Protective Effect of Occupational Complexity on Working Memory in Patients with Frontal Lobe Tumors

Kota Ebina  
Kanazawa University

Mie Matsui  (✉ miematsui@staff.kanazawa-u.ac.jp)  
Kanazawa University

Masashi Kinoshita  
Kanazawa University

Daisuke Saito  
Yasuda Women's University

Mitsutoshi Nakada  
Kanazawa University

Research Article

Keywords: magnetic resonance imaging, working memory, frontal lobe tumors

DOI: https://doi.org/10.21203/rs.3.rs-227304/v1

License: © This work is licensed under a Creative Commons Attribution 4.0 International License.  
Read Full License
Abstract

Cognitive reserve (CR) is the capacity to cope with cognitive impairments due to brain damage by neurological disease. CR is increased by intellectually enriching activities, such as education, occupation, and leisure. After brain tumor resection, patients show working memory impairment because of damage to fronto-parietal networks, such as the superior longitudinal fascicle (SLF). To date, whether occupational experience represented as CR impacts postoperative working memory impairment in patients with frontal lobe tumors remains unknown. We hypothesized that occupational experience predicted postoperative working memory and that higher damage in the SLF was associated with poorer working memory. We enrolled 27 patients who had undergone tumor resection. Patient's occupational experience was estimated using an occupational complexity index based on a dictionary of occupational titles. Working memory was measured using verbal and spatial working memory tasks.

Our results showed that patients who had engaged in more complex occupations showed higher performance of postoperative working memory, which supported the previous CR hypothesis. In conclusion, CR has protective effects against working memory impairment in patients with frontal lobe tumors. CR measures, such as occupational experience, will help more accurately predict the severity of working memory deficits and the likelihood of recovery in the postoperative period.

Introduction

Working memory is the ability to temporarily retain and manipulate information, essential for language comprehension, learning, and reasoning\(^1\). It is related to several daily life actions, such as conversation, calculation and judgment. Previous studies have shown that fronto-parietal networks including the dorsolateral prefrontal cortex (DLPFC), supplementary motor area (SMA), cingulate cortex, and parietal lobe are involved in working memory\(^2\)\(^3\)\(^4\). In the subcortical region, a wide network of white matter tracts, including the superior longitudinal fascicle (SLF), inferior longitudinal fascicle (ILF) and inferior fronto-occipital fascicle (IFOF) have been reported to play a critical role in working memory\(^5\)\(^6\)\(^7\).

Maximal resection is known to be an effective treatment for brain tumors, especially for low-grade gliomas, because it contributes to improved overall survival\(^8\). However, damage to the cerebral cortex and white matter neural networks after tumor resection can lead to higher cognitive function impairment\(^6\)\(^9\)\(^10\). Since cognitive impairments after tumor resection affect the patient’s quality of life\(^9\), a balance between life expectancy and functional prognosis is key in brain tumor treatments. Given the indispensable role of working memory for patients’ daily life, awake brain surgery has been performed to preserve it, which can be achieved by identifying the functional boundaries in the DLPFC\(^11\) and SMA\(^12\). In addition to cortical areas, white matter tracts, such as the SLF, connecting the frontal and parietal lobes, also play a critical role in working memory, and damage to the SLF has been suggested to influence chronic postoperative working memory impairments\(^6\)\(^13\). The accurate prediction of the severity of working memory deficits in the postoperative period and likelihood of recovery is crucial for improving the quality of life and functional prognosis of patients with brain tumor after the resection.
The cognitive reserve (CR) concept has been proposed to explain the discrepancy between brain neuropathology and clinical symptoms, and the inter-individual variability in the severity of clinical symptoms even in cases with similar degrees of brain damage\(^{[4]}\).\(^{[5]}\). Previous studies have shown that intellectually enriching experiences, such as education, occupation, leisure activities and social participation, as well as premorbid intelligence quotient (IQ), contribute to CR development\(^{[6]}\).\(^{[7]}\)\(^{[8]}\)\(^{[9]}\). Most studies on CR have focused on education as a proxy measure for CR, reporting that individuals with higher levels of education show less cognitive decline in old age and a lower risk of dementia\(^{[10]}\)\(^{[11]}\). Despite the low number of studies involving occupational experience used as a CR proxy, it has become the focus of attention as a possible factor affecting CR because most people engage in occupations for long periods in their lifetime. Previous studies used a measure of "occupational complexity", which indicates how much specialization and complex judgment is required in occupations\(^{[22]}\)\(^{[23]}\). Occupational complexity is an index originally created for job matching, wherein each occupation is assigned a score in three domains: complexity related to information processing ("data"), complexity related to interpersonal processing ("people"), and complexity related to the use of machines, tools, and handling ("things")\(^{[24]}\). Previous studies in older adults suggest that high occupational complexity over a lifetime contributes to CR development and plays a role in preventing cognitive decline and the onset of dementia in old age\(^{[22]}\)\(^{[25]}\)\(^{[26]}\). Several previous studies in stroke patients have shown that using years of education as a CR proxy was associated with cognitive function after stroke, and that patients with higher levels of education showed higher cognitive performance, including word fluency and working memory, than those with lower levels of education\(^{[27]}\)\(^{[28]}\)\(^{[29]}\)\(^{[30]}\). In studies on patients with traumatic brain injuries, a higher premorbid IQ as a CR proxy was associated with less cognitive decline after injury\(^{[31]}\)\(^{[32]}\). Further, CR has been shown to have a protective effect against working memory impairments from traumatic brain injury and stroke\(^{[28]}\)\(^{[32]}\)\(^{[33]}\)\(^{[34]}\). Considering the above evidence, CR should have protective effects against cognitive impairments, including working memory, in patients who have undergone brain tumor resection\(^{[35]}\). However, no studies have investigated the relationship between occupational complexity as CR proxy and working memory in patients with frontal lobe tumors.

