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‘Whose atlas I use, his song I sing?’ − The impact of anatomical atlases on fiber tract contributions to cognitive deficits after stroke

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Abstract

Nowadays, different anatomical atlases exist for the anatomical interpretation of the results from neuroimaging and lesion analysis studies that investigate the contribution of white matter fiber tract integrity to cognitive (dys)function. A major problem with the use of different atlases in different studies, however, is that the anatomical interpretation of neuroimaging and lesion analysis results might vary as a function of the atlas used. This issue might be particularly prominent in studies that investigate the contribution of white matter fiber tract integrity to cognitive (dys)function. We used a single large-sample dataset of right brain damaged stroke patients with and without cognitive deficit (here: spatial neglect) to systematically compare the influence of three different, widely-used white matter fiber tract atlases (1 histology-based atlas and 2 DTI tractography-based atlases) on conclusions concerning the involvement of white matter fiber tracts in the pathogenesis of cognitive dysfunction. We both calculated the overlap between the statistical lesion analysis results and each long association fiber tract (topological analyses) and performed logistic regressions on the extent of fiber tract damage in each individual for each long association white matter fiber tract (hodological analyses). For the topological analyses, our results suggest that studies that use tractography-based atlases are more likely to conclude that white matter integrity is critical for a cognitive (dys)function than studies that use a histology-based atlas. The DTI tractography-based atlases classified approximately 10 times as many voxels of the statistical map as being located in a long association white matter fiber tract than the histology-based atlas. For hodological analyses on the other hand, we observed that the conclusions concerning the overall importance of long association fiber tract integrity to cognitive function do not necessarily depend on the white matter atlas used, but conclusions may vary as a function of atlas used at the level of individual fiber tracts. Moreover, these analyses revealed that hodological studies that express the individual extent of injury to each fiber tract as a binomial variable are more likely to conclude that white matter integrity is critical for a cognitive function than studies that express the individual extent of injury to each fiber tract as a continuous variable.

Keywords

White matter atlas; Diffusion MRI; Tractography; Histology; Lesion analysis

1 Introduction

The analysis of neuroimaging data in healthy subjects and the analysis of brain lesion locations in neurological patients are frequently-used approaches to investigate the neuroanatomy associated with cognitive functions in humans. While these techniques differ in many of their analysis details and contribute complementary information, they have in common that as a final step of the analyses a statistical map of significantly activated or lesioned voxels is related to an anatomical atlas. This step allows us to identify the brain structures involved and thus represents a critical stage in the data analysis pipeline.

Nowadays, there are several different atlases to choose from. Atlases can be derived from single-subject or multi-subject data, where multi-subject (probabilistic) atlases are preferable as they are able to quantify the intersubject variability in location and extent of each anatomical structure. Additionally, the parcellation of distinct structures in atlases can be based on different characteristics of the underlying brain, e.g. macrostructure, cytoarchitecture, etc. The use of different atlases in different studies, however, potentially represents a significant problem: the anatomical interpretation of neuroimaging and lesion analysis results might vary as a function of the atlas used. This issue might be particularly prominent in studies that investigate the contribution of white matter fiber tract integrity to cognitive (dys)function, i.e. in studies that aim to assess whether a certain white matter structure contributes or not.

There are currently several multi-subject probabilistic white matter fiber tract atlases to choose from, the most popular ones being the histology-based Jülich probabilistic cytoarchitectonic fiber tract atlas (“Jülich atlas”, Bürgel et al., 2006), the tractography-based probabilistic fibers atlas from the Mori group (“Mori atlas”, Zhang et al., 2010) and the tractography-based diffusion atlas of white matter fiber tracts from the Catani group (“Catani atlas”, Thiebaut de Schotten et al., 2011), each containing most major long association white matter fiber tracts. However, it is immediately obvious when inspecting the probabilistic fiber tract maps from these atlases (see for example Figure 4 in Thiebaut de Schotten et al., 2011, as well as Figure 2 in the current paper) that the volumes of the long association fiber tracts from the tractography-based Mori and Catani atlases are considerably larger than the volumes of the long association fiber tracts from the histology-based Jülich atlas. This could mean that an activated or lesioned voxel is more likely to be classified as being located in a long

association white matter fiber tract when using the Mori and Catani atlases than when using the Jülich atlas, and that thus these different white matter atlases might result in different conclusions concerning the involvement of white matter fiber tracts in cognitive (dys)function.

As such, the aim of the current paper is to investigate this possibility. In theory, we could have focused on any cognitive (dys)function. Here, we used a single large-sample dataset, consisting of 140 right brain damaged stroke patients with and without spatial neglect, to systematically compare the influence of three different, widely-used white matter fiber tract atlases (Jülich, Mori or Catani) on conclusions concerning the involvement of white matter fiber tracts in the pathogenesis of cognitive dysfunction.

Previous findings have supported different conclusions concerning the importance of intrahemispheric long association white matter fiber tract damage to spatial neglect. Whereas the results of some studies suggest that white matter damage is a minor predictor of spatial neglect (Karnath et al., 2009, 2011), the results from other studies suggest that white matter damage is a major predictor of spatial neglect (i.e. Lunven et al., 2015; Thiebaut de Schotten et al., 2014; Verdon et al., 2010). Interestingly, however, these different anatomical papers used different white matter fiber tract atlases. While those papers that found that white matter damage is a minor predictor of spatial neglect (Karnath et al., 2009, 2011) used the histology-based Jülich atlas, those papers that found that white matter damage is a major predictor of spatial neglect (i.e. Lunven et al., 2015; Thiebaut de Schotten et al., 2014; Verdon et al., 2010) used one of the tractography-based DTI atlases. Thus, it is theoretically possible that these different conclusions concerning the importance of intrahemispheric long association white matter fiber tract damage to spatial neglect can be (partly) attributed to the white matter atlas used to determine whether a voxel-coordinate was located in a white matter fiber tract or not.

