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Severity-dependent interhemispheric white matter connectivity predicts post-stroke neglect recovery

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2	Severity-dependent interhemispheric white matter
3	connectivity predicts post-stroke neglect recovery
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33 Abstract

34 Left-sided spatial neglect is a very common and challenging issue after right-hemispheric 35 stroke, which strongly and negatively affects daily living behaviour and recovery of stroke 36 survivors. The mechanisms underlying recovery of spatial neglect remain controversial, 37 particularly regarding the involvement of the intact, contralesional hemisphere, with potential contributions ranging from maladaptive to compensatory. In the present prospective, 38 39 observational study, we assessed neglect severity in 54 right-hemispheric stroke patients (32 40 male; 22 female) at admission to and discharge from inpatient neurorehabilitation. We demonstrate that the interaction of initial neglect severity, and spared-white matter (dis) 41 connectivity resulting from individual lesions (as assessed by diffusion tensor imaging, DTI) 42 explains a significant portion of the variability of post-stroke neglect recovery. In mildly 43 impaired patients, spared structural connectivity within the lesioned hemisphere is sufficient 44 45 to attain good recovery. Conversely, in patients with severe impairment, successful recovery critically depends on structural connectivity within the intact hemisphere and between 46 hemispheres. These distinct patterns, mediated by their respective white matter connections, 47 48 may help to reconcile the dichotomous perspectives regarding the role of the contralesional 49 hemisphere as exclusively compensatory or not. Instead, they suggest a unified viewpoint 50 wherein the contralesional hemisphere can - but must not necessarily - assume a compensatory role. This would depend on initial impairment severity and on the available, 51 spared structural connectivity. In the future, our findings could serve as a prognostic 52 53 biomarker for neglect recovery and guide patient-tailored therapeutic approaches.

Significance Statement 56

57 Visuospatial neglect is a common and challenging issue affecting the daily living of stroke survivors. 58 Mechanisms underlying the recovery of neglect, especially the contribution of the intact 59 hemisphere, remain controversial, ranging from maladaptive to compensatory. In 54 neglect 60 patients, we show that a tight interaction of initial neglect severity and structural (dis)connectivity profiles relate to good recovery: in mild neglect, spared ipsilesional structural connectivity is 61 sufficient for good recovery; conversely, in more severe neglect, structural connectivity within the 62 contralesional hemisphere and between hemispheres plays a central role. These findings may help 63 to reconcile rival models concerning the role of the contralesional hemisphere in neglect recovery 64 after stroke. Furthermore, they could serve as a prognostic biomarker and guide patient-tailored 65 rt keuroscher Meuroscher 66

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71 Introduction

Post-stroke cognitive impairment affects up to 80% of stroke survivors (Jokinen et al., 2015). In
particular, left-sided spatial neglect is extremely common in patients with right-hemispheric lesion
(40-80%; (Azouvi et al., 2003; Kaufmann, Cazzoli, et al., 2020; Ringman et al., 2004), strongly and
negatively affecting everyday behaviour (Azouvi et al., 2003) and stroke recovery (Nijboer et al.,
2014).

Despite its high prevalence and negative impact, the neural mechanisms underlying neglect recovery 77 are still lively debated (Corbetta & Shulman, 2011; Kinsbourne, 1987; Lunven et al., 2015; McDonald 78 et al., 2019; Umarova et al., 2017). Numerous functional magnetic resonance imaging (fMRI) studies 79 evidenced the importance of inter-hemispheric communication and the activity within the 80 contralesional hemisphere both for the acute severity and recovery of spatial neglect. On one hand, 81 82 several studies proposed a maladaptive role of the intact, left hemisphere: A pathological hyperactivity in left superior parietal regions (Corbetta et al., 2005; Koch et al., 2013) and a disruption of 83 their inter-and intrahemispheric functional connectivity (Baldassarre et al., 2014; Carter et al., 2010; 84 He et al., 2007; Ramsey et al., 2016) correlated with acute neglect severity, while their normalisation 85 86 with neglect recovery at the chronic stage (Corbetta et al., 2005; He et al., 2007; Ramsey et al., 87 2016). On the other hand, other studies conversely suggested a compensatory role of activations within the left, intact hemisphere in the early acute phase (Umarova et al., 2011) and in successful 88 spatial neglect recovery (Umarova et al., 2016). Fittingly, findings concerning the role of white 89 matter (dis)connectivity in spatial neglect severity and recovery evidenced diverging patterns. 90 Various studies showed the role of white matter fronto-parietal and occipito-frontal tracts within the 91 92 ipsilesional (e.g., (Karnath et al., 2009; Lunven et al., 2015)) or the contralesional, intact hemisphere 93 (e.g., (Lunven et al., 2018; Umarova et al., 2017; Umarova et al., 2014)). Moreover, some studies showed the relevance of inter-hemispheric white matter tracts (e.g., (Bozzali et al., 2012; Lunven et al., 2015; 94 95 Umarova et al., 2014; Wiesen et al., 2020)), while others did not (e.g., (Karnath et al., 2009; Sperber

96 et al., 2020)). Therefore, the considerable inter-individual variability commonly observed in neglect

97 recovery (McDonald et al., 2019) seems mirrored by a range of diverse explanatory accounts.

98 Studies on post-stroke motor recovery in animals and humans provide a potential avenue to 99 reconcile these diverse perspectives (Biernaskie et al., 2005; Hayward et al., 2022; Stewart et al., 100 2017; van Meer et al., 2012): the role of the ipsi- and contralesional hemispheres, subtended by the respective white matter connections, depends on the initial severity of motor deficits (Stewart et al., 101 2017). In mild motor deficits, the recruitment of the spared ipsilesional motor network is sufficient. 102 103 Conversely, in more severe motor deficits, the involvement of the intact contralesional hemisphere 104 becomes essential for recovery, facilitated by preserved inter-hemispheric white matter connectivity 105 (Stewart et al., 2017). Regarding human cognition, a similar debate concerns language recovery after stroke, i.e., the contralesional hemisphere seems not to consistently support or hinder recovery, but 106 107 its role would vary, amongst others, according to initial impairment severity (e.g. (Bartolomeo & 108 Thiebaut de Schotten, 2016; Crinion & Leff, 2007; Crosson et al., 2019; Hartwigsen & Saur, 2019; Thompson & Den Ouden, 2008)). 109

To the best of our knowledge, no previous study has investigated how initial neglect severity
modulates the role of white matter (dis)connectivity in the ipsi- and contralesional hemispheres in
supporting neglect recovery.

Here, we aimed to prospectively investigate severity-dependent white matter (dis)connectivity
profiles, as assessed by diffusion tensor imaging (DTI), and evaluate their contribution to neglect
recovery. Specifically, our objective was to investigate the essential interplay of three variables that
were thus far examined only separately and are known to play a substantial role: (1) lesion volume
(Munsch et al., 2016), (2) white matter (dis)connections resulting from specific lesion locations (i.e.,
lesion to white matter fibre tracts interconnecting cortical areas (Talozzi et al., 2023)), and (3) initial
neglect severity (Rost et al., 2016).

