

# 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

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## 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

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

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## <sup>28</sup> Introduction

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

<sup>40</sup> Recent efforts have concentrated on exploiting network aspects of the structural (Tu-  
<sup>41</sup> ladhar, Dijk, et al., 2016; Tuladhar, Tay, et al., 2020; Lawrence, Zeestraten, et al., 2018)  
<sup>42</sup> and functional (Dey et al., 2016; Schulz et al., 2021) organization of the brain to under-  
<sup>43</sup> stand the relation between cSVD and clinical deficits in cognition and other domains re-  
<sup>44</sup> liant on distributed processing. Reduced structural network efficiency has repeatedly  
<sup>45</sup> been described as a causal factor in the development of cognitive impairment, in partic-  
<sup>46</sup> ular executive dysfunction und reduced processing speed, in cSVD (Lawrence, Chung,  
<sup>47</sup> et al., 2014; Shen et al., 2020; Reijmer et al., 2016; Prins et al., 2005). Findings with  
<sup>48</sup> respect to functional connectivity results(FC), on the other hand, are more heteroge-  
<sup>49</sup> neous, perhaps due to its limited reproducibility in than their SC counterparts, perhaps  
<sup>50</sup> because FC measurements are prone to be affected by hemodynamic factors and noise,  
<sup>51</sup> resulting in relatively low reliability, especially with resting-state scans of short duration  
<sup>52</sup> (Laumann, Gordon, et al., 2015). This problem is exacerbated in the presence of cSVD  
<sup>53</sup> and dependence on made worse by the arbitrary processing choices (Lawrence, Tozer,  
<sup>54</sup> et al., 2018; Gesierich et al., 2020).

<sup>55</sup> As a promising new avenue, time-varying, or dynamic, functional connectivity approaches

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

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

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

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

80 Both hypotheses will be tested in an independent subsample of the HCHS study popu-  
81 lation using the same imaging protocols, examination procedures and analysis pipelines  
82 as in (Schlemm et al., 2022). The robustness of associations will be explored in a multi-  
83 verse approach by varying key steps in the analysis pipeline.

## 84 Methods

### 85 Study population

86 The paper will analyze data from the Hamburg City Health Study (HCHS), which is an  
87 ongoing prospective, population-based cohort study aiming to recruit a cross-sectional

| 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 <u>of</u> 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 <u>the</u> 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;<br>$P > 0.05 \rightarrow$ insufficient evidence to reject the null hypothesis | Functional brain dynamics are not related to subcortical ischemic vascular disease. |

**Table 1.** Study Design Template

<sup>88</sup> sample of 45 000 adult participants from the city of Hamburg, Germany (Jagodzinski et  
<sup>89</sup> al., 2020). From the first 10 000 participants of the HCHS we will aim to include those  
<sup>90</sup> who were documented to have received brain imaging (n=2652) and exclude those who  
<sup>91</sup> were analyzed in our previous report (Schlemm et al., 2022). The ethical review board of  
<sup>92</sup> the Landesärztekammer Hamburg (State of Hamburg Chamber of Medical Practitioners)  
<sup>93</sup> approved the HCHS (PV5131), all participants provided written informed consent.

#### <sup>94</sup> **Demographic and clinical characterization**

<sup>95</sup> From the study database we will extract participants' age at the time of inclusion in years,  
<sup>96</sup> their self-reported gender and the number of years spent in education. During the visit  
<sup>97</sup> at the study center, participants undergo cognitive assessment using standardized tests.  
<sup>98</sup> We will extract from the database their performance scores in the Trail Making Test part  
<sup>99</sup> B, measured in seconds, as an operationalization of executive function and psychomotor  
<sup>100</sup> processing speed (Tombaugh, 2004; Arbuthnott and Frank, 2000).

#### <sup>101</sup> **MRI acquisition and preprocessing**

<sup>102</sup> The magnetic resonance imaging protocol for the HCHS includes structural and resting-  
<sup>103</sup> state functional sequences. The acquisition parameters on a 3 T Siemens Skyra MRI scan-  
<sup>104</sup> ner (Siemens, Erlangen, Germany) have been reported before (Petersen et al., 2020; Frey  
<sup>105</sup> et al., 2021) and are given as follows:

<sup>106</sup> For  $T_1$ -weighted anatomical images, a 3D rapid acquisition gradient-echo sequence  
<sup>107</sup> (MPRAGE) was used with the following sequence parameters: repetition-repetition time  
<sup>108</sup> TR = 2500 ms, echo time TE = 2.12 ms, 256 axial slices, slice thickness ST = 0.94 mm, and  
<sup>109</sup> in-plane resolution IPR =  $(0.83 \times 0.83) \text{ mm}^2$ .