2 Materials and Methods

2.1 Lesion data

The lesion dataset consisted of 140 lesions maps obtained from patients with acute right hemisphere stroke. This dataset was collected as part of a study on the neuroanatomy of acute

spatial neglect (Karnath et al., 2004). Full details concerning patient characteristics, clinical assessment, imaging protocols, lesion delineation etc. can be found in our previous work (Karnath et al., 2004). Briefly, following standardized neuropsychological testing for spatial neglect, patients were divided into a group of 78 patients with spatial neglect and a group of 62 control patients without spatial neglect. We opted to keep the behavioural data binomial, to allow comparison with previous studies where most of the evidence for or against a major role for white matter damage in spatial neglect was obtained using a binomial measure of neglect (Karnath et al., 2009; Verdon et al., 2010; Thiebaut de Schotten et al., 2014). Magnetic resonance imaging (MRI) or computerized tomography (CT) was conducted in each patient to visualise the location of the lesion. At that time, lesions were manually drawn on axial slices of a T1-weighted MRI template scan located in standard MNI stereotaxic space (Colin 27 average brain https://www.bic.mni.mcgill.ca/ServicesAtlases/Colin27) using MRIcro software (Rorden and Brett, 2000). Lesions were mapped onto the slices that correspond to z-coordinates -40, -32, -24, -16, -8, 0, 8, 16, 24, 32, 40, 50 and 60 mm in standard stereotaxic space using the identical or the closest matching axial slices of each individual.

2.2 Fiber tract atlases

We used fiber tract data from the 3 previously mentioned freely available probabilistic fiber tract atlases, each providing the probability that a certain fiber tract was observed in a normal population for each voxel in the brain. The first atlas was the histology-based Jülich atlas ("Jülich atlas"; Bürgel et al., 2006), which used a modified myelin-staining technique to identify fiber tracts in 10 post-mortem human brains. This atlas describes, for each voxel in the brain, the relative frequency that a certain fiber tract was present, ranging from 0% (tract present in 0 of the 10 post-mortem brains) to 100% (tract present in 10 of the 10 post-mortem brains) in steps of 10%. The second atlas was the tractography-based Mori atlas (Zhang et al., 2010), which used deterministic diffusion tensor imaging (DTI) fiber tracking to identify fiber tracts in 20 participants. This atlas describes, for each voxel in the brain, the relative frequency that a certain fiber tract was present ranging from 0% (tract present in 0 of the 20 participants) to 100% (tract present in 20 of the 20 participants) in steps of 5%. The third atlas was the tractography-based atlas Catani atlas (Thiebaut de Schotten et al., 2011), which used deterministic DTI fiber tracking to identify fiber tracts in 40 participants. This atlas describes, for each voxel in the brain, the relative frequency that a certain fiber tract was present using the probability values >50% (tract present in more than 20 of the 40

participants), >75% (tract present in more than 30 of the 40 participants) and >90% (tract present in more than 36 of the 40 participants).

From each atlas, we used 4 long association fiber tracts of the right hemisphere, namely the cingulum (Cing), inferior occipital fasciculus (IOF), superior longitudinal fasciculus/arcuate fasciculus (SLF/AF) and uncinate fasciculus (UF). We chose these fiber tracts as the long association fiber tracts are thought to be most relevant to higher cognitive functions and, critically, because these 4 long association fiber tracts were present in all 3 atlases which allowed us to meaningfully compare the atlases. Each atlas was transformed to standard MNI stereotaxic space when necessary. Since both the cingulum (Cing) and the superior longitudinal fasciculus / arcuate fasciculus (SLF/AF) were divided into several smaller overlapping sub-tracts in some, but not all of the atlases, we additionally calculated a maximum probability summary map for these fiber tracts to enable comparisons between atlases. This maximum probability summary map was obtained by first calculating a maximum probability map for each sub-tract of the fiber tract (e.g. in the case of 3 sub-tracts, voxels where the fiber tract probability for sub-tract 1 is higher than both the fiber tract probability of sub-tract 2 and the fiber tract probability of sub-tract 3, etc.) and then adding these mutually exclusive maximum probability maps of the sub-tracts together. In all subsequent comparisons between the atlases we used these maximum probability summary maps.

2.3 Fiber tract analysis: voxelwise topological analyses

In our first approach, we used a statistical map that contained the voxels where the presence of a lesion was significantly associated with the presence of spatial neglect (see Figure 1). This statistical map was originally generated in a previous study using the same patient data (Karnath et al., 2009). To identify, for each atlas, the fiber tracts associated with the presence of spatial neglect, we calculated the percentage of the statistical map that overlapped with each of the 4 long association fiber tracts (i.e. what proportion of the differential damage between patients with and without neglect can be attributed to fiber tract damage). Note that this approach corresponds to the standard use of an anatomical atlas where the atlas is used to determine in which structures of the brain the significant results are located. We expected this percentage overlap to vary systematically as a function of atlas-specific fiber tract volumes.

We first compared the Jülich and the Mori atlas including every voxel of each tract, i.e. all voxels with a fiber tract probability of >0%. We could not include the Catani atlas in this first comparison, as this atlas does not contain fiber tract probability values equal to or smaller than 50%. In a second step, we then compared all 3 atlases, including only those voxels of each tract with a fiber tract probability of >50%.