120 1 Materials and Methods

121 1.1 Patients

122 This is a prospective, observational study, including 54 patients with left-sided spatial neglect in daily 123 living (i.e., Catherine Bergego Scale, CBS≥1; (Azouvi et al., 2003)), after a first right-hemispheric 124 subacute stroke (time between stroke and MRI mean=22.44 days, SD=11.32), who were treated on the neurorehabilitation ward at the Luzerner Kantonsspital [age: mean=71.69, SD=10.70 years; 125 59.26% male, 50 patients were right-handed (3 left-handed, 1 ambidextrous); normalized lesion 126 127 volume mean=50.67, SD=63.83 cc³; days on the neurorehabilitation unit mean=52.00, SD=23.70; a lesion overlay plot is shown in Figure 1A]. Besides neglect in daily living, the main inclusion criteria 128 129 were age above 18 years, normal or corrected-to-normal visual acuity, and the ability and willingness 130 to undergo an additional MRI. Patients with other neurological disorders, major psychiatric disorders, and/or alcohol or drug abuse were excluded. 131 The patients' inclusion flow-chart based on the STROBE guidelines is presented in Figure 2. In detail, 132 a total of 47 first-ever right hemisphere stroke patients, who participated in our prospective 133 observational study (Kaufmann et al., 2022), agreed on the additional acquisition of a DTI sequence 134 for the present study. Another 23 first-ever right-hemispheric stroke patients were prospectively 135 136 asked to participate in the present study between July 2020 and September 2021 (including a 1-year study stop due to the COVID-19 pandemic). Of these 70 patients who were identified and assessed 137 for eligibility, 13 were excluded based on the pre-defined inclusion/exclusion criteria (13 did not 138 present with left-sided spatial neglect in daily living (CBS = 0; (Azouvi et al., 2003)). 57 patients were 139 140 included in the study and their data were pre-processed. In 3 patients, the scan data were not usable 141 due to motion artefacts. 54 patients completed the study without missing data and were included in the final analyses. 142

144 Written, informed consent was obtained from all patients. The study was approved by the local

145 Ethics Committee (BASEC 2017-00827) and performed according to the latest Declaration of

146 Helsinki.

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148	Figure 1
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158	1.2 Experimental Design and Statistical Analysis
159	1.2.1 Behavioural measure
160	Neglect in deily living was evaluated using the Catherine Dergage Scale (CBS (Aseuryi et al. 2002)) a
100	Neglect in daily living was evaluated using the Catherine Bergego Scale (CBS (Azouvi et al., 2005)), a
161	systematic acological observation scale, which is reliable valid, and sensitive in assessing changes in
101	systematic, ecological observation scale, which is reliable, valid, and sensitive in assessing changes in
162	neglect severity throughout rebabilitation (Azouvi, 2017: Azouvi et al., 2003). Ten observations
102	
163	during daily living are rated on a 0 (no neglect) to 3 (severe neglect) scale, resulting in a CBS total
105	adding daily inving the rated of a o (no neglect) to o (severe neglect) state, resulting in a ebo total
164	score of 0-30 (1–10 indicating mild neglect, 11-30 moderate-to-severe neglect; (Azouvi, 2017)). The
-	
165	CBS was administered at admission to and discharge from inpatient neurorehabilitation.
166	1.2.2 Neural correlates
167	For each patient, three MRI sequences (two anatomical: FLAIR, T2-MPRAGE; and one DTI) were
168	acquired on 3T Siemens Magnetom scanners (35 on Skyra, 19 on Vida). To account for potential
169	between-scanner differences (Zhou et al., 2018), a corresponding binary covariate was included in all
170	analyses. The respective imaging parameters and the pre-processing steps are described below.
171	1.2.2.1 Details of anatomical imaging and pre-processing steps
172	High-resolution MPIs were acquired in all nations using two sequences: 1) a ELAIP sequence
1/2	The solution wints were acquired in an patients using two sequences. 1) at LAIN sequence
173	(TR/TE-5000/389 msec, yoyal size-0.4 x0.4 x 0.9 mm), which was used for identification and
113	(The re-source source size-on- xon- xon- xon- xon- which was used for identification and
174	demarcation of the lesions: 2) a MPRAGE sequence (TR/TE= $2240/3$ 72 msec voxel size=0.9 v0.9v0.9
±/ Ŧ	
175	mm)(Kaufmann et al., 2023).
-	

176 To calculate the patients' individual lesion volume, individual stroke lesions were manually

177 delineated on the high-resolution structural MRI images by an experienced rater and normalised

178 into MNI space.

179 The detailed pre-processing steps have been previously described in (Kaufmann et al., 2018) and in

180 (Kaufmann et al., 2023). In short, the anatomical FLAIR images were registered to the MPRAGE

181 images and used for lesion mapping, i.e., the manual delineation of the individual patients' lesion

182 borders. Images were then normalised into MNI space with the Clinical Toolbox for SPM12 run on

183 MATLAB ((Rorden et al., 2012); spm <u>http://www.fil.ion.ucl.ac.uk/</u>; Matlab 2020b, The MathWorks,

184 Inc. <u>https://www.mathworks.com/products/matlab.html</u>), applying enantiomorphic normalization

185 (Nachev et al., 2008). Subsequently, each lesion was visually inspected and manually corrected if

needed.

The patients' individual lesion volumes (in the standard MNI152 space) were extracted using the
MRIcron software (https://www.nitrc.org/projects/mricron). To account for potential confounding
effects of lesion volume (Vogt et al., 2012), a corresponding covariate was included in all analyses.

190 *1.2.2.2 Details of DTI imaging and pre-processing steps*

191 A diffusion-weighted spin echo, echo-planar imaging sequence was used to obtain a DTI diffusion

scheme with a total of 64 diffusion sampling directions, a b-value of 1000 s/mm² and the following

193 imaging parameters: 1.7 x 1.7 x 4.0 mm³, 30 slices, FoV=220 mm, TR/TE=4100/95 ms.

194 The detailed pre-processing steps have been previously described in (Pastore-Wapp et al., 2022). In

short, the DTI images were pre-processed using DTIPrep (Liu et al., 2010), a software for automatic

196 image quality control and preparation. Pre-processing included image information check, data

197 cropping, slice-wise, interlace-wise, and gradient-wise intensity artifact correction, eddy current and

198 head motion correction, as well as computing of individual DTI for each patient.

199 1.2.3 Statistical analysis of neural correlates

200 To investigate, how initial neglect severity modulates the role of white matter (dis)connectivity in

201 the ipsi- and contralesional hemispheres in supporting neglect recovery, we used diffusion MRI

202 connectometry as implemented in DSIstudio (https://dsi-studio.labsolver.org). After pre-processing, 203 all 54 diffusion MRI scans were included in a connectometry database with an in-plane resolution of 204 1.72 mm, and the accuracy of the b-table orientation was examined by comparing fibre orientations 205 with those of a population-averaged template (Yeh, 2022). The diffusion data were reconstructed in 206 the MNI space to obtain the spin distribution function(Yeh et al., 2010; Yeh & Tseng, 2011). A 207 diffusion sampling length ratio of 1.25 was used. The output resolution in diffeomorphic 208 reconstruction was 1.72 mm isotropic. The restricted diffusion was quantified using restricted 209 diffusion imaging (Yeh et al., 2017). The tensor metrics were calculated using DWI with b-value lower than 1750 s/mm². 210

Correlational tractography, with the aim of putting fractional anisotropy (FA) values in relation to 211 neglect recovery (i.e., CBS at discharge from inpatient neurorehabilitation), was calculated with a 212 nonparametric Spearman rank-based correlation. We employed a multiple regression model to 213 control for factors such as initial neglect severity (i.e., at admission to inpatient neurorehabilitation; 214 e.g. (Rost et al., 2016)), rehabilitation duration (Young & Forster, 2007), age (Lewis et al., 2022), 215 lesion volume, time between stroke and MRI (Umarova et al., 2017) and scanner type (Zhou et al., 216 217 2018) by adjusting the diffusion metrics using partial correlations, as implemented in DSIstudio. 218 For the correlational tractography, the deterministic fibre tracking algorithm (Yeh et al., 2013) was 219 used with a T-score threshold of 2. A seeding region was placed at whole-brain level, excluding the 220 cerebellum from the analysis. The tracks were filtered by topology-informed pruning (Yeh et al., 2019) with 4 iterations and a FDR threshold of 0.05. To estimate the false discovery rate, a total of 221 222 4000 randomized permutations were applied to obtain the null distribution of the track length. Significant results were automatically segmented to define the underlying fibre tracks, which were 223 224 then manually verified for accuracy by experienced raters (BK and TN). The analyses were performed 225 and visualized in DSIstudio (https://dsi-studio.labsolver.org/).