<sup>110</sup>  $T_2$ -weighted fluid attenuated inversion recovery (FLAIR) images were acquired with

111 the following sequence parameters: TR = 4700 ms, TE = 392 ms, 192 axial slices, ST =  
112 0.9 mm, IPR =  $(0.75 \times 0.75) \text{ mm}^2$ .

113 125 resting state functional MRI volumes were acquired (TR = 2500 ms; TE = 25 ms;  
114 flip angle = 90°; slices = 49; ST = 3 mm; slice gap = 0 mm; IPR =  $(2.66 \times 2.66) \text{ mm}^2$ ). Subjects  
115 were asked to keep their eyes open and to think of nothing.

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

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

## 125 Quantification of WMH load

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

## 133 Brain state estimation

134 Output from fMRIprep will be post-processed using xcpEngine v1.2.1 to obtain de-confounded  
135 spatially averaged BOLD time series (Circi, Wolf, et al., 2017). For the primary analysis we  
136 will use the 36p regression strategy and the Schaefer-400 parcellation (Schaefer et al.,  
137 2018), as in (Schlemm et al., 2022).

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

140 Co-activation pattern (CAP) analysis will be performed by first aggregating parcellated,  
141 de-confounded BOLD signals into a  $(n_{\text{parcels}} \times \sum_i n_{\text{time points},i})$  feature matrix, where  $n_{\text{time points},i}$   
142 denotes the number of retained volumes for subject  $i$  after confound regression. Cluster-

<sup>143</sup> ing will be performed using the  $k$ -means algorithm ( $k = 5$ ) with distance measure given  
<sup>144</sup> by 1 minus the sample Pearson correlation between points, as implemented in Matlab  
<sup>145</sup> R2021a. We will estimate subject- and state-specific fractional occupancies, which are  
<sup>146</sup> defined as the proportion of BOLD volumes assigned to each brain state (Vidaurre et al.,  
<sup>147</sup> 2018). The two states with the highest average occupancy will be identified as the basis  
<sup>148</sup> for further analysis.

## <sup>149</sup> Statistical analysis

<sup>150</sup> For demographic (age, gender, years of education) and clinical (TMT-B) variables the num-  
<sup>151</sup> ber of missing records will be reported. For non-missing values, we will provide descrip-  
<sup>152</sup> tive summary statistics using median and interquartile range. The proportion of men  
<sup>153</sup> and women in the sample will be reported. Regression modelling will be carried out as  
<sup>154</sup> a complete-case analysis.

<sup>155</sup> As a first outcome-neutral quality check of the implementation of the MRI process-  
<sup>156</sup> ing pipeline, brain state estimation and co-activation pattern analysis, we will compare  
<sup>157</sup> fractional occupancies between brain states. We expect that the average fractional oc-  
<sup>158</sup> cupancy in two high-occupancy states is higher than the average fractional occupancy in  
<sup>159</sup> the other three states. Point estimates and 95% confidence intervals will be presented  
<sup>160</sup> for the difference in average fractional occupancy to check this assertion.

<sup>161</sup> For further analyses, non-zero WMH volumes will be subjected to a logarithmic trans-  
<sup>162</sup> formation. Zero values will retain their value zero; to compensate, all models will include  
<sup>163</sup> a binary indicator for zero WMH volume if at least one non-zero value is present.

<sup>164</sup> To assess the primary hypothesis of a negative association between the extent of is-  
<sup>165</sup> chemic white matter disease and time spent in high-occupancy brain states, we will per-  
<sup>166</sup> form a fixed-dispersion beta-regression to model the logit of the conditional expectation  
<sup>167</sup> of the average fractional occupancy of two high-occupancy states as an affine function of  
<sup>168</sup> the logarithmized WMH load. Age and gender will be included as covariates. The strength  
<sup>169</sup> of the association will be quantified as an odds ratio per interquartile ratio of the WMH  
<sup>170</sup> burden distribution and accompanied by a 95% confidence interval. Significance testing  
<sup>171</sup> of the null hypothesis of no association will be conducted at the conventional significance  
<sup>172</sup> level of 0.05. Estimation and testing will be carried out using the 'betareg' package v3.1.4  
<sup>173</sup> in R v4.2.1.