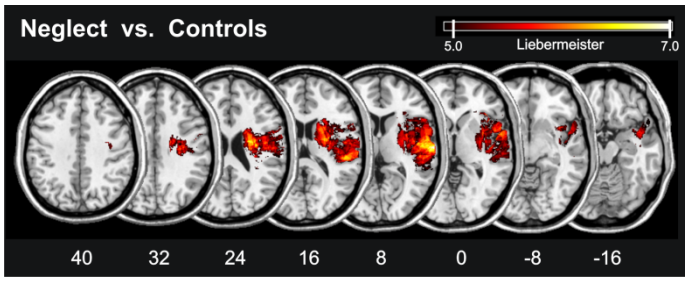

Figure 1: The statistical map containing the results of a voxel-wise statistical lesion-behaviour mapping analysis of 140 right-sided stroke patients with the Liebermeister test. This figure shows the voxels where the presence of a lesion was significantly associated with the presence of spatial neglect in the acute phase of stroke, Bonferroni corrected for multiple comparisons at a p-threshold of .05. The image is in neurological orientation and slice numbers reflect MNI z-coordinates. Taken from Karnath et al. (2009), with permission from Oxford University Press.

2.4 Fiber tract analysis: tract-wise hodological analyses

When investigating which fiber tracts are associated with the presence of a neuropsychological deficit, the classical voxelwise topological approach might underestimate the importance of fiber tracts (Rudrauf et al., 2008). In contrast to cortical areas, the behavioural consequences of damage to a long-range fiber tract might be identical regardless of where along the tract the damage occurs, even if the actual lesions of patients with damage to a certain tract do not necessarily overlap. As such, a tract-wise hodological approach, quantifying the extent of damage to a certain fiber tract in each individual patient, might be more sensitive to the potential contribution of a fiber tract to a neuropsychological deficit. Thus, in our second approach, we calculated, for each atlas, the extent of injury to each of the 4 long association fiber tracts for each individual patient on a voxel-by-voxel basis. Subsequently, we performed logistic regressions for each atlas. In these logistic regressions, we predicted the absence or presence of spatial neglect using the individual extent of injury to each long association fiber tract as a predictor and individual lesion size as a covariate of no interest. Note that, while this approach might be more sensitive to white matter contributions, it completely ignores potential (topological) grey matter structure contributions.

First, we performed these logistic regressions for the Jülich and Mori atlases, calculating the individual extent of injury to each long association fiber tract including every voxel of every tract, i.e. all voxels with a fiber tract probability of >0%. In these logistic regressions the individual extent of injury to each long association fiber tract was expressed as a continuous variable "percentage of fiber tract damaged", which we obtained by determining for each individual patient the percentage of the tract damaged, weighting each lesioned voxel by its fiber tract probability value (analogously to the approach taken in Karnath et al., 2009). In other words, for each fiber tract of each atlas, we performed the following steps: (1) We calculated the volume of the intersection between each individual patient lesion and the fiber tract map, weighting each voxel in the intersection map by the fiber tract probability value at that voxel coordinate. (2) We divided this weighted intersection volume by the total volume of the fiber tract, again weighting each voxel in this fiber tract map by its fiber tract probability value. In a second step, we performed these logistic regressions for all 3 atlases, calculating the individual extent of injury to each long association fiber tract, including only those voxels of each tract with a fiber tract probability higher than 50% to allow inclusion of the Catani atlas. In these logistic regressions, we again used the continuous "percentage of fiber tract damaged" variable as an indicator of the individual extent of injury to each long association fiber tract, but we additionally also used a binomial measure "presence or absence of fiber tract disconnection" as an indicator of the extent of injury to each long association fiber tract. This binomial variable was obtained by determining for each individual patient whether or not the lesion included at least 1 voxel where the fiber tract probability was higher than 50% (analogously to the approach taken in Thiebaut de Schotten et al., 2014). In other words, for each fiber tract of each atlas, we performed the following steps: (1) We created a thresholded map that solely contained the voxels where the fiber tract probability was higher than 50%. (2) We determined for each individual patient whether or not there was any overlap between the lesion map and this thresholded map.

Overall, we expected the overlap of the individual lesion maps with each long association fiber tract to vary systematically as a function of atlas-specific fiber tract volumes. However, for the continuous variable "percentage of fiber tract damaged", a larger fiber tract volume would result in both a larger numerator (overlap likely to be larger for larger fiber tracts) and a larger denominator (larger size of the fiber tracts), which should mitigate the mere effect of tract volume. As such, we did not expect these differences in tract volumes between the atlases to result in systematic differences in the percentage of fiber tract damaged by the

individual lesion maps. As a consequence, should there be differences in the average percentage of fiber tract damaged between patients with and patients without neglect, we did not expect these differences to differ systematically as a function of the difference in tract volumes between the atlases. Moreover, we likewise did not expect systematic differences in the results of the logistic regressions as a function of the difference in tract volumes between the atlases.

On the other hand, for the binomial variable "presence or absence of fiber tract disconnection" we expected the overall percentage of patients with fiber tract disconnection to be systematically larger for fiber tracts from an atlas in which fiber tract volumes tend to be larger than for the same fiber tracts from an atlas in which fiber tract volumes tend to be smaller. The effect this would have on any differences in the percentage of patients with fiber tract disconnection between patients with and patients without neglect and the results of the logistic regressions is, however, virtually impossible to predict. This would depend on whether the increase in percentage of patients with fiber tract disconnection with increasing tract volumes within each patient group can be expressed as a fixed constant or a scaling factor and on whether this increase in percentage of patients with fiber tract disconnection is comparable within each patient group.

