JNeurosci
THE JOURNAL OF NEUROSCIENCE

Research Articles | Behavioral/Cognitive

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https://doi.org/10.1523/JNEUROSCI.1311-23.2024

Received: 13 July 2023
Revised: 15 December 2023
Accepted: 15 March 2024

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

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Keywords: white matter connectivity, neglect recovery, stroke, outcome, DTI, activities of daily living

Number of pages 32; Number of figures 3; Number of tables 3; Number of multimedia 0; Number of 3D models 0; Number of words in the Abstract 235/250, Introduction 650/650, Discussion 1306/1500.

Conflict of interest: The authors declare no competing financial interests.

Acknowledgement: This work was supported by the Swiss National Science Foundation (SNSF). We are very grateful to all the patients who took part in our study, and we would also like to thank the clinical team at the Kantonsspital Luzern for their assistance and support.

Abstract

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

Significance Statement

Visuospatial neglect is a common and challenging issue affecting the daily living of stroke survivors. Mechanisms underlying the recovery of neglect, especially the contribution of the intact hemisphere, remain controversial, ranging from maladaptive to compensatory. In 54 neglect 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 sufficient for good recovery; conversely, in more severe neglect, structural connectivity within the contralesional hemisphere and between hemispheres plays a central role. These findings may help to reconcile rival models concerning the role of the contralesional hemisphere in neglect recovery after stroke. Furthermore, they could serve as a prognostic biomarker and guide patient-tailored therapeutic approaches.

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 are still lively debated (Corbetta & Shulman, 2011; Kinsbourne, 1987; Lunven et al., 2015; McDonald et al., 2019; Umarova et al., 2017). Numerous functional magnetic resonance imaging (fMRI) studies evidenced the importance of inter-hemispheric communication and the activity within the contralesional hemisphere both for the acute severity and recovery of spatial neglect. On one hand, 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 their inter-and intrahemispheric functional connectivity (Baldassarre et al., 2014; Carter et al., 2010; He et al., 2007; Ramsey et al., 2016) correlated with acute neglect severity, while their normalisation with neglect recovery at the chronic stage (Corbetta et al., 2005; He et al., 2007; Ramsey et al., 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 spatial neglect recovery (Umarova et al., 2016). Fittingly, findings concerning the role of white matter (dis)connectivity in spatial neglect severity and recovery evidenced diverging patterns. Various studies showed the role of white matter fronto-parietal and occipito-frontal tracts within the ipsilesional (e.g., (Karnath et al., 2009; Lunven et al., 2015)) or the contralesional, intact hemisphere (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; Umarova et al., 2014; Wiesen et al., 2020)), while others did not (e.g., (Karnath et al., 2009; Sperber et al., 2020)). Therefore, the considerable inter-individual variability commonly observed in neglect recovery (McDonald et al., 2019) seems mirrored by a range of diverse explanatory accounts.

Studies on post-stroke motor recovery in animals and humans provide a potential avenue to reconcile these diverse perspectives (Biernaskie et al., 2005; Hayward et al., 2022; Stewart et al., 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., 2017). In mild motor deficits, the recruitment of the spared ipsilesional motor network is sufficient. Conversely, in more severe motor deficits, the involvement of the intact contralesional hemisphere becomes essential for recovery, facilitated by preserved inter-hemispheric white matter connectivity (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 its role would vary, amongst others, according to initial impairment severity (e.g.(Bartolomeo & Thiebaut de Schotten, 2016; Crinion & Leff, 2007; Crosson et al., 2019; Hartwigsen & Saur, 2019; Thompson & Den Ouden, 2008)).

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).

1 Materials and Methods

1.1 Patients

This is a prospective, observational study, including 54 patients with left-sided spatial neglect in daily living (i.e., Catherine Bergego Scale, CBS≥1; (Azouvi et al., 2003)), after a first right-hemispheric 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; 59.26% male, 50 patients were right-handed (3 left-handed, 1 ambidextrous); normalized lesion volume mean=50.67, SD=63.83 cc^3; 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 were age above 18 years, normal or corrected-to-normal visual acuity, and the ability and willingness to undergo an additional MRI. Patients with other neurological disorders, major psychiatric disorders, and/or alcohol or drug abuse were excluded.