The first aim of this study was to investigate whether damage of the fronto-parietal networks of white matter tracts is associated with working memory impairments. The second was to determine whether occupational complexity predicts working memory in patients who underwent frontal tumor resection.

In this study, we focused on the bilateral SLFs I, II, and III, which are large fronto-parietal tracts, and investigated the relationships between damage to these tracts and working memory decline after tumor resection. Next, we investigated the association between the occupational complexity of the patients' lifetime and working memory.

Our hypothesis was that the high disconnection ratio of SLFs is associated with low working memory, and the occupational complexity score in the main patient's occupation would predict working memory performance after tumor resection.
Results

Demographics, Occupational Complexity and Neurocognitive Data

Table 1 shows the patient's demographics, occupational complexity scores, and cognitive data. Occupational complexity scores in “data”, “people” and “thing” domain were determined for the job in which the patients had been employed for the longest period of time in the patient's occupational history. The average main occupation number of years in the patients’ lifetime was 21.4 (SD = 15.1). The scores of all domains of occupational complexity (“data”, “people”, and “things”) were summed up and used as the total score of occupational complexity. For all participants, the mean of occupational complexity scores in the “thing” (Mean = 4.6, SD = 1.6) domain was slightly higher than that in the “data” (Mean = 3.6, SD = 1.2) and “people” (Mean = 3.4, SD = 1.8) domain.

|                          | Means (SD) | Min | Max |
|--------------------------|------------|-----|-----|
| **Demographics**         |            |     |     |
| Age (years)              | 52 (13.6)  | 22.8| 81.8|
| Education (years)        | 13.8 (1.7) | 12  | 16  |
| **Occupational Complexity** |          |     |     |
| Total                    | 11.7 (3.6) | 5.2 | 18.2|
| Data                     | 3.6 (1.2)  | 1.7 | 5.6 |
| People                   | 3.4 (1.8)  | 1.5 | 7.1 |
| Things                   | 4.6 (1.6)  | 1.3 | 6.8 |
| **Cognition & WM**       |            |     |     |
| MMSE                     | 27.6 (2.9) | 19  | 30  |
| JART                     | 100.3 (11.1)| 75  | 114 |
| Digit span backward      | 4.0 (1.1)  | 2   | 6   |
| Tapping span backward    | 4.3 (1.1)  | 3   | 7   |
| Verbal 2-back (%)        | 83.7 (20.2)| 41  | 100 |
| Spatial 2-back (%)       | 80.2 (16.6)| 47  | 100 |

Table 1. Participants’ demographics, occupational complexity, and neurocognitive data. WM: working memory, MMSE: Mini-Mental State Examination, JART: Japanese Adult Reading Test, Education: years of education.

Lesion Mapping and Disconnectome Maps

Figure 1a shows the resection cavities’ overlap map in all patients (N = 27). The map indicated that the right frontal lobe had more resection cavities’ overlap. The resection cavities showed the greatest overlap in the right superior frontal gyrus, including the supplementary motor area (Fig. 1a). The disconnectome maps, with more voxel clusters on the dorsal and ventral fronto-parietal pathway, are shown in Fig. 1b. The voxels shown by disconnectome maps were overlaid with SLF I, II, and III on the Montreal Neurological Institute (MNI) template (Fig. 2). As a result, the voxels of potentially damaged white matter tracts were found to be particularly located in the right SLF I and right SLF II.
Correlations between Working Memory and Damage of White Matter Tracts

