzed in our previous report (Schlemm et al., 2022). The ethical review board of
⁸⁹ the Landesärztekammer Hamburg (State of Hamburg Chamber of Medical Practitioners)
⁹⁰ approved the HCHS (PV5131), all participants provided written informed consent.

⁹¹ Demographic and clinical characterization

⁹² From the study database we will extract participants' age at the time of inclusion in years,
⁹³ their self-reported gender and the number of years spent in education. During the visit
⁹⁴ at the study center, participants undergo cognitive assessment using standardized tests.
⁹⁵ We will extract from the database their performance scores in the Trail Making Test part
⁹⁶ B, measured in seconds, as an operationalization of executive function and psychomotor
⁹⁷ processing speed (Tombaugh, 2004; Arbuthnott and Frank, 2000).

⁹⁸ MRI acquisition and preprocessing

⁹⁹ The magnetic resonance imaging protocol for the HCHS includes structural and resting-
¹⁰⁰ state functional sequences. The acquisition parameters on a 3 T Siemens Skyra MRI scan-
¹⁰¹ ner (Siemens, Erlangen, Germany) have been reported before (Petersen et al., 2020; Frey
¹⁰² et al., 2021) and are given as follows:

¹⁰³ For T_1 -weighted anatomical images, a 3D rapid acquisition gradient-echo sequence
¹⁰⁴ (MPRAGE) was used with the following sequence parameters: repetition time TR = 2500 ms,
¹⁰⁵ echo time TE = 2.12 ms, 256 axial slices, slice thickness ST = 0.94 mm, and in-plane resolu-
¹⁰⁶ tion IPR = $(0.83 \times 0.83) \text{ mm}^2$.

¹⁰⁷ T_2 -weighted fluid attenuated inversion recovery (FLAIR) images were acquired with
¹⁰⁸ the following sequence parameters: TR = 4700 ms, TE = 392 ms, 192 axial slices, ST =
¹⁰⁹ 0.9 mm, IPR = $(0.75 \times 0.75) \text{ mm}^2$.

¹¹⁰ 125 resting state functional MRI volumes were acquired (TR = 2500 ms; TE = 25 ms;
¹¹¹ flip angle = 90°; slices = 49; ST = 3 mm; slice gap = 0 mm; IPR = $(2.66 \times 2.66) \text{ mm}^2$). Subjects

112 were asked to keep their eyes open and to think of nothing.

113 We will verify the presence and voxel-dimensions of expected MRI data for each par-
114 ticipant and exclude those for whom at least one of T_1 -weighted, FLAIR and resting-state
115 MRI is missing. We will also exclude participants with a neuroradiologically confirmed
116 space-occupying intra-axial lesion. To ensure reproducibility, no visual quality assess-
117 ment on raw images will be performed.

118 For the remaining participants, structural and resting-state functional MRI data will
119 be preprocessed using FreeSurfer v6.0 (<https://surfer.nmr.mgh.harvard.edu/>), and fmriPrep
120 v20.2.6 (Esteban et al., 2019), using default parameters. Participants will be excluded if
121 automated processing using at least one of these packages fails.

122 **Quantification of WMH load**

123 For our primary analysis, the extent of ischemic white matter disease will be operational-
124 ized as the total volume of supratentorial WMHs obtained from automated segmentation
125 using a combination of anatomical priors, BIANCA (Griffanti, Zamboni, et al., 2016) and
126 LOCATE (Sundaresan et al., 2019), post-processed with a minimum cluster size of 30 vox-
127 els, as described in (Schlemm et al., 2022). In an exploratory analysis, we partition voxels
128 identified as WMH into deep and periventricular components according to their distance
129 to the ventricular system (cut-off 10 mm, (Griffanti, Jenkinson, et al., 2018))

130 **Brain state estimation**

131 Output from fMRIprep will be post-processed using xcpEngine v1.2.1 to obtain de-confounded
132 spatially averaged BOLD time series (Ciric, Wolf, et al., 2017). For the primary analysis we
133 will use the 36p regression strategy and the Schaefer-400 parcellation (Schaefer et al.,
134 2018), as in (Schlemm et al., 2022).

135 Different atlases and confound regression strategies, as implemented in xcpEngine,
136 will be included in the exploratory multiverse analysis.