- 226 1.2.4 Multiple regression analysis
- To evaluate the relative contribution of the FA-values in the significant white matter fibres on 227
- 228 neglect recovery, all connectometry analyses were followed by post-hoc, forced entry multiple
- 229 regression models, also considering the above-described factors (initial neglect severity (Rost et al.,
- 230 2016)), rehabilitation duration (Young & Forster, 2007), age (Lewis et al., 2022), lesion volume, time
- between stroke and MRI (Umarova et al., 2017) and scanner type (Zhou et al., 2018)). 231
- 232
- 233
- 234

- 235 2 Results
- 236 2.1 Overall patient sample
- 237 2.1.1 Descriptive statistics
- A high inter-individual variability was found in all patient characteristics: age, lesion volume,
- 239 rehabilitation duration, time between stroke and MRI, and initial neglect severity.
- 240 2.1.2 Connectometry analysis
- 241 The connectometry analysis over all patients (n=54) revealed a significant correlation between
- 242 neglect recovery and fibres within both hemispheres (right: corticospinal tract (CST), Inferior Fronto-
- 243 Occipital Fasciculus (IFOF), Superior Longitudinal Fasciculus II (SLF II); left: CST, IFOF). Furthermore,
- the FA-values of the inter-hemispheric tracts, i.e., Forceps major and minor of the Corpus Callosum,
- 245 were correlated with neglect recovery.
- 246 Correspondingly, a partial correlation revealed a significant relationship between the FA-values in
- the significant fibre tracts and neglect recovery (r=-0.32, p=0.027; controlling for initial neglect
- 248 severity, lesion volume, rehabilitation duration, time between stroke and MRI, age, and scanner
- 249 type).
- 250
- 251 2.1.3 Multiple regression analysis
- To evaluate the relative contribution of the FA-values in the significant white matter fibres on neglect recovery, a subsequent multiple regression model was computed and revealed significant [F(7,46)=5.84, p<.001; Table I], explaining 39% of the variance. Significant predictors for neglect recovery were the FA-values in the significant tracts ($\beta_{standardized}=-.28, t=-2.24, p=.030$) and the initial neglect severity ($\beta_{standardized}=.558, t=4.13, p<.001$).

258 Intermediate conclusion

- 259 Good neglect recovery was associated with the preservation of a heterogeneous white matter
- 260 connectivity pattern, widely distributed across both hemispheres. Critically, our regression analyses,
- as well as previous evidence in the motor domain (Biernaskie et al., 2005; Hayward et al., 2022;
- 262 Stewart et al., 2017; van Meer et al., 2012), highlighted the importance of the initial neglect severity
- 263 in conjunction with preserved white matter connectivity. We therefore re-run all analyses using
- initial neglect severity to categorize patients as having mild (a CBS of 1–10 (Azouvi, 2017)) or
- 265 moderate-to-severe (CBS 11-30 (Azouvi, 2017)) spatial neglect.
- 271
- 2.2 Severity-dependent analyses: mild and moderate-to-severe neglect
- **272** 2.2.1 Descriptive statistics
- 273 Independent t-tests comparing the two groups revealed a longer rehabilitation duration for patients
- with moderate-to-severe neglect (mean (SD) mild=39.69 (18.81), moderate-to-severe=63.43 (22.22);
- t(52)=4.22, p<.001); *Figure 3*). The two groups, however, did not differ in terms of age [mean (SD)
- 276 mild=71.81 (10.49), moderate-to-severe=71.57 (11.09); t(52)=-.08, p=.936], days between stroke and
- 277 MRI [mean (SD) mild=22.39(10.87), moderate-to-severe=22.50 (11.91); t(52)=.04, p=.971], lesion
- 278 volume in cc³ [mean (SD) mild=33.60 (47.29), moderate-to-severe=66.52 (73.40); t(52)=1.94,
- 279 p=.058)], or scanner type (mild 17:9, moderate-to-severe 18:10; Mann-Whitney U=360.00,
- 280 peract=.999). Furthermore, the two groups did not significantly differ in terms of lesion topography
- 281 [no significant group difference was found in a lesion analysis using NiiStat
- 282 (https://www.nitrc.org/projects/niistat/) with 4000 permutations, FWE <0.05, restricted to voxels
- with an overlap of $n \ge 20\%$ of the patients and the Freedman-Lane method (Winkler et al., 2014)].
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289 2.2.2 Connectometry Analysis

For both subgroups, lesion extension and location (*Figure 3A*), as well as recovery patterns (*Figure 1B*), showed a typical and high inter-individual variability.

292 Connectometry analysis in patients with mild neglect (n=26) revealed a significant correlation 293 between the CBS values at discharge from inpatient neurorehabilitation and FA-values of fibres in 294 the right hemisphere only: CST, IFOF, and SLF II (*Figure 1C*). In patients with moderate-to-severe 295 neglect (n=28) significant fibres were found within either hemisphere (i.e., CST and IFOF in both 296 hemispheres), as well as between hemispheres, i.e., in the corpus callosum (forceps major and 297 tapetum, *Figure 1C*).

Subsequent partial correlations between the corresponding FA and CBS values at discharge from inpatient neurorehabilitation (controlling for initial neglect severity, age, lesion volume, time between stroke and MRI, rehabilitation duration and scanner type) highlighted the consistency of the results (mild neglect; r=-.52, p=.019; moderate-to-severe neglect r=-.58, p=.005, *Figure 1B*).

302 We also performed an additional connectometry analysis, comparing the white-matter connectivity 303 profiles of mild versus moderate-to severe neglect patients, in order to investigate whether our 304 results would be influenced by this factor. This analysis revealed significantly lower FA values in the 305 corpus callosum, the IFOF and the SLF in the right hemisphere of the moderate-to-severe neglect 306 group. This is in line with the previous literature, showing more severe and long-lasting neglect after 307 a lesion involving these white matter fibre tracts (Bozzali et al., 2012; Kwon et al., 2022; Lunven et 308 al., 2015). Critically, however, our analysis showed that FA values concerning the IFOF in the left, 309 contralesional hemisphere were not different between the two groups. This result suggests that 310 different white matter (dis)connectivity patterns subtend spatial neglect severity at admission to 311 inpatient neurorehabilitation and spatial neglect recovery over time.