The Tractotron in the BCBtoolkit (http://toolkit.bcblab.com/) was used to calculate the disconnection ratio of SLFs. To determine whether greater SLF damage is likely to decrease working memory post-operatively, we used Spearman rank correlation coefficients to examine the association between the SLF’s disconnection ratio and working memory. We observed significant negative correlations between digit span backward scores and disconnection ratio of right SLF I ($r = -0.53, p < 0.05$). Tapping span backward scores were significantly associated with the disconnection ratio of the left SLF II ($r = -0.75, p < 0.05$). Verbal 2-back task scores were significantly correlated to disconnection ratio of left SLF II ($r = -0.75, p < 0.05$) and left SLF III ($r = -0.83, p < 0.05$). There was no significant relationship between the spatial 2-back scores and the disconnection ratio of any SLF (Supplementary table 1).

Regression analysis of occupational complexity and working memory after tumor resection

To investigate whether occupational complexity scores can predict working memory scores, multiple regression analysis was performed with occupational complexity scores as a predictor variable and working memory scores as dependent variable. Regarding multiple regression analysis, since years of education and Japanese Adults Reading Test (JART) scores are considered as one factor in CR, these variables were included as adjusting variables in the model. Similarly, age was entered into the model as an adjusting variable, because age affects the scores on the working memory task. The results of multiple regression analysis revealed that the total scores of occupational complexity significantly predicted digit span backward scores ($\beta = 0.51, p < 0.05$: Table 2) and verbal 2-back scores ($\beta = 0.4, p < 0.05$: Table 3). The total scores of occupational complexity were not significantly correlated with tapping span backward and spatial 2-back scores. The digit span backward scores ($\beta = 0.52, p < 0.05$: Table 2) and verbal 2-back task scores ($\beta = 0.47, p < 0.05$: Table 3) were significantly predicted by the occupational complexity “data” domain scores. The occupational complexity “data” domain scores were not correlated with tapping span backward and spatial 2-back scores, while the “people” and “things” domain scores were not significantly associated with any working memory variables. For details on the results of multiple regression analysis, see Supplementary tables 2 and 3.
| Predictor           | B   | β   | t    | p    | 95% CI    | R²  | Adj R² | F   |
|---------------------|-----|-----|------|------|-----------|-----|--------|-----|
| Regression          |     |     |      |      |           | 0.49| 0.39   | 4.76|
| Age                 | -0.04| -0.42| -2.51| 0.02| -0.07; 0.01|     |        |     |
| JART                | 0.04| 0.36| 2.21 | 0.04| 0.00; 0.07 |     |        |     |
| Education           | 0.00| 0.00| -0.03| 0.98| -0.26; 0.25|     |        |     |
| Occupation total    | 0.15| 0.51| 2.67 | 0.01| 0.03; 0.27 |     |        |     |
| Regression          |     |     |      |      |           | 0.47| 0.37   | 4.46|
| Age                 | -0.03| -0.39| -2.29| 0.03| -0.06; 0.00|     |        |     |
| JART                | 0.05| 0.49| 2.77 | 0.01| 0.01; 0.09 |     |        |     |
| Education           | -0.02| -0.03| -0.17| 0.87| -0.3; 0.25 |     |        |     |
| Occupation data     | 0.49| 0.53| 2.51 | 0.02| 0.08; 0.89 |     |        |     |
| Regression          |     |     |      |      |           | 0.39| 0.27   | 3.22|
| Age                 | -0.04| -0.40| -2.14| 0.05| -0.07; 0.00|     |        |     |
| JART                | 0.04| 0.38| 2.11 | 0.05| 0.00; 0.07 |     |        |     |
| Education           | 0.02| 0.04| 0.17 | 0.87| -0.27; 0.32|     |        |     |
| Occupation people   | 0.23| 0.38| 1.69 | 0.11| -0.05; 0.51|     |        |     |
| Regression          |     |     |      |      |           | 0.42| 0.30   | 3.56|
| Age                 | -0.03| -0.34| -1.93| 0.07| -0.06; 0.00|     |        |     |
| JART                | 0.02| 0.24| 1.37 | 0.19| -0.01; 0.06|     |        |     |
| Education           | 0.14| 0.22| 1.24 | 0.23| -0.10; 0.38|     |        |     |
| Occupation things   | 0.23| 0.35| 1.95 | 0.07| -0.02; 0.48|     |        |     |

Table 2. The results of multiple regression analysis for predicting digit span backward scores from age, JART, years of education, and occupational complexity variables (total score, data domain score, people domain score, and things domain score). CI: confidence interval, Adj R² = Adjusted R², JART: Japanese Adult Reading Test, Education: years of education, Occupation Total: Occupation complexity total score, Occupation data: Occupation complexity data domain score, Occupation people: Occupation complexity people domain score, Occupation things: Occupation complexity things domain score.
Discussion