<sup>174</sup> To assess the secondary hypothesis of an association between time spent in high-  
<sup>175</sup> occupancy brain states and executive dysfunction, we will perform a generalized linear

176 regression with a Gamma response distribution to model the logarithm of the condi-  
177 tional expected completion time in part B of the TMT as an affine function of the average  
178 fractional occupancy of two high-occupancy states. Age, gender, years of education and  
179 logarithmized WMH load will be included as covariates. The strength of the association  
180 will be quantified as a multiplicative factor per percentage point and accompanied by a  
181 95% confidence interval. Significance testing of the null hypothesis of no association will  
182 be conducted at the conventional significance level of 0.05. Estimation and testing will  
183 be carried out using the `glm` function included in the 'stats' package from R v4.2.1.

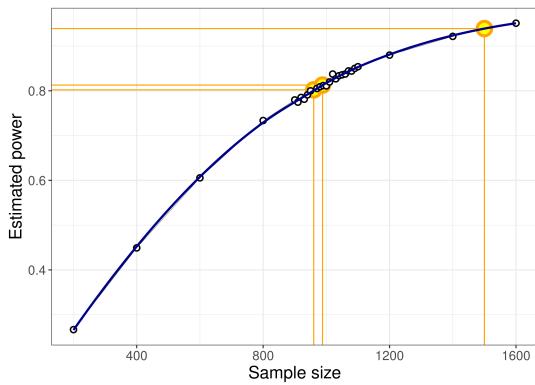
184 Sample size calculation is based on ~~the data presented in, where an odds ratio of was~~  
185 ~~reported as the primary~~ an effect size on the odds ratio scale of 0.95, corresponding to  
186 an absolute difference in the probability of occupying a DMN-related brain state between  
187 the first and third WMH-load quartile of 1.3 percentage points, and between the 5%  
188 95% percentile of 3.1 percentage points. Approximating half the difference in fractional  
189 occupancy of DMN-related states between different task demands (rest vs n-back) in  
190 healthy subjects, which was estimated to lie between 6 and 7 percentage points (Corn-  
191 blath et al., 2020), this value represent a plausible choice for the smallest effect size of  
192 interest theoretical and practical interest. It also equals the effect size estimated based  
193 on the data presented in (Schlemm et al., 2022).

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

200 It is seen that a sample size of 960 would allow replication of the reported effect with  
201 a power of 80.2 %. We anticipate a sample size of 1500, which yields a power of 93.9 %.

## 202 Multiverse analysis

203 Both in (Schlemm et al., 2022) and for our primary replication analysis we made certain  
204 analytical choices in the operationalisation of brain states and ischemic white matter dis-  
205 ease, namely the use of the 36p confound regression strategy, the Schaefer-400 parcella-  
206 tion and a BIANCA/LOCATE-based WMH segmentation algorithm. ~~If the hypothesized~~ The  
207 robustness of the association between WMH burden and time spent in high-occupancy  
208 states ~~can be replicated using these primary analytical choices, its robustness~~ with regard



**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 %).

| Name of the atlas | #parcels | Reference                    |
|-------------------|----------|------------------------------|
| Desikan-Killiany  | 86       | Desikan et al., 2006         |
| AAL               | 116      | Tzourio-Mazoyer et al., 2002 |
| Harvard-Oxford    | 112      | Makris et al., 2006          |
| glasser360        | 360      | Glasser et al., 2016         |
| gordon333         | 333      | Gordon et al., 2016          |
| power264          | 264      | Power, Cohen, et al., 2011   |
| schaefner{N}      | 100      | Schaefer et al., 2018        |
|                   | 200      |                              |
|                   | 400      |                              |