Multiple Regression Analysis 312 2.2.3

Subsequent multiple regression models, used to evaluate the relative contribution of the FA-values 313 314 in the significant white matter fibres on recovery, revealed significant in both groups. In mild 315 neglect, the model explained 34.5% of the variance [F(7,18)=2.88, p=.033; Table II]. Predictors for recovery were the initial neglect severity ($\beta_{standardized}$ =.44, t=2.37, p=.029), FA-values within the 316 identified tracts ($\beta_{standardized}$ =-.58, t=-2.59, p=.019), and the duration of neurorehabilitation 317 ($\beta_{standardized}$ =- .45, t=-2.61, p=.044). In moderate-to-severe neglect, the subsequent multiple 318 regression model explained 37.8% of the variance [F(7,20)=3.35, p=.016; Table III]. Predictors for 319 recovery were the initial neglect severity ($\beta_{standardized}$ =.60, t=3.43, p=.003) and the FA-values within 320 the identified tracts ($\beta_{standardized}$ =-.55, t=-3.19, p=.005). 321 322 323 324 Table II and III 325 Meuroscia about here

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328 3 Discussion

In this prospective, longitudinal study with clinical outcomes, we investigate how initial neglect severity modulates the role of, white matter (dis)connectivity within and between the ipsi- and contralesional hemispheres in supporting neglect recovery, as assessed by DTI and controlling for lesion volume.

We demonstrate, for the first time, that neglect recovery relies on a tight interaction between the 333 334 spared white matter connectivity profile and the initial neglect severity. In mildly impaired patients, spared portions of the attention networks within the ipsilesional hemisphere (i.e., intact SLF II and 335 336 IFOF) are sufficient to attain good recovery. In contrast, in moderate-to-severely impaired patients, spared portions of the attention network within the ipsilesional hemisphere (right IFOF) seems not 337 to be sufficient. Indeed, good recovery is also associated with white matter connectivity within the 338 339 attentional networks of the contralesional hemisphere (left IFOF) and, critically, with interhemispheric structural connectivity through callosal fibres (Forceps Major and Tapetum). 340

The present findings have the potential to reconcile the previously divergent accounts of neglect 341 recovery, wherein improvement has been attributed to either the damaged or intact hemisphere 342 343 (Bartolomeo, 2021; Corbetta & Shulman, 2011; Kinsbourne, 1987; Nyffeler et al., 2019). Our results support the notion that neglect recovery is characterized by different combinations of preserved 344 345 brain areas and their connectivity, as a function of the initial neglect severity. Specifically, they suggest that the recovery of mild neglect may rely on the preserved specialisation of the lesioned 346 hemisphere. However, in cases of more severe neglect, this specialisation may become 347 348 unsustainable, necessitating the compensatory involvement of the contralesional hemisphere. These 349 differential patterns, suggested by the respective white matter connections, would challenge the 350 opposing views regarding the role of the contralesional hemisphere as solely compensatory or not 351 (Baldassarre et al., 2014; Carter et al., 2010; Corbetta et al., 2005; He et al., 2007; Koch et al., 2013; 352 Ramsey et al., 2016; Umarova et al., 2016; Umarova et al., 2011). Instead, they would reconcile 353 these views into a unified perspective: the contralesional hemisphere can - but must not necessarily

- assume a compensatory role. This is would be contingent upon the initial severity of the
impairment and the availability of spared connectivity.

356 A SLF II disconnection is typically associated with more severe and chronic neglect (Karnath et al., 357 2011; Lunven et al., 2015). In our study, a spared right hemisphere SLF II in mild neglect is related to 358 recovery of the latter, thus suggesting a compensatory role in recovery. This would obviously be impossible in more severe neglect with SLF II disconnection. The explanation of the role of the IFOF 359 (spared right IFOF in mild, spared right and additionally left IFOF in moderate-to-severe neglect) is 360 more speculative. First, our findings show that a spared right IFOF is related to recovery in mild as 361 362 well as moderate-to-severe neglect, thus suggesting a compensatory role in both. The IFOF is mainly supplied by the posterior cerebral artery (Price & Moss, 2014), and is therefore less likely to be 363 disconnected by middle cerebral artery strokes (Price & Moss, 2014), which most typically affect the 364 365 SLF and causes neglect (Corbetta & Shulman, 2011). Second, in our study, a spared left IFOF (but not 366 a spared left SLF) is related to recovery from moderate-to-severe neglect, jointly with callosal interhemispheric connectivity. This could be speculatively due to the prominent compensatory role of 367 contralateral homologues (Saur et al., 2006; Stewart et al., 2017): the intact right IFOF would call for 368 369 compensation from the left IFOF, but the disconnected right SLF would not be able to call for compensation form the left SLF. This hypothesis needs to be investigated in future studies. 370

Our findings extend the results obtained in animal stroke models (Caleo, 2015; van Meer et al., 2012), as well as those on post-stroke recovery from motor (Biernaskie et al., 2005; van Meer et al., 2012) and language (Crinion & Leff, 2007; Hartwigsen & Saur, 2019; Thompson & Den Ouden, 2008) deficits in humans. For the first time, our findings show the relevance and generalisability of these findings to spatial neglect and point to a consistent organisation of severity-dependent brain recovery mechanisms across different functional domains and species.

Finally, the severity-dependent white matter connectivity profiles revealed in our study can help to
explain the substantial variability observed in the effectiveness of therapeutic interventions
commonly observed in spatial neglect (McDonald et al., 2019). Indeed, it is reasonable to assume

that the mechanisms of action of various therapeutic approaches, such as those targeting the
ipsilesional or contralesional hemisphere, may be more effective in certain patients and less so in
others, depending on the spared patterns of white matter connectivity that trigger different
recovery processes.

384 Limitations

We studied a sample exclusively composed of patients with left-sided neglect, a common sequela of 385 right-hemispheric stroke (Azouvi et al., 2003; Kaufmann, Cazzoli, et al., 2020, p. 20; Ringman et al., 386 2004). Future studies shall investigate whether the identified mechanisms are laterality-independent 387 388 and also apply to right-sided neglect after left-hemispheric stroke. Furthermore, lesion distribution 389 depends on vascular territories, and is typically associated with a substantial overlap in the territory of the right middle cerebral artery in neglect. This overlap can potentially restrict the identification 390 of stronger associations with fibres in this region. Nevertheless, our results highlight recovery 391 patterns supported by fibres within both the lesioned and the contralesional intact hemisphere, thus 392 relativizing this potential bias (Nijboer et al., 2014). Finally, since our findings reveal the importance 393 394 of severity-dependent white matter (dis)connectivity profiles for neglect recovery in daily living, 395 future studies should aim to further explore the potential of these patterns in predicting overall rehabilitation outcomes and their relationship to specific therapeutic approaches. Additionally, 396 397 future studies should investigate how the interplay of spatial neglect with other, often co-occurring cognitive impairments such as non-spatial attentional deficits (Husain & Rorden, 2003) and executive 398 399 function deficits (Kaufmann et al., 2018, 2023; Kaufmann, Knobel, et al., 2020) affect the recovery of 400 spatial neglect itself in the context of white matter (dis)connections. The same applies to the 401 different aspects that characterise neglect as a multicomponent syndrome (see, e.g., (Gainotti et al., 402 1991; Kerkhoff, 2001)). Furthermore, these future studies should ideally be multimodal (i.e., 403 simultaneously including, amongst other, structural and functional imaging, metabolic, and 404 mechanistic variables), since this approach seems to hold promise for even better prediction of 405 stroke recovery (e.g., (Bonkhoff & Grefkes, 2022).