The patients' inclusion flow-chart based on the STROBE guidelines is presented in *Figure 2.* In detail, a total of 47 first-ever right hemisphere stroke patients, who participated in our prospective observational study (Kaufmann et al., 2022), agreed on the additional acquisition of a DTI sequence for the present study. Another 23 first-ever right-hemispheric stroke patients were prospectively 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 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 (CBS = 0; (Azouvi et al., 2003)). 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.

Written, informed consent was obtained from all patients. The study was approved by the local Ethics Committee (BASEC 2017-00827) and performed according to the latest Declaration of Helsinki.

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1.2 Experimental Design and Statistical Analysis

1.2.1 Behavioural measure

Neglect in daily living was evaluated using the Catherine Bergego Scale (CBS (Azouvi et al., 2003)), a systematic, ecological observation scale, which is reliable, valid, and sensitive in assessing changes in neglect severity throughout rehabilitation (Azouvi, 2017; Azouvi et al., 2003). Ten observations during daily living are rated on a 0 (no neglect) to 3 (severe neglect) scale, resulting in a CBS total score of 0-30 (1–10 indicating mild neglect, 11-30 moderate-to-severe neglect; (Azouvi, 2017)). The CBS was administered at admission to and discharge from inpatient neurorehabilitation.

1.2.2 Neural correlates

For each patient, three MRI sequences (two anatomical: FLAIR, T2-MPRAGE; and one DTI) were acquired on 3T Siemens Magnetom scanners (35 on Skyra, 19 on Vida). To account for potential between-scanner differences (Zhou et al., 2018), a corresponding binary covariate was included in all analyses. The respective imaging parameters and the pre-processing steps are described below.

1.2.2.1 Details of anatomical imaging and pre-processing steps

High-resolution MRIs were acquired in all patients using two sequences: 1) a FLAIR sequence (TR/TE=5000/389 msec, voxel size=0.4 x0.4 x 0.9 mm), which was used for identification and demarcation of the lesions; 2) a MPRAGE sequence (TR/TE=2240/3.72 msec, voxel size=0.9 x0.9x0.9 mm)(Kaufmann et al., 2023).

To calculate the patients' individual lesion volume, individual stroke lesions were manually delineated on the high-resolution structural MRI images by an experienced rater and normalised into MNI space.

The detailed pre-processing steps have been previously described in (Kaufmann et al., 2018) and in (Kaufmann et al., 2023). In short, the anatomical FLAIR images were registered to the MPRAGE images and used for lesion mapping, i.e., the manual delineation of the individual patients' lesion borders. Images were then normalised into MNI space with the Clinical Toolbox for SPM12 run on MATLAB ((Rorden et al., 2012); spm http://www.fil.ion.ucl.ac.uk/ ; Matlab 2020b, The MathWorks, Inc. https://www.mathworks.com/products/matlab.html), applying enantiomorphic normalization (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.

1.2.2.2 Details of DTI imaging and pre-processing steps

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 imaging parameters: 1.7 x 1.7 x 4.0 mm^3, 30 slices, FoV=220 mm, TR/TE=4100/95 ms.

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 image quality control and preparation. Pre-processing included image information check, data cropping, slice-wise, interlace-wise, and gradient-wise intensity artifact correction, eddy current and head motion correction, as well as computing of individual DTI for each patient.

1.2.3 Statistical analysis of neural correlates

To investigate, how initial neglect severity modulates the role of white matter (dis)connectivity in the ipsi- and contralesional hemispheres in supporting neglect recovery, we used diffusion MRI connectometry as implemented in DSIstudio (https://dsi-studio.labsolver.org). After pre-processing, all 54 diffusion MRI scans were included in a connectometry database with an in-plane resolution of 1.72 mm, and the accuracy of the b-table orientation was examined by comparing fibre orientations with those of a population-averaged template (Yeh, 2022). The diffusion data were reconstructed in the MNI space to obtain the spin distribution function(Yeh et al., 2010; Yeh & Tseng, 2011). A diffusion sampling length ratio of 1.25 was used. The output resolution in diffeomorphic reconstruction was 1.72 mm isotropic. The restricted diffusion was quantified using restricted diffusion imaging (Yeh et al., 2017). The tensor metrics were calculated using DWI with b-value lower than 1750 s/mm².