137 Co-activation pattern (CAP) analysis will be performed by first aggregating parcellated,
138 de-confounded BOLD signals into a ($n_{\text{parcels}} \times \sum_i n_{\text{time points},i}$) feature matrix, where $n_{\text{time points},i}$
139 denotes the number of retained volumes for subject i after confound regression. Cluster-
140 ing will be performed using the k -means algorithm ($k = 5$) with distance measure given
141 by 1 minus the sample Pearson correlation between points, as implemented in Matlab
142 R2021a. We will estimate subject- and state-specific fractional occupancies, which are
143 defined as the proportion of BOLD volumes assigned to each brain state (Vidaurre et al.,

¹⁴⁴ 2018). The two states with the highest average occupancy will be identified as the basis
¹⁴⁵ for further analysis.

¹⁴⁶ Statistical analysis

¹⁴⁷ For demographic (age, gender, years of education) and clinical (TMT-B) variables the num-
¹⁴⁸ ber of missing records will be reported. For non-missing values, we will provide descrip-
¹⁴⁹ tive summary statistics using median and interquartile range. The proportion of men
¹⁵⁰ and women in the sample will be reported. Regression modelling will be carried out as
¹⁵¹ a complete-case analysis.

¹⁵² As a first outcome-neutral quality check of the implementation of the MRI process-
¹⁵³ ing pipeline, brain state estimation and co-activation pattern analysis, we will compare
¹⁵⁴ fractional occupancies between brain states. We expect that the average fractional oc-
¹⁵⁵ cupancy in two high-occupancy states is higher than the average fractional occupancy in
¹⁵⁶ the other three states. Point estimates and 95% confidence intervals will be presented
¹⁵⁷ for the difference in average fractional occupancy to check this assertion.

¹⁵⁸ For further analyses, non-zero WMH volumes will be subjected to a logarithmic trans-
¹⁵⁹ formation. Zero values will retain their value zero; to compensate, all models will include
¹⁶⁰ a binary indicator for zero WMH volume if at least one non-zero value is present.

¹⁶¹ To assess the primary hypothesis of a negative association between the extent of is-
¹⁶² chemic white matter disease and time spent in high-occupancy brain states, we will per-
¹⁶³ form a fixed-dispersion beta-regression to model the logit of the conditional expectation
¹⁶⁴ of the average fractional occupancy of two high-occupancy states as an affine function of
¹⁶⁵ the logarithmized WMH load. Age and gender will be included as covariates. The strength
¹⁶⁶ of the association will be quantified as an odds ratio per interquartile ratio of the WMH
¹⁶⁷ burden distribution and accompanied by a 95% confidence interval. Significance testing
¹⁶⁸ of the null hypothesis of no association will be conducted at the conventional significance
¹⁶⁹ level of 0.05. Estimation and testing will be carried out using the 'betareg' package v3.1.4
¹⁷⁰ in R v4.2.1.

¹⁷¹ To assess the secondary hypothesis of an association between time spent in high-
¹⁷² occupancy brain states and executive dysfunction, we will perform a generalized linear
¹⁷³ regression with a Gamma response distribution to model the logarithm of the condi-
¹⁷⁴ tional expected completion time in part B of the TMT as an affine function of the average
¹⁷⁵ fractional occupancy of two high-occupancy states. Age, gender, years of education and
¹⁷⁶ logarithmized WMH load will be included as covariates. The strength of the association

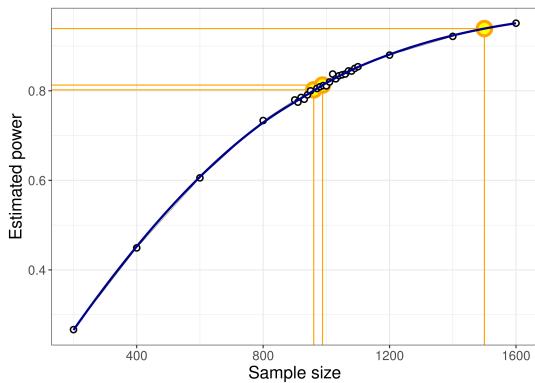


Figure 1. Estimated power for different sample sizes is obtained as the proportion of synthetic data sets in which the null hypothesis of no association between WMH volume and time spent in high-occupancy brain states can be rejected at the $\alpha = 0.05$ significance level. Proportions are based on a total of 10 000 synthetic data sets obtained by bootstrapping the data presented in (Schlemm et al., 2022). Highlighted in orange are the smallest sample size ensuring a power of at least 80 % ($n = 960$), the sample size of the pilot data ($n = 988$, post-hoc power 81.3 %), and the expected sample size for this replication study ($n = 1500$, a-priori power 93.9 %).

177 will be quantified as a multiplicative factor per percentage point and accompanied by a
 178 95% confidence interval. Significance testing of the null hypothesis of no association will
 179 be conducted at the conventional significance level of 0.05. Estimation and testing will
 180 be carried out using the `glm` function included in the 'stats' package from R v4.2.1.