3 Results

3.1 Fiber tract atlases

As can be seen from Figure 2, long association fiber tract volumes tended to be larger in the DTI atlases from the Catani and Mori groups than in the histological atlas from the Jülich group (see also Inline Supplementary Table 1 and Inline Supplementary Figure 1). To statistically assess this observation, we compared the tract volumes between the atlases. We first compared the tract volumes between the Jülich and the Mori atlas using all fiber probabilities with a Mann-Whitney-U test for independent samples. This analysis revealed that the tract volumes of the 4 long association fiber tracts were significantly larger in the Mori atlas than in the Jülich atlas ($U = 16$, $z = 2.309$, $p = .0145$). Secondly, we compared the tract volumes between all 3 atlases using the parts of the fiber tract where the fiber tract probability was higher than 50% with a Kruskal-Wallis test for independent samples. This analysis revealed that the tract volumes between the 3 atlases were significantly different (H_2

= 7.423, p = .024). Posthoc Mann-Whitney-U tests demonstrated that tract volumes were significantly larger in both the Mori (U = 16, z = 2.309, p = .0435), and the Catani (U = 0, z = 2.309, p = 0.0435) atlas when compared to tract volumes in the Jülich atlas, whereas the tract volumes did not differ significantly between the Mori and the Catani atlas (U = 9, z = 0.289, p > .9999). Reported p-values were Bonferroni corrected for multiple comparisons when appropriate.

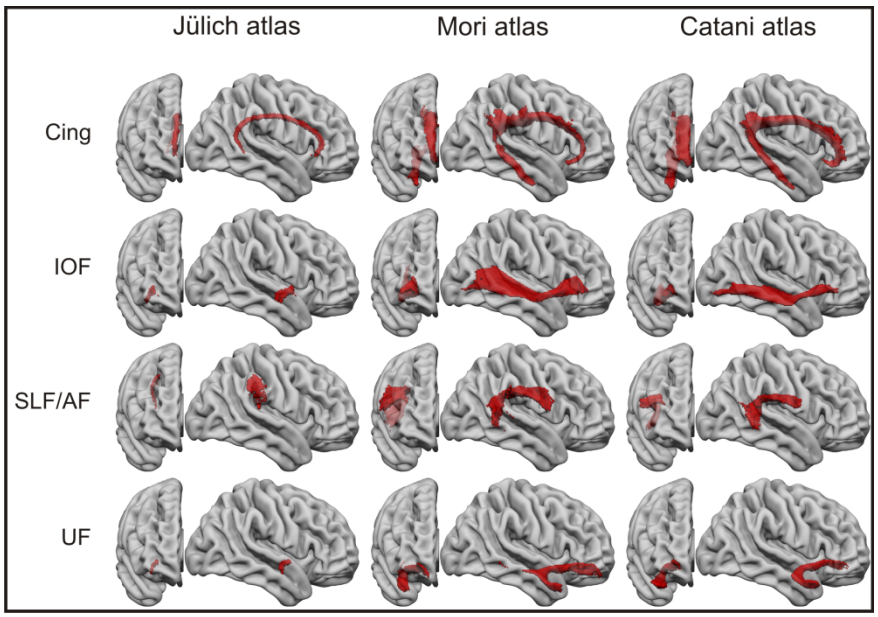

Figure 2: The 4 long association fiber tracts used from each atlas. To allow the depiction of all 3 atlases, only voxels where the fiber tract probability value was higher than 50% are shown for each fiber tract and atlas (see Inline Supplementary Figure 1 to see all voxels where the fiber tract probability value was higher than 0% for each fiber tract of the Jülich and Mori atlas). For each fiber tract from each atlas, a coronal (left) and sagittal (right) view is shown. All images are shown in neurological orientation. Surface rendering of both fiber tracts and brain were performed with SurfIce (https://www.nitrc.org/projects/surfice/). The resulting images thus display a transparent view of the fiber tracts within the brain. Abbreviations: Cing = cingulum, IOF = inferior occipital fasciculus, SLF = superior longitudinal fasciculus, AF = arcuate fasciculus, UF = uncinate fasciculus.

3.2 Fiber tract analysis: voxelwise topological analyses

The percentage of the statistical map, indicating voxels where the presence of lesion was associated with the presence of spatial neglect, that overlapped with each of the 4 long association fiber tracts for each of the atlases, is shown in Figure 3. In line with the observation that tract volumes are larger in the DTI atlases from the Mori and the Catani groups than in the histological atlas from the Jülich group, a larger percentage of the statistical map was classified as a long association fiber tract when using the DTI atlases than when using the histological atlas. When using all fiber tract probabilities, the Jülich atlas

classified in total 4.4% of the statistical map as one of the 4 long association fiber tracts, whereas the Mori atlas classified in total 26.9% of the statistical map. Thus, the Mori atlas classified 6.2 times as many voxels of the statistical map as one of the 4 long association fiber tracts than the Jülich atlas. When using only fiber tract probabilities larger than 50% to allow inclusion of the Catani atlas in the comparison, the Jülich atlas classified in total 0.3% of the statistical map as one of the 4 long association fiber tracts, whereas the Mori and Catani atlas classified respectively 3.3% and 2.6% of the statistical map as one of the 4 long association fiber tracts. Thus, the Mori and Catani atlas now classified respectively 12.0 and 9.7 times as many voxels of the statistical map as one of the 4 long association fiber tracts than the Jülich atlas. This difference between the atlases was particularly pronounced for the SLF/AF.