The purpose of this study was to clarify whether SLF damage was associated with working memory impairments, and whether occupational experience, considered as a component of CR, predicted working memory after tumor resection in patients with frontal lobe lesions. Working memory was estimated using the digit span backward, tapping span backward, verbal 2-back, and spatial 2-back tasks, and the level of cognitive activity in the patients' main occupation was assessed using the occupational complexity variables. The results of multiple regression analysis for predicting scores of verbal 2-back task from age, JART, years of education, and occupational complexity variables (total score, data domain score, people domain score, and things domain score) CI: confidence interval, Adj R²: Adjusted R², JART: Japanese Adult Reading Test, Education: years of education, Occupation Total: Occupation complexity total score, Occupation data: Occupation complexity data domain score, Occupation people: Occupation complexity people domain score, Occupation things: Occupation complexity things domain score.

Table 3. The results of multiple regression analysis for predicting scores of verbal 2-back task from age, JART, years of education, and occupational complexity variables (total score, data domain score, people domain score, and things domain score) CI: confidence interval, Adj R²: Adjusted R², JART: Japanese Adult Reading Test, Education: years of education, Occupation Total: Occupation complexity total score, Occupation data: Occupation complexity data domain score, Occupation people: Occupation complexity people domain score, Occupation things: Occupation complexity things domain score.
index. In this study, we showed that a larger disconnection ratio of SLFs was significantly associated with lower working memory performance, and that occupational complexity scores significantly predicted working memory after tumor resection. Furthermore, we found that the occupational complexity “data” domain predicts verbal working memory scores. In recent years, the effects of CR have been investigated not only in dementia or aging, but also in a broader range of disorders, such as traumatic brain injury and stroke\cite{28,30,33}; however, no study had focused on occupational complexity as a CR in patients with frontal lobe tumors. To our knowledge, this is the first study to demonstrate that occupational complexity, as a CR, predicts working memory after tumor resection in patients with frontal lobe tumors.

To investigate the relationship between damage to the fronto-parietal networks and working memory after brain tumor resection, we analyzed the relationships between the disconnection ratio of the SLFs I, II, and III and working memory scores. The results of correlation analysis showed that SLFs’ disconnection ratio was significantly associated with working memory. Although spatial 2-back task scores were not significantly associated with SLFs’ disconnection ratio, an overall negative association was observed. In particular, a higher disconnection ratio of the right SLF I was associated with lower rates of correct responses in the spatial 2-back task (Supplementary Table 1). On the other hand, the significant negative associations between tapping span backward scores and the disconnection ratio of the left SLF II were unexpected, since visuospatial information processing has been considered to localize mainly in the right hemisphere. However, previous studies indicated that visuospatial working memory tasks recruited activation within broader areas, including the bilateral white matter networks\cite{5,36}. Therefore, our finding of negative associations between tapping span backward scores and the left SLF disconnection ratio is consistent with these reports.

We showed that higher occupational complexity is associated with higher verbal working memory after tumor resection. Previous studies in patients with brain lesions have shown that CR proxies, such as premorbid IQ and education, were associated with neuropsychological outcomes, including working memory\cite{32,28}. Furthermore, among the three domains of occupational complexity, scores of the “data” domain predicted verbal working memory scores. These results are consistent with previous studies showing that higher levels of occupational complexity, especially in the “data” domain, were associated with higher cognitive function, including working memory, in healthy participants\cite{37,38}.

Our findings that “people” and “things” occupational complexity were not significantly associated with working memory were unexpected. One possible explanation is that since the included patients belonged to a wide range of ages, we did not consider the tie that participants engaged in their primary occupation. In a previous study, for individuals whose principal occupation duration was > 23 years, “people” or “things” were associated with a lower risk of dementia\cite{25}. Occupation duration may also be an important factor affecting CR. Further studies considering occupation duration are needed to investigate the effects of CR on occupational complexity.