406 Conclusions

407 The present study establishes that the recovery of spatial neglect is related to a close interaction 408 between individual white matter (dsy)connectivity patterns determined by specific lesion profiles, 409 and initial severity of neglect. In cases of mild neglect spared white matter connectivity within the 410 ipsilesional hemisphere is sufficient for achieving substantial recovery. However, in more severe neglect, successful recovery critically depends on the additional white matter connectivity within the 411 contralesional intact hemisphere. This newly identified interaction emerges as a new factor in 412 413 explaining the variability observed in neglect recovery, and potentially reconciles conflicting viewpoints regarding the role of the contralesional hemisphere. Our data suggest that the 414 contralesional hemisphere has the potential to assume a compensatory role, but this is contingent 415 upon initial severity of impairment and presence of spared structural connectivity. 416 In the future, incorporating combined information on white matter (dis)connectivity and the initial 417 severity of neglect may serve as a valuable prognostic biomarker for predicting neglect recovery. 418 This information could guide the stratification of patients into tailored therapeutic approaches, such 419 as determining which hemisphere and site to target with excitatory or inhibitory non-invasive brain 420 Neurosci stimulation techniques. 421

422 4 Figure Legends

423 Figure 1 – White matter connectivity profiles in patients with mild and moderate-to-severe neglect 424 Figure 1. (A) Lesion overlay plot for the 54 patients included in this study and (B) inter-individual 425 variability in recovery depending on white matter (dis)connectivity. For both groups, the scatter 426 plots represent the partial correlations between the FA-values in the significant fibre tracts and neglect recovery, while controlling for initial neglect severity, lesion volume, rehabilitation duration, 427 time between stroke and MRI, age, and scanner type (i.e., FA-value corrected, CBS corrected). (C) 428 Recovery of mild neglect (left, n=26) depends on the spared connectivity of the attentional network 429 within the lesioned hemisphere. In moderate-to-severe neglect (right, n=28) recovery additionally 430 depends on the connectivity of the attentional network within the contralesional, intact hemisphere 431 and on the inter-hemispheric connectivity with the latter. The corticospinal tract revealed significant 432 433 in all connectometry analyses and was therefore not discriminative between sub-groups. An intact 434 CST has been repeatedly shown to correlate with motor recovery and is a common component in daily living activities.^{e.g.} (Feng et al., 2015) Since motor recovery is not primarily within the scope of 435 the present study, and for enhanced clarity of the graphical illustrations, we decided to not present 436 the CST in the figures. 437

438

439 Figure 2 – STROBE inclusion flow chart

Figure 2. Patients' inclusion flow-chart based on the STROBE guidelines: of the 70 patients with firstever right hemisphere stroke who were identified and assessed for eligibility , 13 were excluded based on the pre-defined inclusion/exclusion criteria (13 did not present with left-sided spatial neglect in daily living). 57 patients were included in the study and their data were pre-processed. In 3 patients, the scan data were not usable due to motion artefacts. 54 patients completed the study without missing data and were included in the final analyses.

447 Figure 3 – Demographic variables for patients with mild and moderate-to-severe neglect

- 448 Figure 3. (A) Lesion overlay plots and (B) demographic variables for patients of the two sub-groups
- of mild (M, violet) and moderate-to-severe (S, orange) neglect. Significant between-group 449
- reners 450 differences are highlighted by an asterisk (p<.05*, p<.001***), non-significant differences are noted
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454 5 Tables

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456 **Table I. Results of the multiple regression analyses over all patients**

457 Results of the multiple regression analyses over all patients (n=54), with CBS at discharge from

- 458 inpatient neurorehabilitation as dependent variable, and initial neglect severity (i.e., CBS at
- 459 admission to inpatient neurorehabilitation), age, time between stroke and MRI, rehabilitation

460 duration, scanner type, lesion volume as independent variables).

	βstd	Т	p	R^2_{adj}	F	ρ
					S	
Model I – all patients (n=54)				.39	5.84	<.001***
FA-values in significant tracts	28	-2.24	.030 *			
CBS at admission of inpatient neurorehabilitation	.56	4.13	<.001 ***	Vo.		
rehabilitation duration	14	-1.01	.316			
age	05	41	.683			
time between stroke and MRI	.06	.51	.614			
scanner type	.02	.16	.873			
Lesion volume	.19	1.65	.106			
	6	0				
p<.05*, p<.001***	0					
C.						
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464 Table II. Results of the multiple regression analyses for patients with mild neglect

- Results of the multiple regression analyses for patients with mild neglect (n=26), with CBS at 465
- 466 discharge from inpatient neurorehabilitation as dependent variable, and initial neglect severity (i.e.,
- 467 CBS at admission to inpatient neurorehabilitation), age, time between stroke and MRI, rehabilitation
- duration, scanner type, lesion volume as independent variables. 468

	βstd	Т	р	R^2_{adj}	F	p
Model II – mild neglect (n=26)				.35	2.88	.033*
FA-values in significant tracts	58	-2.59	.019 *			0
CBS at the admission of inpatient neurorehabilitation	.44	2.37	.029 *		5)
rehabilitation duration	45	-2.16	.044 *			
age	02	09	.933	V.O.		
time between stroke and MRI	.27	1.33	.199			
scanner type	.02	.09	.928			
Lesion volume	.14	.74	.469			
		X				
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471 Table III. Results of the multiple regression analyses for patients with moderate-to-severe neglect

472 Results of the multiple regression analyses for patients with moderate-to-severe neglect (n=28), with

473 CBS at discharge from inpatient neurorehabilitation as dependent variable and initial neglect

474 severity (i.e., CBS at admission to inpatient neurorehabilitation), age, time between stroke and MRI,

- 475 rehabilitation duration, scanner type, lesion volume as independent variables.
- 476

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	β_{std}	Т	p	R^2_{adj}	F	p
						\mathbf{C}
Model III – moderate-to-severe negl	ect (n=28)			.38	3.35	.016*
FA-values in significant tracts	55	-3.19	.005 **	•	N	
CBS at the admission of inpatient neurorehabilitation	.60	3.43	.003 **	~?		
rehabilitation duration	.02	.14	.894			
age	19	-1.16	.259			
time between stroke and MRI	.20	1.24	.228			
scanner type	.13	.74	.469			
Lesion volume	.25	1.58	.130			
		X				

Data availability 6 479

480 The conditions of our ethics approval do not permit the public archiving of the data supporting the

481 conclusions of this study. Based on the Swiss Human Research Act, HRA (Humanforschungsgesetz,

482 HfG) in Switzerland, readers seeking access to the data and the study materials must therefore

483 complete a formal data sharing agreement to obtain the data. Interested readers should contact the

484 corresponding author for more information and help.