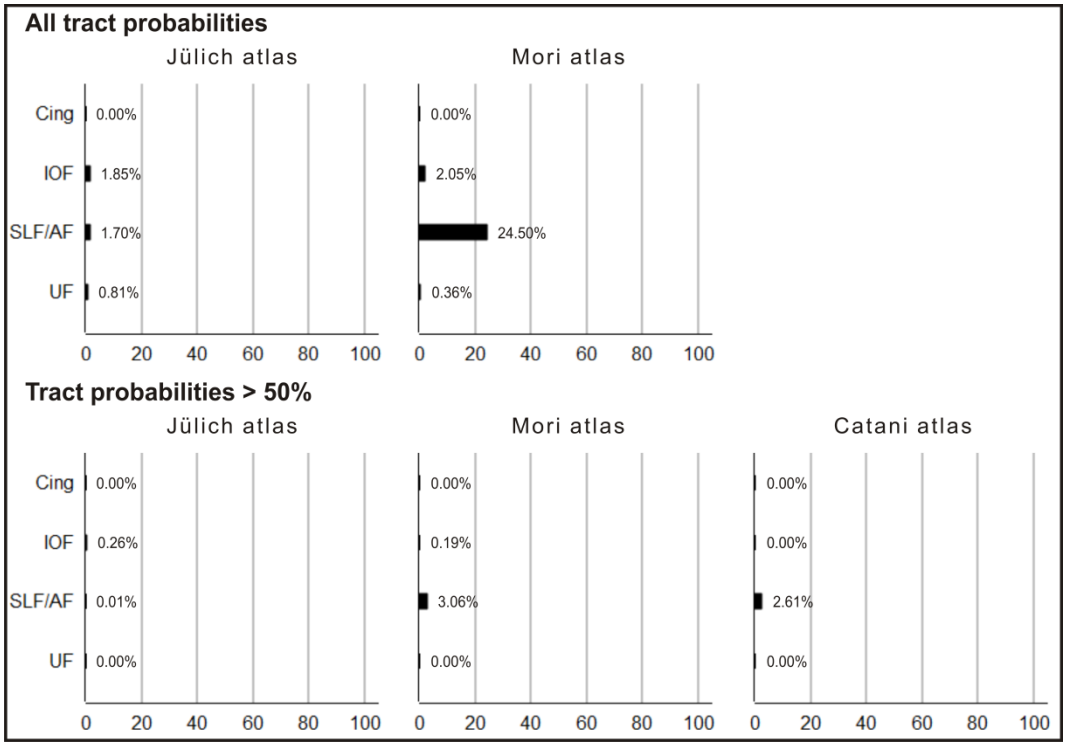

Figure 3: Percentage of the statistical lesion map that overlapped with each of the 4 long association fiber tracts for each atlas. Percentages overlap are given both using the entire fiber tract (all tract probabilities) and using only the part of the fiber tract where fiber tract probability was higher than 50%. Abbreviations as in Figure 2.

3.3 Fiber tract analysis: tract-wise hodological analyses

3.3.1 Percentage of fiber tract damaged. The results from the tract-wise hodological approach using all fiber tract probability values and the continuous variable "percentage of fiber tract damaged" are shown in Figure 4 (upper row) and Table 1 (upper part). As can be seen in Figure 4 and in line with our predictions, the value of the continuous variable "percentage of fiber tract damaged" (ranging from 0% to 100%) was comparable between the histological

Jülich atlas and the Mori DTI atlas. Likewise, the difference in the average percentage of fiber tract damaged between patients with and patients without neglect was comparable between these atlases. Specifically, the mean percentage of fiber tract damaged was 10.0% when using the Jülich atlas (17.0% in patients with and 3.1% in patients without neglect) and 10.8% when using the Mori atlas (16.3% in patients with and 5.2% in patients without neglect). The results from the logistic regressions (Table 1, upper part) suggest that there were no fiber tracts in either atlas where the continuous variable "percentage of fiber tract damaged" could significantly predict the presence of spatial neglect. However, in the Cing of the Jülich atlas, the percentage of fiber tract damaged significantly predicted the absence of spatial neglect after correcting for the effect of lesion size. Odds ratios indicated that the effect size was relatively small: a 1% increase in the percentage of the Cing damaged increased the likelihood of not having neglect by a factor of 1.149. For all other fiber tracts from all atlases, the percentage of fiber tract damaged did not significantly predict the absence of spatial neglect.

The results from the tract-wise hodological approach using only fiber tract probability values higher than 50% are shown in Figure 4 (lower row) and Table 1 (lower part). Again, both the percentage of fiber tract damaged and the difference in percentage of fiber tract damaged between patients with and patients without neglect were comparable between the atlases. Specifically, the mean percentage of fiber tract damaged was 10.0% when using the Jülich atlas (17.1% in patients with and 2.9% in patients without neglect), 12.4% when using the Mori atlas (19.3% in patients with and 5.5% in patients without neglect) and 11.1% when using the Catani atlas (17.4% in patients with and 4.9% in patients without neglect). The results from the logistic regressions (Table 1, lower part) suggest that the percentage of fiber tract damaged could significantly predict the presence of spatial neglect in the UF of the Jülich atlas after correcting for the effect of lesion size. Again, odds ratios indicated that the effect size was relatively small: a 1% increase in the percentage of the UF damaged increased the likelihood of having neglect by a factor of 1.037. For all other fiber tracts from all atlases, the percentage of fiber tract damaged did not significantly predict the presence or absence of spatial neglect.