The present study showed no significant association between occupational complexity and spatial working memory, including the tapping span backward and spatial 2-back tasks. This result can be
explained by the feature of functional compensation, considered as one of the mechanisms governing the protective effect of CR. Functional compensation refers to recruiting alternative neural networks in order to cope with brain pathology. This compensation is related to brain anatomy, which leads to dynamic, redistributable, and reorganizable neural networks\[^{39}\]. A study focusing on compensation in CR found that individuals with high white matter hyperintensities and high education levels (i.e. individuals with larger brain damage and higher CR) compensatively recruited broader areas, including the putamen and thalamus, in addition to the fronto-parietal network, during working memory tasks\[^{40}\]. In the study of gliomas, the functional compensatory capacity has been shown to differ between cortical and subcortical regions, wherein white matter tracts experienced lower functional compensation than cortical areas\[^{41}\]. In addition, a previous study reported that right SLF I and II damage led to chronic impairments in spatial working memory\[^{6}\]. In our study, the disconnectome maps showed that the right SLF I and II were particularly damaged. Considering these findings, CR may not play a protective role by compensation if white matter tracts, such as SLFs, are damaged. With respect to verbal working memory, in addition to the DLPFC, the superior temporal gyrus and middle temporal gyrus, are highly compensatory regions, are also involved verbal working memory\[^{41}\],\[^{42}\],\[^{43}\],\[^{44}\]. Therefore, regarding the verbal working memory of patients with frontal lobe tumors, patients with higher CR can better cope with the decline in verbal working memory by using these highly compensatory networks, even if fronto-parietal networks are damaged. To elucidate the mechanism of CR in brain tumor patients, further studies are needed to clarify which neural networks are actually used as compensatory mechanisms.

The present study has several limitations. First, we did not include patients with severe brain lesions in this study. Thus, it is unclear whether occupational complexity as CR index affects working memory after tumor resection in patients with more severe lesions and cognitive impairment. Second, the sample size was relatively small, and the statistical power low. Overall, our results were consistent with previous studies; however, further investigation with an increased sample size is needed. Third, since this study is a cross-sectional study using data after tumor resection, we were not able to investigate changes in working memory before and after surgery. Therefore, further studies focusing on changes of working memory from preoperative to postoperative conditions are needed to clarify the protective effects of occupational complexity. Lastly, the present study has shown that patients engaged in occupations with higher complexity suffer less working memory impairments after tumor resection; however, the neural mechanisms underlying the protective effects of occupational complexity have not been elucidated. In patients with high levels of occupational complexity, it is unclear which compensatory brain areas are utilized to cope with working memory decline. To clinically apply CR in the future, further research elucidating the neural mechanisms of CR in patients with brain tumors is essential.

**Conclusion**

Working memory impairments have been reported after frontal lobe tumor resection. We found that damage to fronto-parietal white matter networks is associated with working memory impairments and occupational complexity, as CR plays a protective role against working memory impairments. The present
study is the first to show that a patient’s occupational complexity predicts their working memory after tumor resection. In particular, our results show that higher levels of occupational complexity were associated with verbal working memory. These findings support previous studies on the association between CR and cognitive deficits caused by brain damage due to neurological diseases. These findings can help us more accurately predict the severity of working memory deficits in the postoperative period of patients with frontal lobe tumors.

Methods

Participants

Twenty-seven patients with a tumor located within the frontal lobe (right hemisphere = 17, left hemisphere = 10) participated in this study (age: 52 ± 13.6 years). These patients were diagnosed with brain tumors including oligodendroglioma (n = 10), anaplastic astrocytoma or oligodendroglioma (n = 7), diffuse astrocytoma (n = 4), glioblastoma (n = 2), metastatic brain tumor (n = 2), dysembryoplastic neuroepithelial tumor (n = 1), and cavernous angioma (n = 1). Ten patients received radiotherapy. Exclusion criteria were severe cognitive impairments which led to difficulty performing working memory tasks and premorbid IQ scores < 70. Evaluation of occupational complexity and all neurocognitive assessments were performed post-surgery and neurocognitive data were retroactively obtained from clinical records. Participants underwent tumor resection at Kanazawa University Hospital. The demographic characteristics of participants’ are shown in Table 1. This study was approved by the medical ethics committee at Kanazawa University [No. 2018 − 140 (2897)], and performed with written informed consent from all participants after the procedures were fully described to them. This study was conducted in accordance with the guidelines of the Internal Review Board of Kanazawa University.

Evaluation of occupational complexity

Interviews were performed to examine the occupational history of all patients. We determined each occupational complexity score for domain data (range: 0.96–6.91), “people” (range: 1.07–8.8) and “thing” (range: 1.02–6.96) using the Japanese version of the occupational complexity scores based on the DOT 4th revision\[45\]. Occupational complexity scores were chosen for the patient’s main occupation in their occupational history.

Neurocognitive assessment

The digit span task in the backward condition was conducted using a subtest of the Clinical Assessment for Attention (CAT)\[46\]. In it, patients listened to a sequence of numbers presented orally and then immediately reproduced the numbers in the reverse order. The tapping span test was also a subtest of the CAT’s Japanese version to evaluate working memory for visuospatial information. In it, the patients memorized the order in which the tester pointed to the squares in sequence, and immediately afterwards pointed to the squares in the reverse order. For both digit span test and tapping span test, the number of digits achieved by the patients was scored. A higher number of achieved digits implies a higher working
memory performance. The spatial 2-back task\[^6\] was also used to examine working memory for visuospatial information. The stimuli in this task consist of circles that appear in one of nine different locations within the squares. A circular stimulus was presented in one of the nine locations on the screen for 3 seconds, and the patients were asked to judge whether the currently presented stimulus was in the same location as the stimulus presented in the two previous trials. The verbal 2-back task was administered to evaluate working memory for verbal information. The verbal stimuli consisted of Kana (Japanese syllabogram). Similar to the spatial 2-back task, patients responded whether the verbal stimulus presented was the same as that presented two trials earlier. For the spatial 2-back task and verbal 2-back task, 8 trials split in 4 blocks were performed, and the correct answer rate (%) was used as the score.