Correlational tractography, with the aim of putting fractional anisotropy (FA) values in relation to neglect recovery (i.e., CBS at discharge from inpatient neurorehabilitation), was calculated with a nonparametric Spearman rank-based correlation. We employed a multiple regression model to control for factors such as initial neglect severity (i.e., at admission to inpatient neurorehabilitation; e.g. (Rost et al., 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) by adjusting the diffusion metrics using partial correlations, as implemented in DSIstudio.

For the correlational tractography, the deterministic fibre tracking algorithm (Yeh et al., 2013) was used with a T-score threshold of 2. A seeding region was placed at whole-brain level, excluding the 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 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 then manually verified for accuracy by experienced raters (BK and TN). The analyses were performed and visualized in DSIstudio (https://dsi-studio.labsolver.org/).

1.2.4 Multiple regression analysis

To evaluate the relative contribution of the FA-values in the significant white matter fibres on neglect recovery, all connectometry analyses were followed by post-hoc, forced entry multiple regression models, also considering the above-described factors (initial neglect severity (Rost et al., 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)).

The analyses were performed using JASP (https://jasp-stats.org/) and visualized using R (https://cran.r-project.org/).

2 Results

2.1 Overall patient sample

2.1.1 Descriptive statistics

A high inter-individual variability was found in all patient characteristics: age, lesion volume, rehabilitation duration, time between stroke and MRI, and initial neglect severity.

2.1.2 Connectometry analysis

The connectometry analysis over all patients (n=54) revealed a significant correlation between neglect recovery and fibres within both hemispheres (right: corticospinal tract (CST), Inferior Fronto-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, were correlated with neglect recovery.

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 severity, lesion volume, rehabilitation duration, time between stroke and MRI, age, and scanner type).

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).

Intermediate conclusion

Good neglect recovery was associated with the preservation of a heterogeneous white matter 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; Stewart et al., 2017; van Meer et al., 2012), highlighted the importance of the initial neglect severity 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 moderate-to-severe (CBS 11-30 (Azouvi, 2017)) spatial neglect.

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2.2 Severity-dependent analyses: mild and moderate-to-severe neglect

2.2.1 Descriptive statistics

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) mild=71.81 (10.49), moderate-to-severe=71.57 (11.09); $t(52)=-.08$, $p=.936$], days between stroke and MRI [mean (SD) mild=22.39(10.87), moderate-to-severe=22.50 (11.91); $t(52)=.04$, $p=.971$], lesion volume in cc^3 [mean (SD) mild=33.60 (47.29), moderate-to-severe=66.52 (73.40); $t(52)=1.94$, $p=.058$)], or scanner type (mild 17:9, moderate-to-severe 18:10; Mann-Whitney U=360.00, $p_{exact=}.999$). Furthermore, the two groups did not significantly differ in terms of lesion topography [no significant group difference was found in a lesion analysis using NiiStat (https://www.nitrc.org/projects/niistat/) with 4000 permutations, FWE <0.05, restricted to voxels with an overlap of n ≥ 20% of the patients and the Freedman-Lane method (Winkler et al., 2014)].

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Figure 3

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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.

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

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

2.2.3 Multiple Regression Analysis

Subsequent multiple regression models, used to evaluate the relative contribution of the FA-values in the significant white matter fibres on recovery, revealed significant in both groups. In mild 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 identified tracts ($\beta_{standardized}$=-.58, t=-2.59, p=.019), and the duration of neurorehabilitation ($\beta_{standardized}$=- .45, t=-2.61, p=.044). In moderate-to-severe neglect, the subsequent multiple regression model explained 37.8% of the variance [F(7,20)=3.35, p=.016; *Table III*]. Predictors for recovery were the initial neglect severity ($\beta_{standardized}$=.60, t=3.43, p=.003) and the FA-values within the identified tracts ($\beta_{standardized}$=-.55, t=-3.19, p=.005).