181 Sample size calculation is based on an effect size on the odds ratio scale of 0.95, corre-
 182 sponding to an absolute difference in the probability of occupying a DMN-related brain
 183 state between the first and third WMH-load quartile of 1.3 percentage points, and be-
 184 tween the 5% and 95% percentile of 3.1 percentage points. Approximating half the dif-
 185 ference in fractional occupancy of DMN-related states between different task demands
 186 (rest vs n-back) in healthy subjects, which was estimated to lie between 6 and 7 percent-
 187 age points (Cornblath et al., 2020), this value represent a plausible choice for the smallest
 188 effect size of theoretical and practical interest. It also equals the effect size estimated
 189 based on the data presented in (Schlemm et al., 2022).

190 We used simple bootstrapping to create 10 000 hypothetical datasets of size 200, 400,
 191 600, 800, 900, 910, ..., 1100, 1200, 1400, 1500, 1600. Each dataset was subjected to the esti-
 192 mation procedure described above. For each sample size, the proportion of datasets in
 193 which the primary null hypothesis of no association between fractional occupancy and
 194 WMH load could be rejected at $\alpha = 0.05$ was computed and is recorded as a power curve
 195 in Figure 1.

196 It is seen that a sample size of 960 would allow replication of the reported effect with

Name of the atlas	#parcels	Reference	Design	Reference
Desikan-Killiany	86	Desikan et al., 2006	24p	Friston et al., 1996
AAL	116	Tzourio-Mazoyer et al., 2002	24p + GSR	Macey et al., 2004
Harvard-Oxford	112	Makris et al., 2006	36p	Satterthwaite et al., 2013
glasser360	360	Glasser et al., 2016	36p + spike regression	Cox, 1996
gordon333	333	Gordon et al., 2016	36p + despiking	Satterthwaite et al., 2013
power264	264	Power, Cohen, et al., 2011	36p + scrubbing	Power, Mitra, et al., 2014
schaefer{N}	100	Schaefer et al., 2018	aCompCor	Muschelli et al., 2014
	200		tCompCor	Behzadi et al., 2007
	400		AROMA	Pruim et al., 2015

AAL: Automatic Anatomical Labelling

(a) Parcellations

GSR: Global signal regression, AROMA: Automatic Removal of Motion Artifacts

(b) Confound regression strategies, adapted from (Ciric, Wolf, et al., 2017)

Table 2. Multiverse analysis, implemented using xcpEngine (Ciric, Rosen, et al., 2018)

198 Multiverse analysis

199 Both in (Schlemm et al., 2022) and for our primary replication analysis we made certain
200 analytical choices in the operationalisation of brain states and ischemic white matter
201 disease, namely the use of the 36p confound regression strategy, the Schaefer-400 par-
202 cellation and a BIANCA/LOCATE-based WMH segmentation algorithm. The robustness
203 of the association between WMH burden and time spent in high-occupancy states with
204 regard to other choices will be explored in a multiverse analysis (Steegen et al., 2016).
205 Specifically, in an exploratory analysis, we will estimate brain states from BOLD time se-
206 ries processed according to a variety of established confound regression strategies and
207 aggregated over different cortical brain parcellations (Table 2, Ciric, Rosen, et al., 2018;
208 Ciric, Wolf, et al., 2017). Extent of cSVD will additionally be quantified by the volume of
209 deep and periventricular white matter hyperintensities.

210 For each combination of analytical choice of confound regression strategy, parcella-
211 tion and subdivision of white matter lesion load ($9 \times 9 \times 3 = 243$ scenarios in total) we will
212 quantify the association between WMH load and average time spent in high-occupancy
213 brain states using odds ratio and 95 % confidence intervals as described above.

214 No hypothesis testing and will be carried out in these multiverse analyses. They rather
215 serve to inform about the robustness of the outcome of the test of the primary hypothe-
216 sis. Any substantial conclusions about the association between severity of cerebral small
217 pathology and time spent in high-occupancy brain states, as stated in the Scientific Ques-
218 tion in Table 1, will be drawn from the primary analysis using pre-specified methodolog-
219 ical choices.

220 Further exploratory analysis

221 In previous work, two high-occupancy brain states were related to the default-mode net-
222 work (Cornblath et al., 2020). We will further explore this relation by computing, for each
223 individual brain state, the cosine similarity of the positive and negative activations of
224 the cluster's centroid with a set of a-priori defined functional 'communities' or networks
225 (Schaefer et al., 2018; Yeo et al., 2011). Results will be thus visualized as spider plots for
226 the Schaefer, Gordon and Power atlases.