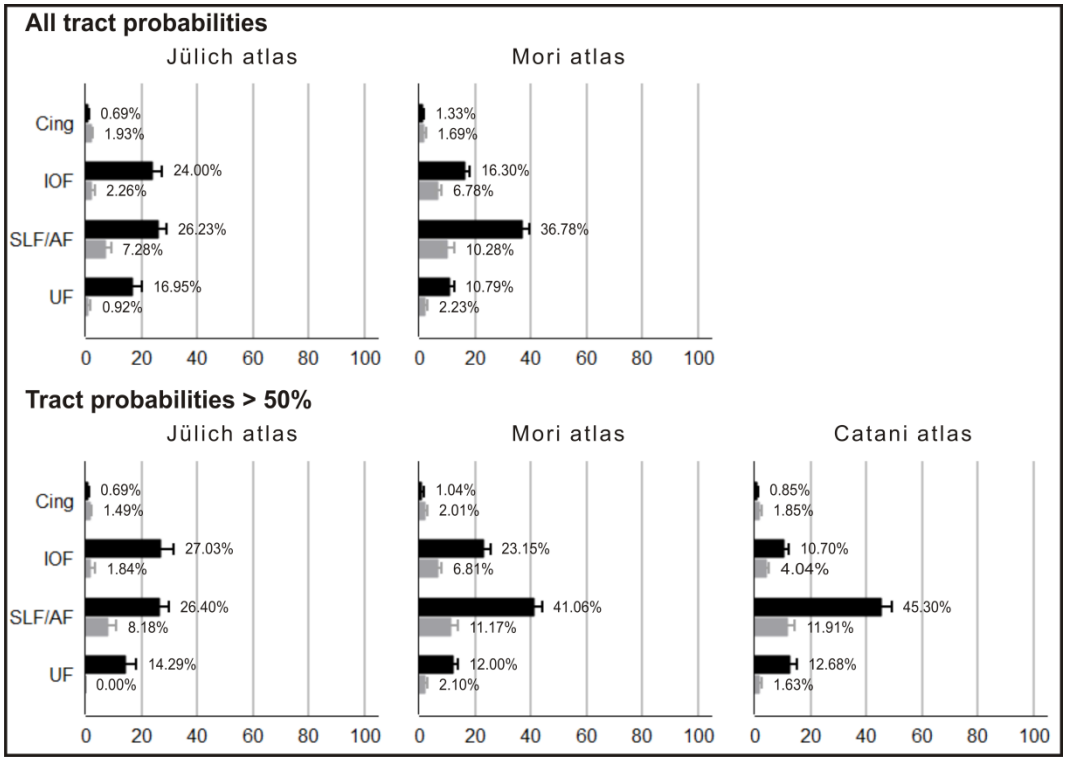

Figure 4: Percentage of damage to each of the 4 long association fiber tracts for each atlas. Percentage of damage is given using either all fiber tract probability values (upper row) or only fiber tract probability values > 50% (lower row). Moreover, the percentage of fiber tract damaged is given separately for patients with neglect (black bars) and patients without neglect (grey bars). Error bars reflect standard error of the mean. Abbreviations as in Figure 2.

Table 1: Results (odds ratios with p-value in brackets) from the logistic regressions to predict the presence or absence of spatial neglect using the percentage of fiber tract damaged in each of the 4 long association fiber tracts as a predictor. Logistic regressions were calculated using either all fiber tract probabilities (upper part) or only fiber tract probabilities > 50% (lower part).

All tract probabilities

	Jülich atlas	**Mori atlas**
Cing	0.870 (.044)	0.991 (.352)
IOF	1.031 (.204)	1.062 (.220)
SLF/AF	1.020 (.552)	1.006 (>.999)
UF	1.047 (.216)	1.001 (>.999)

Tract probabilities > 50%

	Jülich atlas	**Mori atlas**	**Catani atlas**
Cing	0.928 (.340)	0.893 (.060)	0.854 (.096)
IOF	1.024 (.196)	0.995 (>.999)	0.985 (>.999)
SLF/AF	1.008 (>.999)	1.001 (>.999)	1.014 (.748)
UF	1.037 (.044)[a]	1.009 (>.999)	1.022 (>.999)

Lesion size was included as a regressor of no interest. All p-values reported were Bonferroni corrected for multiple comparisons. [a] In light of quasi-complete separation (none of the lesion maps of patients without neglect overlapped with the fiber tract), Firth's penalized likelihood logistic regression was used. Abbreviations as in Figure 2.

3.3.2 Fiber tract disconnection. The results from the tract-wise hodological approach using the binomial variable "presence or absence of fiber tract disconnection" are shown in Figure 5 and Table 2. As can be seen in Figure 5 and in line with our predictions, the overall percentage of patients with fiber tract disconnection was systematically higher when using the larger tract volumes from the DTI atlases than when using the smaller tract volumes from the histological Jülich atlas. Specifically, the percentage of patients with fiber tract disconnection was 23.4% when using the Jülich atlas (34.6% in patients with and 12.1% in patients without neglect), 49.8% when using the Mori atlas (62.2% in patients with and 37.5% in patients without neglect) and 45.4% when using the Catani atlas (59.3% in patients with and 31.5% in patients without neglect). In other words, the percentage of patients with fiber tract disconnection was roughly doubled when using the DTI atlases compared to when using the histological atlas. Nevertheless, the difference in the percentage of patients with fiber tract disconnection between patients with and patients without neglect was comparable between the atlases (Jülich atlas: 22.5, Mori atlas: 24.7, Catani atlas: 27.8). The presence of fiber tract disconnection of the UF of the Jülich atlas and the SLF/AF of the Mori atlas each significantly predicted the presence of spatial neglect after correcting for the effect of lesion size. Odds ratios indicated that patients with disconnection of the UF of the Jülich atlas were almost 19 times more likely to suffer from neglect than patients without disconnection.