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492 References

493	Azouvi, P. (2017). The ecological assessment of unilateral neglect. Ann Phys Rehabil Med, 60(3), 186–
494	190. https://doi.org/10.1016/j.rehab.2015.12.005
495	Azouvi, P., Olivier, S., de Montety, G., Samuel, C., Louis-Dreyfus, A., & Tesio, L. (2003). Behavioral
496	Assessment of Unilateral Neglect: Study of the Psychometric Properties of the Catherine
497	Bergego Scale. Arch Phys Med Rehabil, 84, 51–57. https://doi.org/10.1053/apmr.2003.50062
498	Baldassarre, A., Ramsey, L., Hacker, C. L., Callejas, A., Astafiev, S. V., Metcalf, N. V., Zinn, K.,
499	Rengachary, J., Snyder, A. Z., Carter, A. R., Shulman, G. L., & Corbetta, M. (2014). Large-scale
500	changes in network interactions as a physiological signature of spatial neglect. Brain, 137,
501	3267–3283. https://doi.org/doi:10.1093/brain/awu297
502	Bartolomeo, P. (2021). From competition to cooperation: Visual neglect across the hemispheres. <i>Rev</i>
503	Neurol (Paris), 177, 1104–1111. https://doi.org/10.1016/j.neurol.2021.07.015
504	Bartolomeo, P., & Thiebaut de Schotten, M. (2016). Let thy left brain know what thy right brain
505	doeth: Inter-hemispheric compensation of functional deficits after brain damage.
506	Neuropsychologia, 93, 407–412. https://doi.org/10.1016/j.neuropsychologia.2016.06.016
507	Biernaskie, J., Szymanska, A., Windle, V., & Corbett, D. (2005). Bi-hemispheric contribution to
508	functional motor recovery of the affected forelimb following focal ischemic brain injury in
509	rats: Ipsilateral contribution to motor recovery. European Journal of Neuroscience, 21(4),
510	989–999. https://doi.org/10.1111/j.1460-9568.2005.03899.x
511	Bonkhoff, A. K., & Grefkes, C. (2022). Precision medicine in stroke: Towards personalized outcome
512	predictions using artificial intelligence. <i>Brain</i> , 145(2), 457–475.
513	https://doi.org/10.1093/brain/awab439
514	Bozzali, M., Mastropasqua, C., Cercignani, M., Giulietti, G., Bonni, S., Caltagirone, C., & Koch, G.
515	(2012). Microstructural damage of the posterior corpus callosum contributes to the clinical
516	severity of neglect. PLOS ONE, 7(10), e48079. https://doi.org/10.1371/journal.pone.0048079

- 517 Caleo, M. (2015). Rehabilitation and plasticity following stroke: Insights from rodent models.
- 518 Neuroscience, 311, 180–194. https://doi.org/10.1016/j.neuroscience.2015.10.029
- 519 Carter, A. R., Astafiev, S. V., Lang, C. E., Connor, L. T., Rengachary, J., Strube, M. J., Pope, D. L. W.,
- 520 Shulman, G. L., & Corbetta, M. (2010). Resting interhemispheric functional magnetic
- 521 resonance imaging connectivity predicts performance after stroke. Annals of Neurology,
- 522 *67*(3), 365–375. https://doi.org/10.1002/ana.21905
- 523 Corbetta, M., Kincade, M. J., Lewis, C., Snyder, A. Z., & Sapir, A. (2005). Neural basis and recovery of 524 spatial attention deficits in spatial neglect. *Nat Neurosci*, *8*, 1603–1610.
- 525 Corbetta, M., & Shulman, G. L. (2011). Spatial Neglect and Attention Networks. Annu Rev Neurosci,

526 *34*, 569–599. https://doi.org/10.1146/annurev-neuro-061010-113731

- 527 Crinion, J. T., & Leff, A. P. (2007). Recovery and treatment of aphasia after stroke: Functional imaging
- 528 studies. *Current Opinion in Neurology*, 20(6), 667–673.
- 529 https://doi.org/10.1097/WCO.0b013e3282f1c6fa
- 530 Crosson, B., Rodriguez, A. D., Copland, D., Fridriksson, J., Krishnamurthy, L. C., Meinzer, M., Raymer,
- 531 A. M., Krishnamurthy, V., & Leff, A. P. (2019). Neuroplasticity and aphasia treatments: New
- 532 approaches for an old problem. Journal of Neurology, Neurosurgery & Psychiatry, 90(10),
- 533 1147–1155. https://doi.org/10.1136/jnnp-2018-319649
- 534 Feng, W., Wang, J., Chhatbar, P. Y., Doughty, C., Landsittel, D., Lioutas, V. A., Kautz, S. A., & Schlaug,
- G. (2015). Corticospinal tract lesion load: An imaging biomarker for stroke motor outcomes. *Ann Neurol*, 78(6), 860–870. https://doi.org/10.1002/ana.24510
- 537 Gainotti, G., D'Erme, P., & Bartolomeo, P. (1991). Early orientation of attention toward the half
- 538 space ipsilateral to the lesion in patients with unilateral brain damage. Journal of Neurology,
- 539 *Neurosurgery and Psychiatry*, 54, 1082–1089. https://doi.org/10.1136/jnnp.54.12.1082
- 540 Hartwigsen, G., & Saur, D. (2019). Neuroimaging of stroke recovery from aphasia Insights into
- 541 plasticity of the human language network. *NeuroImage*, *190*, 14–31.
- 542 https://doi.org/10.1016/j.neuroimage.2017.11.056

- 543 Hayward, K. S., Ferris, J. K., Lohse, K. R., Borich, M. R., Borstad, A., Cassidy, J. M., Cramer, S. C.,
- 544 Dukelow, S. P., Findlater, S. E., Hawe, R. L., Liew, S. L., Neva, J. L., Stewart, J. C., & Boyd LA.
- 545 (2022). Observational Study of Neuroimaging Biomarkers of Severe Upper Limb Impairment
- 546 After Stroke. *Neurology*, *99*, e402–e413. https://doi.org/10.1212/WNL.000000000200517
- He, B. J., Snyder, A. Z., Vincent, J. L., Epstein, A., Shulman, G. L., & Corbetta, M. (2007). Breakdown of
- 548 functional connectivity in frontoparietal networks underlies behavioral deficits in spatial
- 549 neglect. Neuron, 53(6), 905–918. https://doi.org/10.1016/j.neuron.2007.02.013
- Husain, M., & Rorden, C. (2003). Non-spatially lateralized mechanisms in hemispatial neglect. *Nature Reviews Neuroscience Volume*, *4*, 26–36.
- Jokinen, H., Melkas, S., Ylikoski, R., Pohjasvaara, T., Kaste, M., Erkinjuntti, T., & Hietanen, M. (2015).
- 553 Post-stroke cognitive impairment is common even after successful clinical recovery.
- 554 *European Journal of Neurology*, 22(9), 1288–1294. https://doi.org/10.1111/ene.12743
- Karnath, H. O., Rennig, J., Johannsen, L., & Rorden, C. (2011). The anatomy underlying acute versus
 chronic spatial neglect: A longitudinal study. *Brain*, *134*, 903–912.
- 557 https://doi.org/10.1093/brain/awq355
- 558 Karnath, H. O., Rorden, C., & Ticini, L. F. (2009). Damage to White Matter Fiber Tracts in Acute
- 559 Spatial Neglect. *Cerebral Cortex*, *19*, 2331–2337.
- 560 Kaufmann, B. C., Cazzoli, D., Pastore-Wapp, M., Vanbellingen, T., Bauer, D., Müri, R. M., Nef, T.,
- 561 Bartolomeo, P., & Nyffeler, T. (2022). Joint impact on attention, alertness and inhibi-tion of
- 562 lesions at a frontal white matter crossroad. *Brain, awac359*.
- 563 https://doi.org/10.1093/brain/awac359
- 564 Kaufmann, B. C., Cazzoli, D., Pastore-Wapp, M., Vanbellingen, T., Pflugshaupt, T., Bauer, D., Müri, R.
- 565 M., Nef, T., Bartolomeo, P., & Nyffeler, T. (2023). Joint impact on attention, alertness and
- 566 inhibition of lesions at a frontal white matter crossroad. *Brain*, *146*(4), 1467–1482.
- 567 https://doi.org/10.1093/brain/awac359