227 In further exploratory analyses we plan to describe the associations between brain
228 state dynamics and other measures of cognitive ability, such as memory and language.

229 Code and pilot data

230 Summary data from the first 1000 imaging data points of the HCHS have been published
231 with (Schlemm et al., 2022) and form the basis for the hypotheses tested in this replication
232 study. We have implemented our prespecified analysis pipeline described above in R
233 and Matlab, and applied it to this previous sample. Data, code and results have been
234 stored on GitHub (https://github.com/csi-hamburg/HCHS_brain_states_RR) und preserved
235 on Zenodo.

236 Thus re-analysing data from 988 subjects, the separation between two high-occupancy
237 and three low-occupancy brain states could be reproduced for all combinations of brain
238 parcellation and confound regression strategies (Figure 2).

239 In a multiverse analysis, the main finding was somewhat robust with respect to these
240 choices: a statistically significant negative association between WMH load and time spent
241 in high-occupancy states was observed in 18/81 scenarios, with 5/81 statistically signifi-
242 cant positive associations occurring with the Desikan–Killiany parcellation only (Figure 3).

243 The secondary finding of an association between greater TMT-B times and lower frac-
244 tional occupancy was similarly robust with 12/81 statistically significant negative and no
245 statistically significant positive associations.

246 Timeline and access to data

247 At the time of planning of this study, all demographic, clinical and imaging data used in
248 this analysis have been collected by the HCHS and are held in the central trial database.
249 Quality checks for non-imaging variables have been performed centrally. WMH segmen-
250 tation based on structural MRI data of the first 10 000 participants of the HCHS has been