Patients with disconnection of the SLF/AF of the Mori atlas were almost 5 times more likely to suffer from neglect than patients without disconnection. Moreover, the presence of fiber tract disconnection of the Cing of the Jülich atlas significantly predicted the absence of spatial neglect after correcting for the effect of lesion size. Odds ratios indicated that patients with disconnection of the Cing of the Jülich atlas were more than 9 times more likely not to suffer from neglect than patients without disconnection. For all other fiber tracts from all atlases, the presence or absence of fiber tract disconnection did not significantly predict the presence or absence of neglect (Table 2).

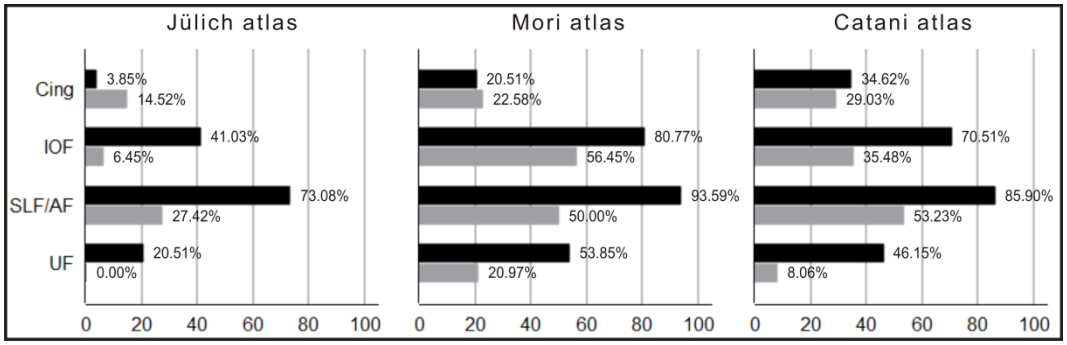

Figure 5: Percentage of patients with disconnection to each of the 4 long association fiber tracts for each atlas. The percentage of patients with fiber tract disconnection is given separately for patients with neglect (black bars) and patients without neglect (grey bars). Abbreviations as in Figure 2.

Table 2: Results (odds ratios with p-values in brackets) from the logistic regressions to predict the presence or absence of spatial neglect using the presence or absence of fiber tract disconnection of each of the 4 long association fiber tracts as a predictor.

	Jülich atlas	**Mori atlas**	**Catani atlas**
Cing	0.108 (.048)	0.510 (.804)	0.822 (>.999)
IOF	2.208 (>.999)	0.594 (>.999)	0.794 (>.999)
SLF/AF	2.620 (.136)	4.953 (.020)	1.219 (>.999)
UF	18.897 (.016)[a]	0.930 (>.999)	2.356 (.628)

Lesion size was included as a regressor of no interest. All p-values reported were Bonferroni corrected for multiple comparisons. [a] In light of quasi-complete separation (none of the lesion maps of patients without neglect overlapped with the fiber tract), Firth's penalized likelihood logistic regression was used. Abbreviations as in Figure 2.

4 Discussion

In the current study, we used a dataset of 140 right brain damaged stroke patients with and without spatial neglect to systematically compare the influence of different white matter fiber tract atlases used (Jülich, Mori, or Catani atlas) on conclusions concerning the involvement of

long association white matter fiber tracts in cognitive (dys)function using both a voxelwise topological and a tract-wise hodological approach.

4.1 Voxelwise topological approach

The voxelwise topological approach corresponds to the standard use of an anatomical atlas where the atlas is used to determine in which structures of the brain the significant results, e.g. from a voxelwise statistical lesion-behaviour mapping analysis, are located. In line with our prediction, the Mori and Catani atlases classified approximately 10 times as many voxels of the statistical map, containing the voxels where the presence of a lesion was significantly associated with the presence of spatial neglect, as being located in a long association white matter fiber tract than the histological Jülich atlas. As such, these results may explain why topological studies that used the histology-based Jülich atlas found that white matter damage is a minor predictor of spatial neglect (Karnath et al., 2009, 2011), whereas topological studies that used one of the tractography-based atlases found that white matter damage is a major predictor of spatial neglect (Lunven et al., 2015; Verdon et al., 2010). Interestingly, we found that these differences between the atlases were particularly pronounced for the SLF/AF. As such, these results might also explain why the studies by Lunven et al. (2015) and Verdon et al. (2010) found that damage to the SLF/AF is a key predictor of spatial neglect, whereas the studies by Karnath et al. (2009, 2011) found only limited evidence for this. Given the prevalence of this topological approach, these results have a significant implication: the topological interpretation of the results of a given study depends considerably on the anatomical atlas used. Specifically, topological studies that use the tractography-based Mori or Catani atlases are more likely to conclude that white matter integrity is critical for a cognitive function than studies that use the histological Jülich atlas.