- 568 Kaufmann, B. C., Cazzoli, D., Pflugshaupt, T., Bohlhalter, S., Vanbellingen, T., Müri, R. M., Nef, T., &
- 569 Nyffeler, T. (2020). Eyetracking during free visual exploration detects neglect more reliably
 570 than paper-pencil tests. *Cortex*, *129*, 223–235. https://doi.org/10.1016/j.cortex.2020.04.021
- 571 Kaufmann, B. C., Frey, J., Pflugshaupt, T., Wyss, P., Paladini, R. E., Vanbellingen, T., Bohlhalter, S.,
- 572 Chechlacz, M., Nef, T., Müri, R. M., Cazzoli, D., & Nyffeler, T. (2018). The spatial distribution
- 573 of perseverations in neglect patients during a nonverbal fluency task depends on the
- 574 integrity of the right putamen. *Neuropsychologia*, *115*, 42–50.
- 575 https://doi.org/10.1016/j.neuropsychologia.2018.01.025
- 576 Kaufmann, B. C., Knobel, S. E. J., Nef, T., Müri, R. M., Cazzoli, D., & Nyffeler, T. (2020). Visual
- 577 Exploration Area in Neglect: A New Analysis Method for Video-Oculography Data Based on
- 578 Foveal Vision. *Frontiers in Neuroscience*, 13:1412. https://doi.org/10.3389/fnins.2019.01412
- 579 Kerkhoff, G. (2001). Spatial hemineglect in humans. *Progress in Neurobiology*, 63(1), 1–27.
- 580 https://doi.org/10.1016/S0301-0082(00)00028-9
- Kinsbourne, M. (1987). Mechanisms of unilateral Neglect. In M. Jeannerod (Ed.), *Neurophysiological and Neuropsychological Aspects of Spatial neglect* (pp. 69–86). Elsevier Science.
- 583 Koch, G., Veniero, D., & Caltagirone, C. (2013). To the Other Side of the Neglected Brain: The
- 584 Hyperexcitability of the Left Intact Hemisphere. *The Neuroscientist*, *19*(2), 208–217.
- 585 https://doi.org/10.1177/1073858412447874
- Kwon, B. M., Lee, J.-Y., Ko, N., Kim, B.-R., Moon, W.-J., Choi, D.-H., & Lee, J. (2022). Correlation of
 Hemispatial Neglect with White Matter Tract Integrity: A DTI Study. *Brain* &
- 588 *Neurorehabilitation*, 15(1), e6. https://doi.org/10.12786/bn.2022.15.e6
- Lewis, J. D., O'Reilly, C., Bock, E., Theilmann, R. J., & Townsend, J. (2022). Aging-Related Differences
 in Structural and Functional Interhemispheric Connectivity. *Cereb Cortex*, *32*(7).
- 591 https://doi.org/10.1093/cercor/bhab275
- Liu, Z., Wang, Y., Gerig, G., Gouttard, S., Tao, R., Fletcher, T., & Styner, M. (2010). Quality Control of
 Diffusion Weighted Images. *Proc SPIE Int Soc Opt Eng*, *7628*.
- 594 https://doi.org/10.1117/12.844748.

- 595 Lunven, M., Rode, G., Bourlon, C., Duret, C., Migliaccio, R., Chevrillon, E., Thiebaut de Schotten, M.,
- 8 Bartolomeo, P. (2018). Anatomical predictors of successful prism adaptation in chronic
 visual neglect. *Cortex*, *120*, 629–641. https://doi.org/10.1016/j.cortex.2018.12.004
- 598 Lunven, M., Thiebaut De Schotten, M., Bourlon, C., Duret, C., Migliaccio, R., Rode, G., & Bartolomeo,
- 599 P. (2015). White matter lesional predictors of chronic visual neglect: A longitudinal study.
- 600 Brain, 138(Pt 3), 746–760. https://doi.org/10.1093/brain/awu389
- 601 McDonald, M. W., Corbett, D., Dijkhuizen, R. M., Farr, T. D., Jeffers, M. S., Black, S. E., Copland, D. A.,
- 602 Kalaria, R. N., Karayanidis, F., Leff, A. P., Nithianantharajah, J., Pendlebury, S., Quinn, T. J.,
- 603 Clarkson, A. N., & O'Sullivan, M. J. (2019). Cognition in stroke rehabilitation and recovery
- 604 research: Consensus-based core recommendations from the second Stroke Recovery and
- 605 Rehabilitation Roundtable. *International Journal of Stroke*, *14*, 774–782.
- 606 https://doi.org/10.1177/1747493019873600
- 607 Munsch, F., Sagnier, S., Asselineau, J., Bigourdan, A., Guttmann, Charles. R., Debruxelles, S., Poli, M.,
- 608 Renou, P., Perez, P., Dousset, V., Sibon, I., & Tourdias, T. (2016). Stroke Location Is an
- 609 Independent Predictor of Cognitive Outcome. *Stroke*, 47(1), 66–73.
- 610 https://doi.org/10.1161/STROKEAHA.115.011242
- 611 Nachev, P., Coulthard, E., Jäger, H. R., Kennard, C., & Husain, M. (2008). Enantiomorphic
- 612 normalization of focally lesioned brains. *Neuroimage*, *39*, 1215–1226.
- 613 https://doi.org/10.1016/j.neuroimage.2007.10.002
- Nijboer, T., Kollen, B. J., & Kwakkel, G. (2014). The Impact of Recovery of Visuo-Spatial Neglect on
 Motor Recovery of the Upper Paretic Limb After Stroke. *PLOS ONE*, *9*(6).
- 616 https://doi.org/10.1371/journal.pone.0100584
- 617 Nyffeler, T., Vanbellingen, T., Kaufmann, B. C., Pflugshaupt, T., Bauer, D., Frey, J., Chechlacz, M.,
- Bohlhalter, S., Müri, R. M., Nef, T., & Cazzoli, D. (2019). Theta burst stimulation in neglect
- 619 after stroke: Functional outcome and response variability origins. *Brain*.
- 620 https://doi.org/10.1093/brain/awz029 BRAIN

- 621 Pastore-Wapp, M., Gyurkó, D. M., Vanbellingen, T., Lehnick, D., Cazzoli, D., Pflugshaupt, T., Pflugi, S.,
- 622 Nyffeler, T., Walther, S., & Bohlhalter, S. (2022). Improved gesturing in left-hemispheric
- 623 stroke by right inferior parietal theta burst stimulation. *Frontiers in Neuroscience*, 16,

624 998729. https://doi.org/10.3389/fnins.2022.998729

625 Price, E. B., & Moss, H. E. (2014). Osborn's Brain: Imaging, Pathology, and Anatomy. Neuro-

626 *Ophthalmology*, 38(2), 96–97. https://doi.org/10.3109/01658107.2013.874459

- 627 Ramsey, L. E., Siegel, J. S., Baldassarre, A., Metcalf, N. V., Zinn, K., Shulman, G. L., & Corbetta, M.
- 628 (2016). Normalization of network connectivity in hemispatial neglect recovery. *Ann Neurol*,

629 80(1), 127–141. https://doi.org/10.1002/ana.24690

- 630 Ringman, J. M., Saver, J. L., Woolson, R. F., Clarke, W. R., & Adams, H. P. (2004). Frequency, risk
- 631 factors, anatomy, and course of unilateral neglect in an acute stroke cohort. *Neurology*,