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Table II and III
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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 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 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) seem~~s~~ not to be sufficient. Indeed, good recovery is also associated with white matter connectivity within the attentional networks of the contralesional hemisphere (left IFOF) and, critically, with inter-hemispheric structural connectivity through callosal fibres (Forceps Major and Tapetum).

The present findings have the potential to reconcile the previously divergent accounts of neglect recovery, wherein improvement has been attributed to either the damaged or intact hemisphere (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 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 hemisphere. However, in cases of more severe neglect, this specialisation may become unsustainable, necessitating the compensatory involvement of the contralesional hemisphere. These differential patterns, suggested by the respective white matter connections, would challenge the opposing views regarding the role of the contralesional hemisphere as solely compensatory or not (Baldassarre et al., 2014; Carter et al., 2010; Corbetta et al., 2005; He et al., 2007; Koch et al., 2013; Ramsey et al., 2016; Umarova et al., 2016; Umarova et al., 2011). Instead, they would reconcile 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.

A SLF II disconnection is typically associated with more severe and chronic neglect (Karnath et al., 2011; Lunven et al., 2015). In our study, a spared right hemisphere SLF II in mild neglect is related to 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 (spared right IFOF in mild, spared right and additionally left IFOF in moderate-to-severe neglect) is more speculative. First, our findings show that a spared right IFOF is related to recovery in mild as 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 disconnected by middle cerebral artery strokes (Price & Moss, 2014), which most typically affect the SLF and causes neglect (Corbetta & Shulman, 2011). Second, in our study, a spared left IFOF (but not a spared left SLF) is related to recovery from moderate-to-severe neglect, jointly with callosal inter-hemispheric connectivity. This could be speculatively due to the prominent compensatory role of contralateral homologues (Saur et al., 2006; Stewart et al., 2017): the intact right IFOF would call for 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.

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.

Limitations

We studied a sample exclusively composed of patients with left-sided neglect, a common sequela of right-hemispheric stroke (Azouvi et al., 2003; Kaufmann, Cazzoli, et al., 2020, p. 20; Ringman et al., 2004). Future studies shall investigate whether the identified mechanisms are laterality-independent and also apply to right-sided neglect after left-hemispheric stroke. Furthermore, lesion distribution 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 of stronger associations with fibres in this region. Nevertheless, our results highlight recovery patterns supported by fibres within both the lesioned and the contralesional intact hemisphere, thus relativizing this potential bias (Nijboer et al., 2014). Finally, since our findings reveal the importance of severity-dependent white matter (dis)connectivity profiles for neglect recovery in daily living, 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, 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 function deficits (Kaufmann et al., 2018, 2023; Kaufmann, Knobel, et al., 2020) affect the recovery of spatial neglect itself in the context of white matter (dis)connections. The same applies to the different aspects that characterise neglect as a multicomponent syndrome (see, e.g., (Gainotti et al., 1991; Kerkhoff, 2001)). Furthermore, these future studies should ideally be multimodal (i.e., simultaneously including, amongst other, structural and functional imaging, metabolic, and mechanistic variables), since this approach seems to hold promise for even better prediction of stroke recovery (e.g., (Bonkhoff & Grefkes, 2022).

Conclusions

The present study establishes that the recovery of spatial neglect is related to a close interaction between individual white matter (dsy)connectivity patterns determined by specific lesion profiles, and initial severity of neglect. In cases of mild neglect spared white matter connectivity within the 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 contralesional intact hemisphere. This newly identified interaction emerges as a new factor in explaining the variability observed in neglect recovery, and potentially reconciles conflicting viewpoints regarding the role of the contralesional hemisphere. Our data suggest that the contralesional hemisphere has the potential to assume a compensatory role, but this is contingent upon initial severity of impairment and presence of spared structural connectivity.

In the future, incorporating combined information on white matter (dis)connectivity and the initial severity of neglect may serve as a valuable prognostic biomarker for predicting neglect recovery. This information could guide the stratification of patients into tailored therapeutic approaches, such as determining which hemisphere and site to target with excitatory or inhibitory non-invasive brain stimulation techniques.