**Magnetic Resonance Image**

T1 MR images were acquired postoperatively using 3DT1-weighted sequences on a 3.0 Tesla MRI scanner (Signa Excite HDx 3.0T, General Electric Medical Systems).

**Disconnection analysis**

Patients’ MRI images were normalized into MNI space using SPM 12 (Statistical Parametric Mapping; https://www.fil.ion.ucl.ac.uk/spm/software/spm12/) implemented in a MATLAB environment (R2019a, version 9.6; The MathWorks, Inc). Next, MRlcron software (https://people.cas.sc.edu/rorden/mricron/index.html) was used to reconstruct resection cavities. All reconstruction resection cavities were first manually drawn by K. E. and subsequently checked by the experienced neurosurgeon (M. K.). The patients damage of white matter tracts was calculated using the Tractotron analysis in the BCB toolkit, which estimates the disconnection ratio of each white matter tract at the individual level. Tractotron determines the damage pattern induced by a lesion in the MNI152 space based on a recently published atlas of tractography-based white matter tracts[^47]. A disconnection rate > 50% is generally considered to represent a disconnection in the white matter tract. We focused on fronto-parietal network tracts which may play an important role in working memory included the bilateral SLF I, SLF II and SLF III.

**Disconnectome maps**

The Disconnectome maps software in the BCBtoolkit[^48] was used to visually represent the disconnected white matter tracts in each patient. The disconnectome map tracks the white matter pathway through each lesion’s region of interest using diffusion-weighted imaging data of healthy participants[^47]. Patients’ lesions in the MNI152 space are registered to each control native space using affine and diffeomorphic deformations[^49][^50] and subsequently used as seed for tractography in Trackvis[^51]. Tractographies from the lesions were transformed in visitation maps[^52], binarized and brought to the MNI152 space using the inverse of precedent deformations. Finally, we produced a percentage overlap map by summing the normalized visitation map of each healthy subject at each point in MNI space. Hence, in the resulting disconnectome map, the value in each voxel considers the interindividual variability of tract
reconstructions in controls, and indicates a probability of disconnection from 0 to 100% for a given lesion\cite{53}.

**Declarations**

**Acknowledgments**

This work was supported by JSPS KAKENHI through a Grant-in-Aid for Scientific Research (B) Number 19H01761 and Grant-in-Aid for Transformative Research Areas (A) Number 20H05803.

**Author Contributions**

In this study, M.M., M.K., and K.E. designed this study. M.M. administered neuropsychological tests and interview for CR to the patients. K.E. and D.S. conducted the statistical analyses and interpretation of neuropsychological data. K.E and M.K. analyzed imaging data. M.K. checked all imaging data. K.E. wrote the initial draft of the manuscript. M.M. and M.N. supervised this study administration. All authors critically revised the manuscript. All authors contributed to and have approved the final manuscript.

**Conflicts of interest**

The author(s) declare no competing interests.

**Data Availability**

The datasets analyzed in this study are available from the corresponding author on reasonable request.

**References**

1. Baddeley, A. Working Memory. *Science (80-. ).* 255, 556–559 (1992).
2. Barbey, A. K., Koenigs, M. & Grafman, J. Dorsolateral prefrontal contributions to human working memory. *Cortex* 49, 1195–1205 (2013).
3. Owen, A. M., McMillan, K. M., Laird, A. R. & Bullmore, E. N-back working memory paradigm: A meta-analysis of normative functional neuroimaging studies. *Hum. Brain Mapp.* 25, 46–59 (2005).
4. Rottschy, C. \textit{et al.} Modelling neural correlates of working memory: A coordinate-based meta-analysis. *Neuroimage* 60, 830–846 (2012).
5. Golestani, A. M. \textit{et al.} Constrained by our connections: White matter’s key role in interindividual variability in visual working memory capacity. *J. Neurosci.* 34, 14913–14918 (2014).
6. Kinoshita, M. \textit{et al.} Chronic spatial working memory deficit associated with the superior longitudinal fasciculus: A study using voxel-based lesion-symptom mapping and intraoperative direct stimulation in right prefrontal glioma surgery. *J. Neurosurg.* 125, 1024–1032 (2016).
7. Lazar, M. Working memory: How important is white matter? *Neuroscientist* 23, 197–210 (2017).
8. Smith, J. S. et al. Role of Extent of Resection in the Long-Term Outcome of Low-Grade Hemispheric Gliomas. *J. Clin. Oncol.* **26**, 1338–1345 (2008).