632 63(3), 468–474. https://doi.org/10.1212/01.WNL.0000133011.10689.CE

- Rorden, C., Bonilha, L., Fridriksson, J., Bender, B., & Karnath, H. O. (2012). Age-specific CT and MRI
 templates for spatial normalization. *Neuroimage*, *61*(4), 957–965.
- 635 https://doi.org/10.1016/j.neuroimage.2012.03.020
- 636 Rost, N. S., Bottle, A., Lee, J. M., Randall, M., Middleton, S., Shaw, L., Thijs, V., Rinkel, G. J. E., &
- 637 Hemmen, T. M. (2016). Stroke Severity Is a Crucial Predictor of Outcome: An International
- 638 Prospective Validation Study. J Am Heart Assoc., 5(e002433).
- 639 https://doi.org/10.1161/JAHA.115.002433
- 640 Saur, D., Lange, R., Baumgaertner, A., Schraknepper, V., Willmes, K., Rijntjes, M., & Weiller, C.
- 641 (2006). Dynamics of language reorganization after stroke. *Brain*, 129, 1371–1384.
- 642 https://doi.org/10.1093/brain/awl090
- 643 Sperber, C., Clausen, J., Benke, T., & Karnath, H.-O. (2020). The anatomy of spatial neglect after
- 644 posterior cerebral artery stroke. *Brain Communications*, *2*(2), fcaa163.
- 645 https://doi.org/10.1093/braincomms/fcaa163
- 646 Stewart, J. C., Dewanjee, P., Tran, G., Quinlan, E. B., Dodakian, L., McKenzie, A., See, J., & Cramer, S.
- 647 C. (2017). Role of corpus callosum integrity in arm function differs based on motor severity

- 648 after stroke. *NeuroImage: Clinical*, 14, 641–647.
- 649 http://dx.doi.org/10.1016/j.nicl.2017.02.023
- Talozzi, L., Forkel, S. J., Pacella, V., Nozais, V., Allart, E., Piscicelli, C., Pérennou, D., Tranel, D., Boes,
- 651 A., Corbetta, M., Nachev, P., & Thiebaut De Schotten, M. (2023). Latent disconnectome
- 652 prediction of long-term cognitive-behavioural symptoms in stroke. *Brain*, *146*(5), 1963–1978.
- 653 https://doi.org/10.1093/brain/awad013
- 654 Thompson, C. K., & Den Ouden, D.-B. (2008). Neuroimaging and recovery of language in aphasia.
- 655 *Current Neurology and Neuroscience Reports*, *8*(6), 475–483.
- 656 https://doi.org/10.1007/s11910-008-0076-0
- 657 Umarova, R., Beume, L., Reisert, M., Kaller, C. P., Klöppel, S., Mader, I., Glauche, V., Kiselev, V. G.,
- 658 Catani, M., & Weiller, C. (2017). Distinct white matter alterations following severe stroke.
 659 *Neurology*, *88*. https://doi.org/10.1212/WNL.0000000003843
- 660 Umarova, R. M., Reisert, M., Beier, T. U., Kiselev, V. G., Klöppel, S., Kaller, C. P., Glauche, V., Mader,
- 661 I., Beume, L., Hennig, J., & Weiller C. (2014). Attention-Network Specific Alterations of
- 662 Structural Connectivity in the Undamaged White Matter in Acute Neglect. *Human Brain*663 *Mapping*, 35, 4678–4692.
- 664 Umarova, R. M., Saur, D., Kaller, C., Vry, M., Glauche, V., Mader, I., Hennig, J., & Weiller, C. (2011).
 665 Acute visual neglect and extinction: Distinct functional state of the visuospatial attention
- 666 system. *Brain*, *134*(11), 3310–3325. https://doi.org/10.1093/brain/awr220
- 667 Umarova, R., Nitschke, K., Kaller, C., Kloppel, S., Beume, L., Mader, I., Martin, M., Hennig, J., &
 668 Weiller, C. (2016). Predictors and signatures of recovery from neglect in acute stroke. *Ann*669 *Neurol*, *79*(4), 673–686. https://doi.org/10.1002/ana.24614
- 670 van Meer, M. P. A., Otte, W. M., van der Marel, K., Nijboer, C. H., Kavelaars, A., van der Sprenkel, J.
- 671 W. B., Viergever, M. A., & Dijkhuizen, R. M. (2012). Extent of Bilateral Neuronal Network
- 672 Reorganization and Functional Recovery in Relation to Stroke Severity. *Journal of*
- 673 *Neuroscience*, *32*(13), 4495–4507. https://doi.org/10.1523/JNEUROSCI.3662-11.2012

- Vogt, G., Laage, R., Shuaib, A., & Schneider, A. (2012). Initial Lesion Volume Is an Independent
- 675 Predictor of Clinical Stroke Outcome at Day 90: An Analysis of the Virtual International
- 676 Stroke Trials Archive (VISTA) Database. *Stroke*.
- 677 https://doi.org/10.1161/STROKEAHA.111.646570
- 678 Wiesen, D., Karnath, H. O., & Sperber, C. (2020). Disconnection somewhere down the line:
- 679 Multivariate lesion-symptom mapping of the line bisection error. *Cortex*, 133, 120–132.
- 680 https://doi.org/10.1016/j.cortex.2020.09.012
- 681 Yeh, F. C. (2022). Population-based tract-to-region connectome of the human brain and its
- 682 hierarchical topology. *Nature Communications*. https://doi.org/10.1038/s41467-022-32595-
- 683

- 684 Yeh, F. C., Liu, L., Hitchens, T. K., & Wu, Y. L. (2017). Mapping Immune Cell Infiltration Using
- 685 Restricted Diffusion MRI. Magn Reson Med., 77, 603–612.
- 686 https://doi.org/10.1002/mrm.26143.
- 687 Yeh, F. C., Panesar, S., Barrios, J., Fernandes, D., Abhinav, K., Meola, A., & Fernandez-Miranda, J. C.
- 688 (2019). Automatic Removal of False Connections in Diffusion MRI Tractography Using
- 689 Topology-Informed Pruning (TIP). *Neurotherapeutics*, *16*, 52–58.
- 690 https://doi.org/10.1007/s13311-018-0663-y
- Yeh, F. C., & Tseng, W. Y. I. (2011). NTU-90: A high angular resolution brain atlas constructed by qspace diffeomorphic reconstruction. *Neuroimage*, *58*, 91–99.
- 693 https://doi.org/10.1016/j.neuroimage.2011.06.021
- 694 Yeh, F. C., Verstynen, T. D., Wang, Y., Fernández-Miranda, J. C., & Isaac, W. Y. (2013). Deterministic
- 695 Diffusion Fiber Tracking Improved by Quantitative Anisotropy. *PLOS ONE, Volume 8 | Issue*696 11 / e80713(11).
- Yeh, F. C., Wedeen, V. J., & Tseng, W. I. (2010). Generalized q-Sampling Imaging. *IEEE TRANSACTIONS* ON MEDICAL IMAGING, 29(9). https://doi.org/10.1109/TMI.2010.204512
- 699 Young, J., & Forster, A. (2007). Rehabilitation after stroke. *BMJ*, 334, 86–90.
- 700 https://doi.org/10.1136/bmj.39059.456794.68

- 701 Zhou, X., Sakaie, K. E., Debbins, J. P., Narayanan, S., Fox, R. J., & Lowe, M. J. (2018). Scan-rescan
- 702 repeatability and cross-scanner comparability of DTI metrics in healthy subjects in the
- 703 SPRINT-MS multicenter trial. *Magnetic Resonance Imaging*, 53, 105–111.
- Meurosciaccepted Manuscrip 704 https://doi.org/10.1016/j.mri.2018.07.011