AAL: Automatic Anatomical Labelling

**(a)** Parcellations

| Design   | Reference                  |
|--|----------------------------|
| 24p  | Friston et al., 1996       |
| 24p + GSR  | Macey et al., 2004         |
| 36p  | Satterthwaite et al., 2013 |
| <del>26p</del> <ins>36p</ins> + spike regression | Cox, 1996                  |
| 36p + despiking                                  | Satterthwaite et al., 2013 |
| 36p + scrubbing                                  | Power, Mitra, et al., 2014 |
| aCompCor   | Muschelli et al., 2014     |
| tCompCor   | Behzadi et al., 2007       |
| AROMA  | Pruim et al., 2015         |

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

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

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

to other choices will be explored in a multiverse analysis (Steegen et al., 2016). Specifically, in an exploratory analysis, we will estimate brain states from BOLD time series processed according to a variety of established confound regression strategies and aggregated over different cortical brain parcellations (Table 2, Circic, Rosen, et al., 2018; Circic, Wolf, et al., 2017). Extent of cSVD will additionally be quantified by the volume of deep and periventricular white matter hyperintensities.

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

No hypothesis testing and ~~, therefore, no adjustment for multiple testing,~~ will be carried out in these ~~non-primary analyses~~, multiverse analyses. They rather serve to

221 inform about the robustness of the outcome of the test of the primary hypothesis. Any  
222 substantial conclusions about the association between severity of cerebral small pathology  
223 and time spent in high-occupancy brain states, as stated in the Scientific Question in  
224 Table 1, will be drawn from the primary analysis using pre-specified methodological choices.