4 Figure Legends

Figure 1 – White matter connectivity profiles in patients with mild and moderate-to-severe neglect

Figure 1. (A) Lesion overlay plot for the 54 patients included in this study and **(B)** inter-individual variability in recovery depending on white matter (dis)connectivity. For both groups, the scatter 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, time between stroke and MRI, age, and scanner type (i.e., FA-value corrected, CBS corrected). **(C)** Recovery of mild neglect (left, n=26) depends on the spared connectivity of the attentional network within the lesioned hemisphere. In moderate-to-severe neglect (right, n=28) recovery additionally depends on the connectivity of the attentional network within the contralesional, intact hemisphere and on the inter-hemispheric connectivity with the latter. The corticospinal tract revealed significant in all connectometry analyses and was therefore not discriminative between sub-groups. An intact 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 the present study, and for enhanced clarity of the graphical illustrations, we decided to not present the CST in the figures.

Figure 2 – STROBE inclusion flow chart

Figure 2. Patients' inclusion flow-chart based on the STROBE guidelines: of the 70 patients with first-ever 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.

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

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 differences are highlighted by an asterisk (p<.05*, p<.001), non-significant differences are noted by “n.s.”.

5 Tables

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

Results of the multiple regression analyses over all patients (n=54), with CBS at discharge from inpatient neurorehabilitation as dependent variable, and initial neglect severity (i.e., CBS at admission to inpatient neurorehabilitation), age, time between stroke and MRI, rehabilitation duration, scanner type, lesion volume as independent variables).

	β_{std}	T	*p*	R^2_{adj}	F	*p*
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 ***			
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			

p<.05, p<.001****

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 discharge from inpatient neurorehabilitation as dependent variable, and initial neglect severity (i.e., CBS at admission to inpatient neurorehabilitation), age, time between stroke and MRI, rehabilitation duration, scanner type, lesion volume as independent variables.

	β_{std}	T	*p*	R^2_{adj}	F	*p*
Model II – mild neglect (n=26)				.35	2.88	.033*
FA-values in significant tracts	-.58	-2.59	.019 *			
CBS at the admission of inpatient neurorehabilitation	.44	2.37	.029 *			
rehabilitation duration	-.45	-2.16	.044 *			
age	-.02	-.09	.933			
time between stroke and MRI	.27	1.33	.199			
scanner type	.02	.09	.928			
Lesion volume	.14	.74	.469			

*p<.05**

Table III. Results of the multiple regression analyses for patients with moderate-to-severe neglect

Results of the multiple regression analyses for patients with moderate-to-severe neglect (n=28), with CBS at discharge from inpatient neurorehabilitation as dependent variable and initial neglect severity (i.e., CBS at admission to inpatient neurorehabilitation), age, time between stroke and MRI, rehabilitation duration, scanner type, lesion volume as independent variables.

	β_{std}	T	*p*	R^2_{adj}	F	*p*
Model III – moderate-to-severe neglect (n=28)				.38	3.35	.016*
FA-values in significant tracts	-.55	-3.19	.005 **			
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			

p<.05, p<.01***

6 Data availability

The conditions of our ethics approval do not permit the public archiving of the data supporting the conclusions of this study. Based on the Swiss Human Research Act, HRA (Humanforschungsgesetz, HfG) in Switzerland, readers seeking access to the data and the study materials must therefore complete a formal data sharing agreement to obtain the data. Interested readers should contact the corresponding author for more information and help.

7 Funding

This work was supported by funding of the Swiss National Science Foundation (SNSF) by SNF Grant No. P2BEP3_195283 to BK, SNF Grant No. Z00P3_154714/1 to DC, as well as 320030_169789 and 32003b_196915 to TN and by Agence Nationale de la Recherche through ANR-16-CE37-0005 and ANR-10-IAIHU-06 to PB.