9. Aaronson, N. K. et al. Compromised Health-Related Quality of Life in Patients With Low-Grade Glioma. *J Clin Oncol* **29**, 4430–4435 (2011).

10. Habets, E. J. J. et al. Tumour and surgery effects on cognitive functioning in high-grade glioma patients. *Acta Neurochir. (Wien)*. **156**, 1451–1459 (2014).

11. Motomura, K. et al. Navigated repetitive transcranial magnetic stimulation as preoperative assessment in patients with brain tumors. *Sci. Rep.* **10**, 1–14 (2020).

12. Nakajima, R. et al. Direct evidence for the causal role of the left supplementary motor area in working memory: A preliminary study. *Clin. Neurol. Neurosurg.* **126**, 201–204 (2014).

13. Duffau, H. Stimulation mapping of white matter tracts to study brain functional connectivity. *Nat. Rev. Neurol.* **11**, 255–265 (2015).

14. Stern, Y. What is cognitive reserve? Theory and research application of the reserve concept. *J. Int. Neuropsychol. Soc.* **8**, 448–460 (2002).

15. Stern, Y. Cognitive reserve. *Neuropsychologia* **47**, 2015–2028 (2009).

16. Valenzuela, M. J. & Sachdev, P. Assessment of complex mental activity across the lifespan: Development of the Lifetime of Experiences Questionnaire (LEQ). *Psychol. Med.* **37**, 1015–1025 (2007).

17. Clinic, M., Bartrés-FazDavid, U. & Yaakov Stern, G. Whitepaper: Defining and investigating cognitive reserve, brain reserve and brain maintenance Reserve, Resilience and Protective Factors PIA Empirical Definitions and Conceptual Frameworks Workgroup Arenaza-UrquijoEider M. HHS Public Access. (2020).

18. Scarmeas, N. & Stern, Y. Cognitive reserve and lifestyle. *J. Clin. Exp. Neuropsychol.* **25**, 625–633 (2003).

19. Pool, L. R. et al. Occupational cognitive requirements and late-life cognitive aging. *Neurology* **86**, 1386–1392 (2016).

20. Anstey, K. & Christensen, H. Education, activity, health, blood pressure and apolipoprotein E as predictors of cognitive change in old age: A review. *Gerontology* **46**, 163–177 (2000).

21. Stern, Y., Alexander, G. E., Prohovnik, I. & Mayeux, R. Inverse relationship between education and parietotemporal perfusion deficit in Alzheimer’s disease. *Ann. Neurol.* **32**, 371–5 (1992).

22. Stern, Y. et al. Relationship between lifetime occupation and parietal flow: Implications for a reserve against Alzheimer’s disease pathology. *Neurology* **45**, 55–60 (1995).

23. Then, F. S. et al. Systematic review of the effect of the psychosocial working environment on cognition and dementia. *Occup. Environ. Med.* **71**, 358–365 (2014).

24. United States Department of Labor: *Dictionary of Occupational titles. 4th rev. ed.* JIST Works Inc. (1992).
25. Kröger, E. et al. Is complexity of work associated with risk of dementia? *Am. J. Epidemiol.* **167**, 820–830 (2008).

26. Andel, R. et al. Complexity of work and risk of Alzheimer’s disease: A population-based study of Swedish twins. *Journals Gerontol. - Ser. B Psychol. Sci. Soc. Sci.* **60**, 251–258 (2005).

27. Umarova, R. M. Adapting the concepts of brain and cognitive reserve to post-stroke cognitive deficits: Implications for understanding neglect. *Cortex* **97**, 327–338 (2017).

28. Umarova, R. M. et al. Cognitive reserve impacts on disability and cognitive deficits in acute stroke. *J. Neurol.* **266**, 2495–2504 (2019).

29. González-Fernández, M. et al. Formal education, socioeconomic status, and the severity of aphasia after stroke. *Arch. Phys. Med. Rehabil.* **92**, 1809–1813 (2011).

30. Kessels, R. P. C. et al. Effect of Formal Education on Vascular Cognitive Impairment after Stroke: A Meta-analysis and Study in Young-Stroke Patients. *J. Int. Neuropsychol. Soc.* **23**, 223–238 (2017).