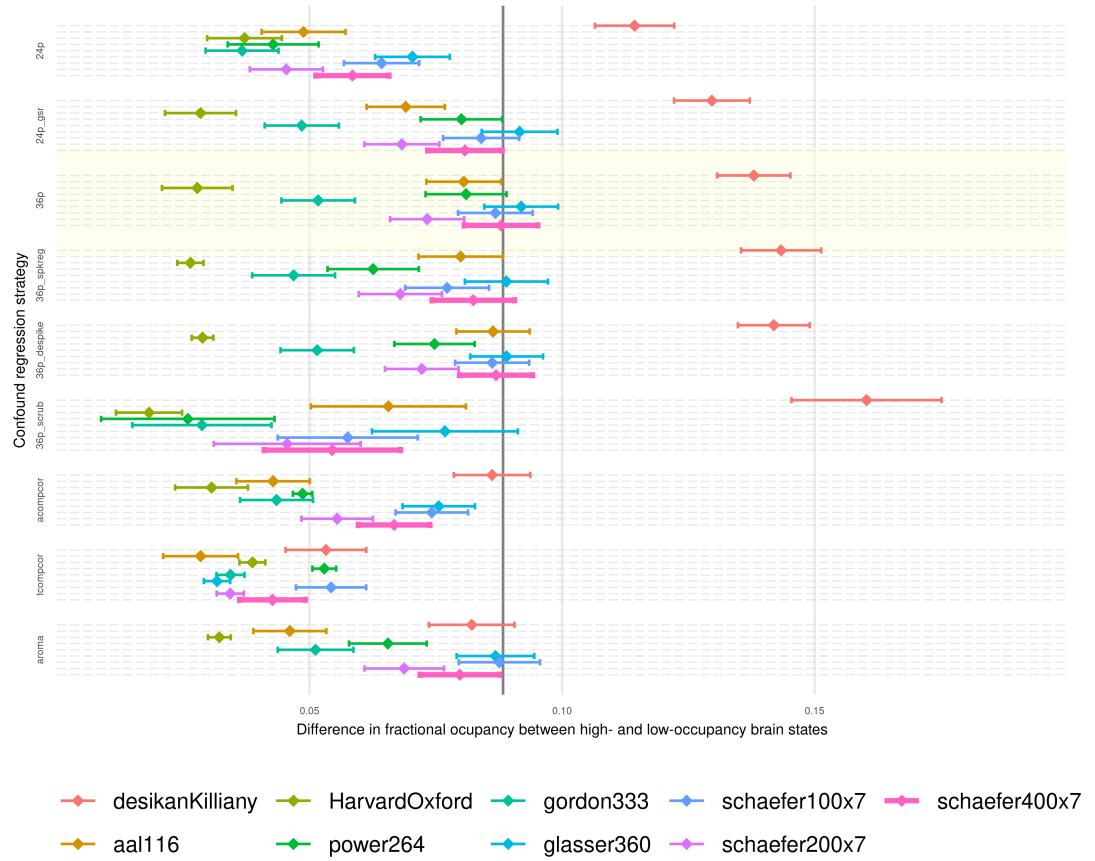


Figure 2. Point estimates (dots) and 95 % confidence intervals (line segments) for the mean difference in fractional occupancy between high- and low occupancy states are shown for different confound regression strategies (groups along the vertical axis) and brain parcellations (color). The difference in FO for a particular choice of regression strategy and brain parcellation is nominally statistically significantly different from zero at a significance level of 5% if the corresponding interval does not contain zero. Hence, the FO difference is significant for *all* processing choices, reflecting the separation between high- und low-occupancy states. The primary choices (36p and schaefer400) are highlighted by a yellow box and thick pink line, respectively. The effect size reported in (Schlemm et al., 2022) is indicated by a vertical line at 0.08830623.

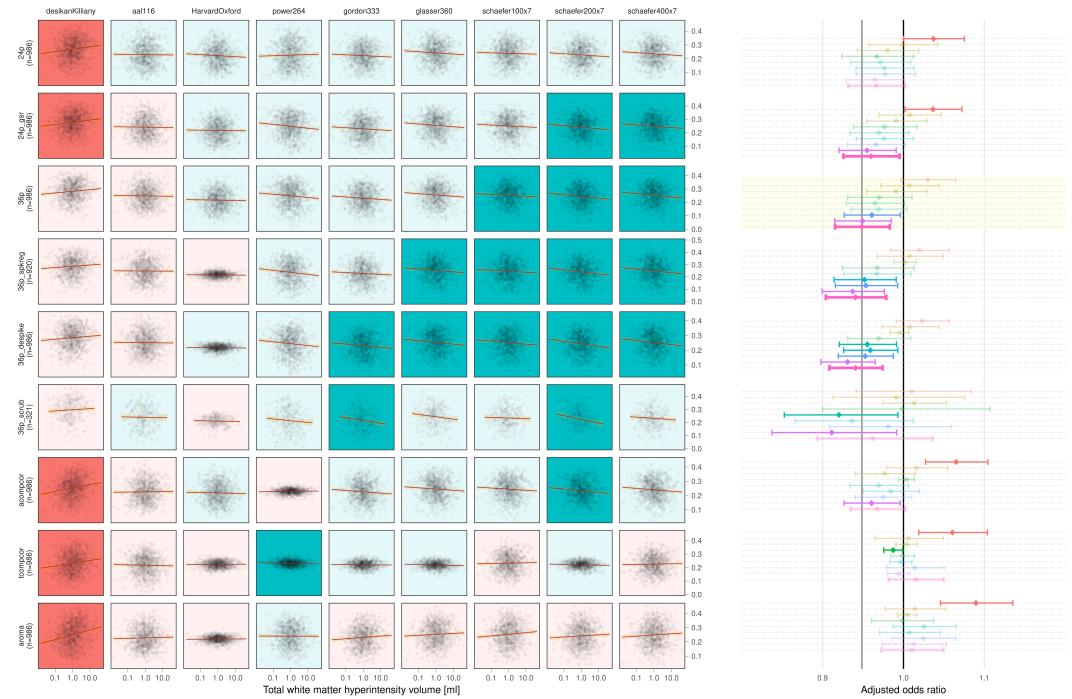


Figure 3. On the left, scatter plots of average fractional occupancies in high-occupancy states against WMH volume on a logarithmic scale (base 10 for easier visualization) for different combinations of confound regression strategies and brain parcellations. Linear regression lines indicate the direction of the unadjusted association between $\log(\text{WMH})$ and occupancy. Background color of individual panels indicates the direction of the association after adjustment for age, sex and zero WMH volume (green, negative; red, positive). A pale background indicates that the association between $\log(\text{WMH})$ and average occupancy is not statistically different from zero. On the right, the same information is shown using point estimates and 95 % confidence intervals for the adjusted odds ratio of the association.

251 performed previously using the BIANCA/LOCATE approach (Rimmele et al., 2022) and re-
252 sults are included in this preregistration (`./derivatives/WMH/cSVD_all.csv`). Functional
253 MRI data and clinical measures of executive dysfunction (TMT-B scores) have not been
254 analyzed by the author. Analysis of the data will begin immediately after acceptance-in-
255 principle of the stage 1 submission of the registered report is obtained. Submission of
256 the full manuscript (stage 2) is planned two months later.

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