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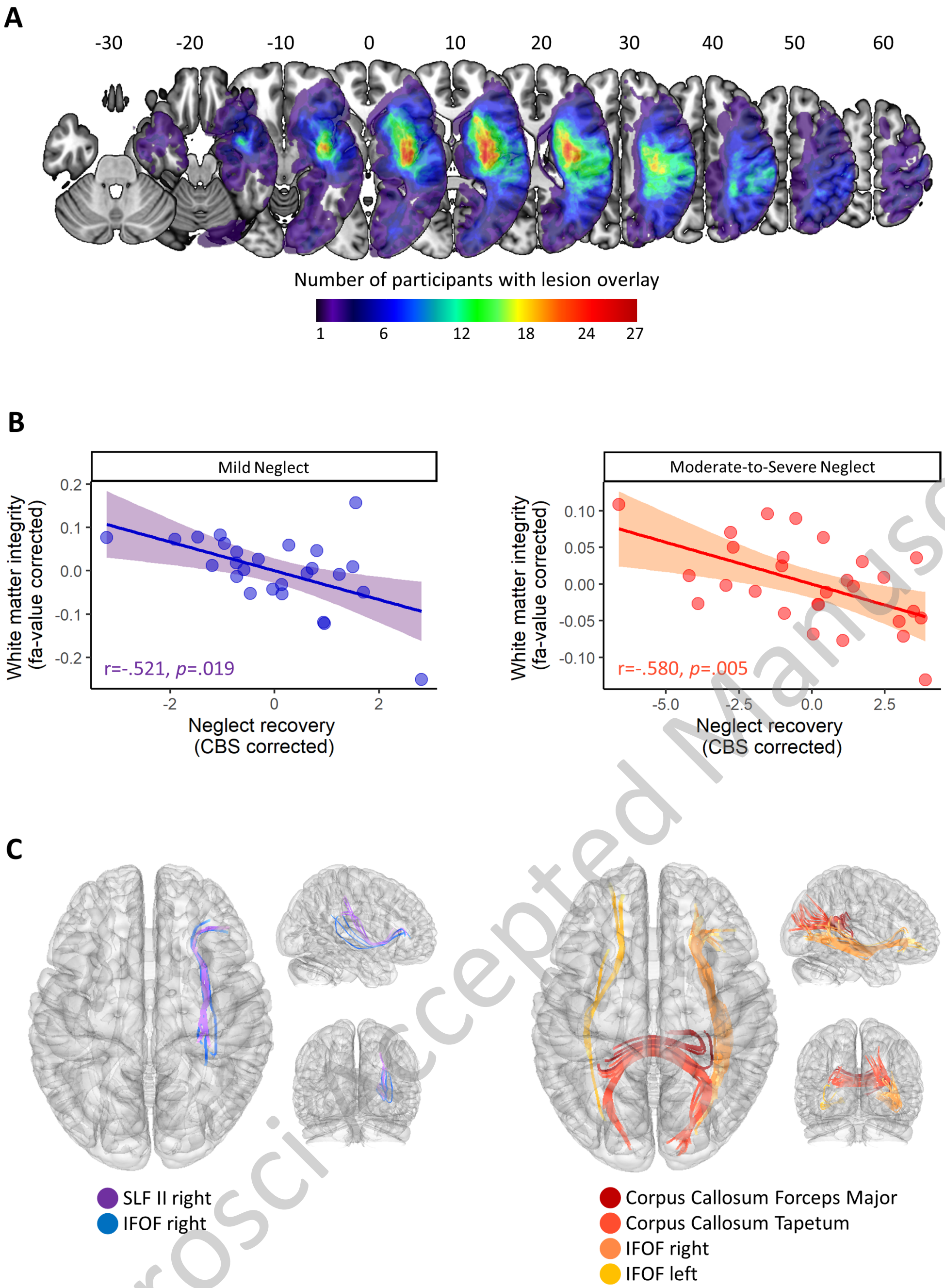
A
-30
-20
-10
0
10
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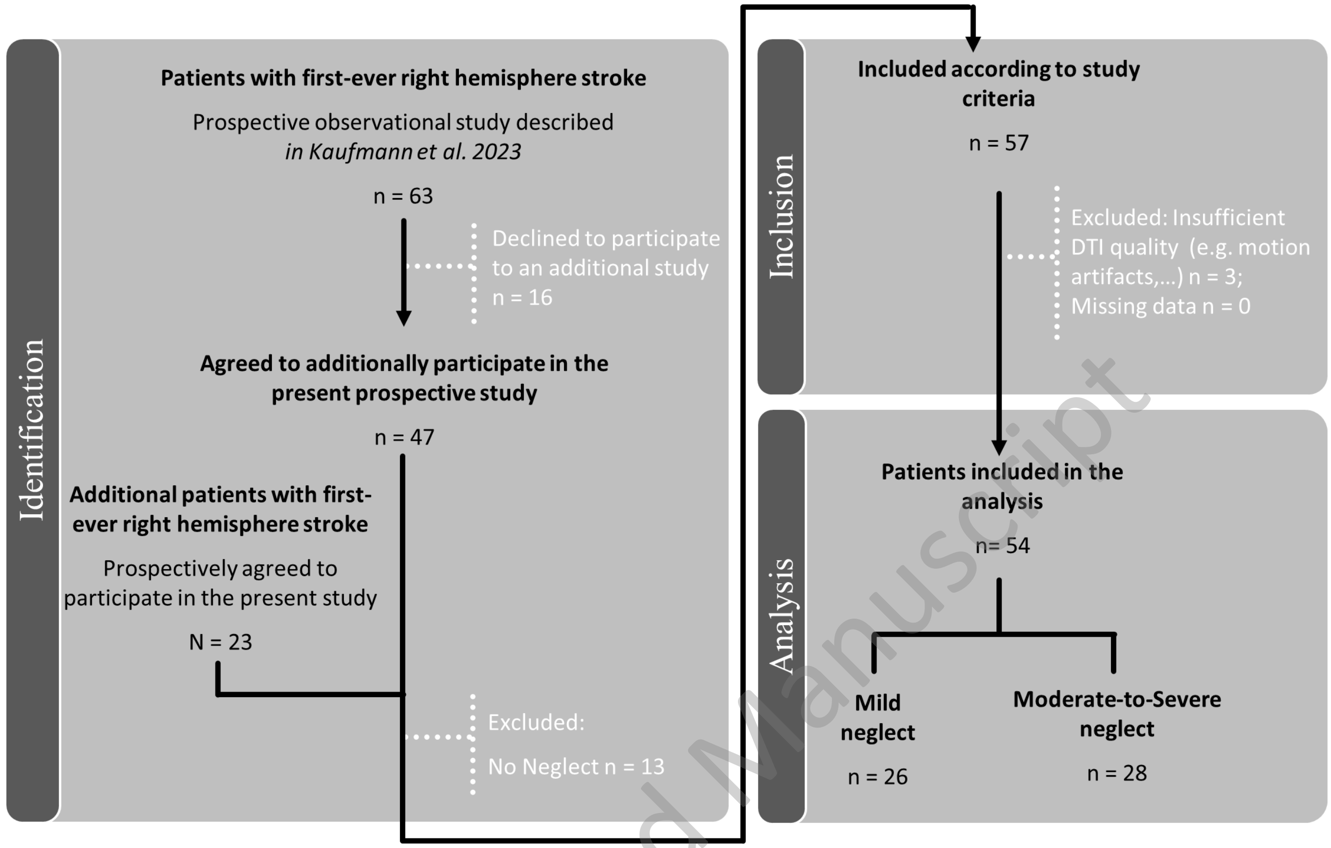
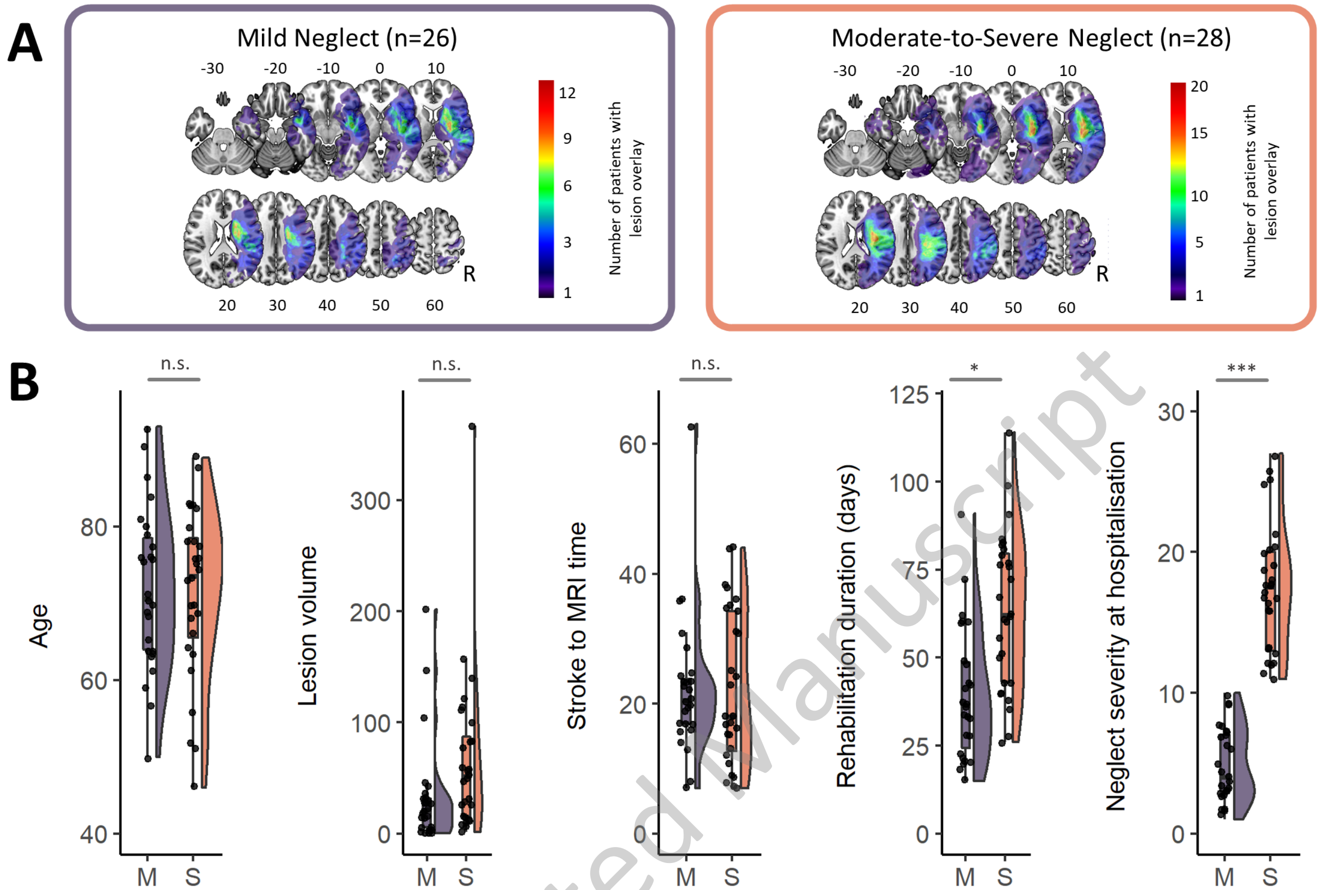
30
40
50
60
Number of participants with lesion overlay
1
6
12
18
24
27
B
Mild Neglect
White matter integrity (fa-value corrected)
Neglect recovery (CBS corrected)
r=-.521, p=.019
Moderate-to-Severe Neglect
r=-.580, p=.005
C
SLF II right
IFOF right
Corpus Callosum Forceps Major
Corpus Callosum Tapetum
IFOF right
IFOF left


Identification
Patients with first-ever right hemisphere stroke
Prospective observational study described
in Kaufmann et al. 2023
n = 63
Declined to participate
to an additional study
n = 16
Agreed to additionally participate in the
present prospective study
n = 47
Additional patients with first-
ever right hemisphere stroke
Prospectively agreed to
participate in the present study
N = 23
Excluded:
No Neglect n = 13
Inclusion
Included according to study
criteria
n = 57
Excluded: Insufficient
DTI quality (e.g. motion
artifacts,...) n = 3;
Missing data n = 0
Analysis
Patients included in the
analysis
n= 54
Mild
neglect
n = 26
Moderate-to-Severe
neglect
n = 28


A
Mild Neglect (n=26)
-30 -20 -10 0 10
20 30 40 50 60
R
12 9 6 3 1
Number of patients with lesion overlay
Moderate-to-Severe Neglect (n=28)
20 15 10 5 1
B
n.s.
Age
Lesion volume
Stroke to MRI time
*
Rehabilitation duration (days)
***
Neglect severity at hospitalisation
M S