31. Kesler, S. R. et al. Premorbid Intellectual Functioning, Education, and Brain Size in Traumatic Brain Injury: An Investigation of the Cognitive Reserve Hypothesis Premorbid Intellectual Functioning, Education, and Brain Size in Traumatic Brain Injury: An Investigation o. **4282**, 37–41 (2010).

32. Sumowski, J. F., Chiaravalloti, N., Krch, D., Paxton, J. & Deluca, J. Education attenuates the negative impact of traumatic brain injury on cognitive status. *Arch. Phys. Med. Rehabil.* **94**, 2562–2564 (2013).

33. MacPherson, S. E. et al. Cognitive Reserve Proxies Do Not Differentially Account for Cognitive Performance in Patients with Focal Frontal and Non-Frontal Lesions. *J. Int. Neuropsychol. Soc.* **1–10** (2020).

34. Leary, J. B. et al. The Association of Cognitive Reserve in Chronic-Phase Functional and Neuropsychological Outcomes Following Traumatic Brain Injury. *J. Head Trauma Rehabil.* **33**, E28–E35 (2018).

35. Nunnari, D., Bramanti, P. & Marino, S. Cognitive reserve in stroke and traumatic brain injury patients. *Neurol. Sci.* **35**, 1513–1518 (2014).

36. Lamp, G., Alexander, B., Laycock, R., Crewther, D. P. & Crewther, S. G. Mapping of the underlying neural mechanisms of maintenance and manipulation in visuo-spatial working memory using an n-back mental rotation task: A functional magnetic resonance imaging study. *Front. Behav. Neurosci.* **10**, 1–10 (2016).

37. Sörman, D. E., Hansson, P., Pritschke, I. & Ljungberg, J. K. Complexity of primary lifetime occupation and cognitive processing. *Front. Psychol.* **10**, 1–12 (2019).

38. Smart, E. L., Gow, A. J. & Deary, I. J. Occupational complexity and lifetime cognitive abilities. *Neurology* **83**, 2285–2291 (2014).

39. Duffau, H. Lessons from brain mapping in surgery for low-grade glioma: Insights into associations between tumour and brain plasticity. *Lancet Neurol.* **4**, 476–486 (2005).
40. Fernández-Cabello, S. et al. White matter hyperintensities and cognitive reserve during a working memory task: a functional magnetic resonance imaging study in cognitively normal older adults. *Neurobiol. Aging* **48**, 23–33 (2016).

41. Herbet, G., Maheu, M., Costi, E., Lafargue, G. & Duffau, H. Mapping neuroplastic potential in brain-damaged patients. *Brain* **139**, 829–844 (2016).

42. Wager, T. D. & Smith, E. E. Neuroimaging studies of working memory: A meta-analysis. *Cogn. Affect. Behav. Neurosci.* **3**, 255–274 (2003).

43. Ivanova, M. V. et al. Neural mechanisms of two different verbal working memory tasks: A VLSM study. *Neuropsychologia* **115**, 25–41 (2018).

44. Emch, M., von Bastian, C. C. & Koch, K. Neural correlates of verbal working memory: An fMRI meta-analysis. *Front. Hum. Neurosci.* **13**, 1–17 (2019).

45. Nagamatsu, N., Sakaguchi, Y. & Tarohmaru, H. Formulation of Job Complexity Score: Proposal for an Occupational Index that Reflects Job Content Namie. *Sociol. Theory Methods* **24**, 77–93 (2009).

46. *Clinical Assessment for Attention*. Japan Society for Higher Brain Dysfunction. Shinko-Igaku Press (2006).

47. Rojkova, K. et al. Atlasing the frontal lobe connections and their variability due to age and education: a spherical deconvolution tractography study. *Brain Struct. Funct.* **221**, 1751–1766 (2016).

48. Foulon, C. et al. Advanced lesion symptom mapping analyses and implementation as BCBtoolkit. *Gigascience* **7**, 1–17 (2018).

49. Klein, A. et al. Evaluation of 14 nonlinear deformation algorithms applied to human brain MRI registration. *Neuroimage* **46**, 786–802 (2009).

50. Avants, B. B. et al. A reproducible evaluation of ANTs similarity metric performance in brain image registration. *Neuroimage* **54**, 2033–2044 (2011).

51. Wang, R. & Benner, T. Diffusion toolkit: a software package for diffusion imaging data processing and tractography. *Proc Intl Soc Mag Reson Med* **15**, 3720 (2007).

52. Thiebaut de Schotten, M. et al. Atlasing location, asymmetry and inter-subject variability of white matter tracts in the human brain with MR diffusion tractography. *Neuroimage* **54**, 49–59 (2011).

53. Thiebaut De Schotten, M. et al. From phineas gage and monsieur leborgne to H.M.: Revisiting disconnection syndromes. *Cereb. Cortex* **25**, 4812–4827 (2015).