225

## 226 **Exploratory-Further exploratory analysis**

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

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

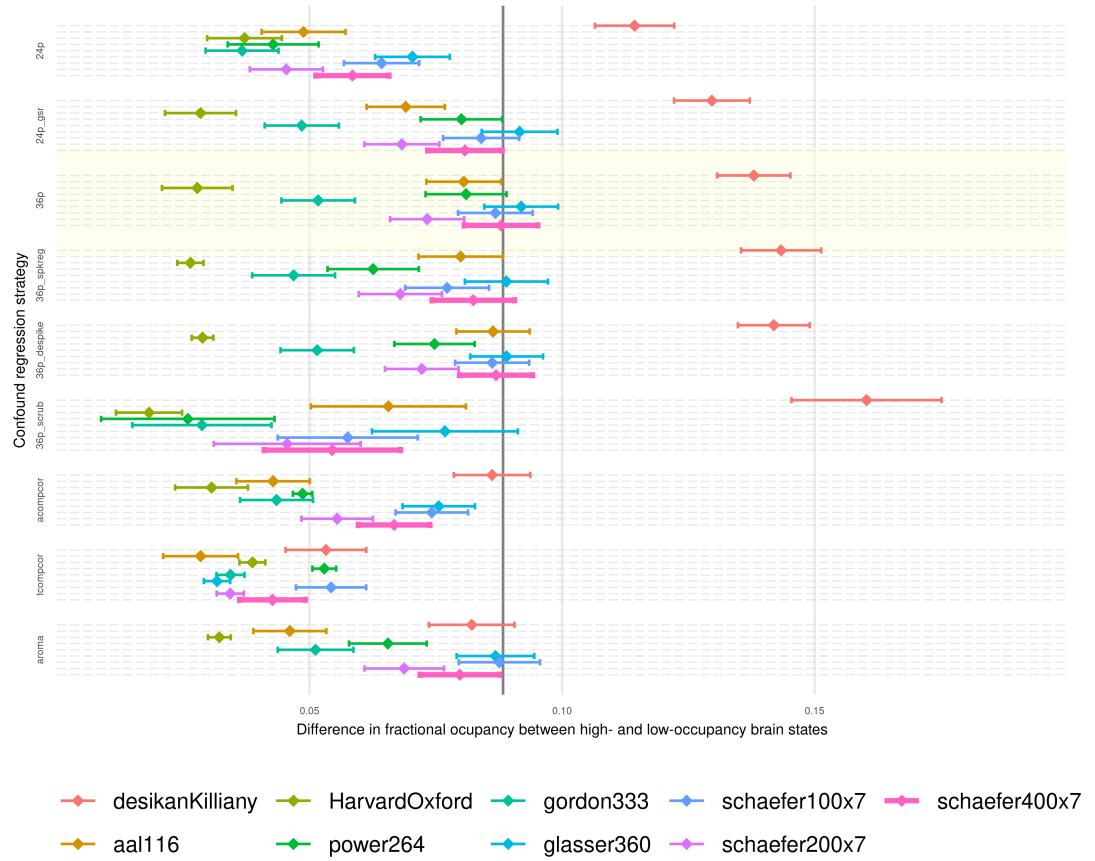
## 235 **Code and pilot data**

236 Summary data from the first 1000 imaging data points of the HCHS have been published  
237 with (Schlemm et al., 2022) and form the basis for the hypotheses tested in this replication  
238 study. We have implemented our prespecified analysis pipeline described above in R  
239 and Matlab, and applied it to this previous sample. Data, code and results have been  
240 stored on GitHub ([https://github.com/csi-hamburg/HCHS\\_brain\\_states\\_RR](https://github.com/csi-hamburg/HCHS_brain_states_RR)) und preserved  
241 on Zenodo.

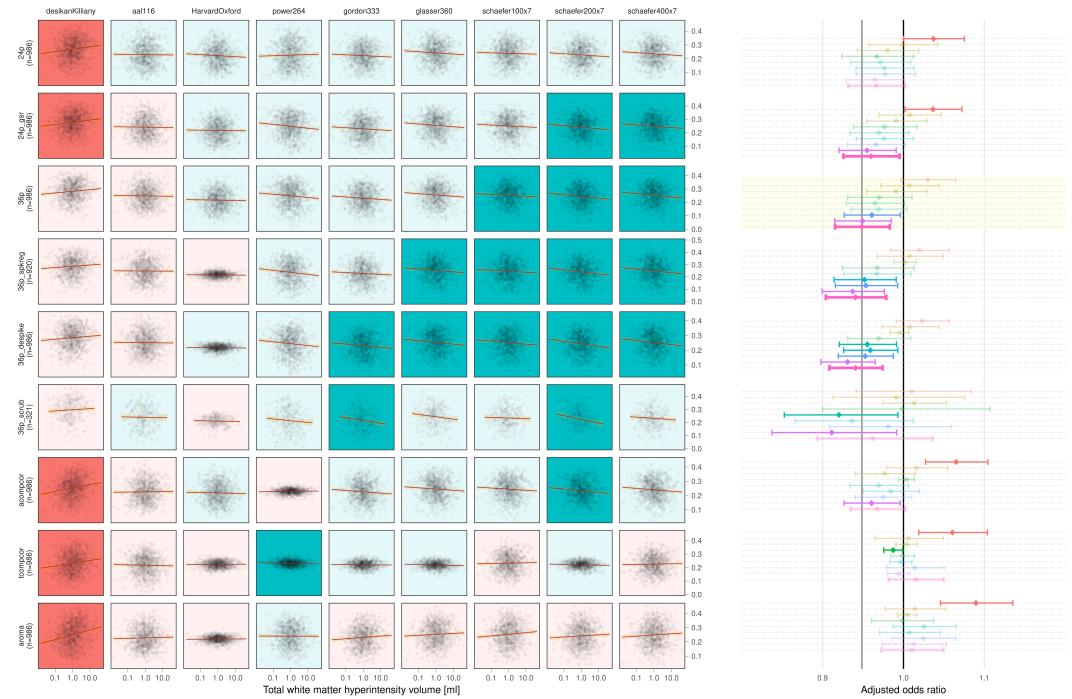
242 Thus re-analysing data from 988 subjects, the separation between two high-occupancy  
243 and three low-occupancy brain states could be reproduced for all combinations of brain  
244 parcellation and confound regression strategies (Figure 2).

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

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



**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.

## **252 Timeline and access to data**

253 At the time of planning of this study, all demographic, clinical and imaging data used in  
254 this analysis have been collected by the HCHS and are held in the central trial database.  
255 Quality checks for non-imaging variables have been performed centrally. WMH segmen-  
256 tation based on structural MRI data of the first 10 000 participants of the HCHS has been  
257 performed previously using the BIANCA/LOCATE approach (Rimmele et al., 2022) and re-  
258 sults are included in this preregistration ([./derivatives/WMH/cSVD\\_all.csv](#) [./derivatives/WMH/cS](#)).  
259 Functional MRI data and clinical measures of executive dysfunction (TMT-B scores) have  
260 not been analyzed by the author. Analysis of the data will begin immediately after acceptance-  
261 in-principle of the stage 1 submission of the registered report is obtained. Submission  
262 of the full manuscript (stage 2) is planned two months later.

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