4.2 Tract-wise hodological approach

While the voxelwise topological approach corresponds to the standard use of an anatomical atlas and is still often used, it might underestimate the importance of white matter fiber tracts to cognitive (dys)function (Rudrauf et al., 2008, see also section 2.4 above). As such, when assessing the contribution of white matter integrity to cognitive (dys)function, a tract-wise hodological approach that respects the anatomo-functional organisation of white matter fiber tracts might be more sensitive. For the tract-wise hodological approach with a continuous "percentage of fiber tract damaged" variable, our results again confirmed our prediction: the percentage of long association white matter tract damaged in individual patients was roughly

identical, regardless of the white matter atlas used to determine whether a voxel coordinate was located in a white matter fiber tract or not. Likewise, the difference in the percentage of fiber tract damaged between patients with and patients without neglect was roughly identical, regardless of the white matter atlas used. While there were thus no overall descriptive differences between the atlases in the percentage of fiber tract damaged, the results from the logistic regressions suggest that, when all fiber tract probability values were used, the percentage of fiber tract damaged in the Cing of the Jülich atlas significantly predicted the absence of spatial neglect. That is, an increase in the continuous extent of fiber tract damage in the Cing of the Jülich atlas was associated with a decrease in the likelihood of having neglect. The size of this effect was, however, relatively small. While this effect was numerically present for the Cing of the Mori atlas as well (as indicated by odds ratios below 1), it failed to reach statistical significance for this atlas. The most likely reason for this difference between atlases is that the fiber tracts in the different atlases do not only differ in volume, but also somewhat in location. Nevertheless, this result does suggest that at the level of individual fiber tracts, results may vary as a function of the white matter atlas used.

Interestingly, when only fiber tract probabilities higher than 50% were used, this effect for the Cing of the Jülich atlas disappeared, to be replaced by a significant association between the continuous extent of fiber tract damage and presence of spatial neglect in the UF of the Jülich atlas. Both these observations might be accounted for by suboptimal sample characteristics. When only fiber tract probability values higher than 50% were used, only 12 patients had lesions that affected the Cing of the Jülich atlas (whereas when all fiber tract probability values were considered, 28 patients had lesions that affected this fiber tract). For the UF of the Jülich atlas, only 10 patients had lesions that affected this fiber tract. That is, for both of these fiber tracts, sample size was rather low. Low sample sizes, and subsequently reduced statistical power, not only reduces the likelihood of detecting a true effect in the data, but also reduces the likelihood that an observed significant effect reflects a true effect (Button et al., 2013; Ingre, 2013). Additionally, all 10 patients with lesions affecting the UF of the Jülich atlas suffered from spatial neglect. That is, none of the lesion maps of patients without neglect overlapped with this fiber tract. While we did for this exact reason employ Firth's penalized likelihood logistic regression for the UF, this quasi-complete separation might have exaggerated the statistical association between the extent of damage to the UF and presence of spatial neglect. Given these suboptimal sample characteristics, these results should probably be interpreted with caution. These results illustrate the importance of ensuring

sufficient sample sizes at the level of individual fiber tracts when performing hodological lesion analyses.

Finally, for the tract-wise hodological approach with a binomial "presence or absence of fiber tract disconnection" variable, our results also confirmed our prediction: the percentage of patients with fiber tract disconnection was roughly doubled when using the Mori and Catani DTI atlases compared to when using the histological Jülich atlas. A priorily, the effects this might have on the difference in the percentage of patients with fiber tract disconnection between patients with and patients without cognitive deficit (and subsequent conclusions concerning the importance of long association fiber tract integrity to cognitive function) are impossible to predict. This ultimately depends on underlying data characteristics, which are likely to vary from study to study. In our study, despite the overall higher percentage of patients with fiber tract disconnection when using the Mori and Catani atlas than when using the Jülich atlas, the difference in the percentage of patients with fiber tract disconnection between patients with and patients without neglect was roughly identical regardless of the white matter atlas used. While there were thus again no overall descriptive differences between the atlases for this tract-wise hodological approach with a binomial variable, the results from the logistic regressions again suggest that there were differences between atlases at the level of the individual fiber tracts. Specifically, in the Jülich atlas, the presence of fiber tract disconnection of the Cing and the UF significantly predicted the absence and presence of spatial neglect respectively. These effects were not present in the Mori and Catani atlases. However, these results for the Jülich atlas should probably be interpreted with caution, given the suboptimal sample characteristics discussed above. In the Mori atlas, the presence of fiber tract disconnection of the SLF/AF significantly predicted the presence of spatial neglect. This effect was numerically present for the SLF/AF of the Jülich and Catani atlases as well, but failed to reach significance for these atlases. Again, the most likely reason for this difference between atlases is that the fiber tracts in the different atlases do not only differ in volume, but also somewhat in location.

Our results thus suggest that for tract-wise hodological analyses, the conclusions concerning the overall importance of long association fiber tract integrity to cognitive function do not necessarily depend on the white matter atlas used, but conclusions may vary as a function of atlas used at the level of individual fiber tracts. Importantly, however, our results also suggest that performing a hodological analysis while expressing the individual extent of injury to

each fiber tract as a binomial variable was associated with larger effect sizes than performing a hodological analysis while expressing the individual extent of injury to each fiber tract as a continuous variable. Specifically, while we did find a significant association between the extent of fiber tract damage and presence or absence of spatial neglect in the Cing and UF of the Jülich atlas when we used a continuous variable in our hodological logistic regressions, the magnitude of this effect was relatively small. When, however, we used a binomial variable in our hodological logistic regressions, the effect size of the significant association between the extent of fiber tract damage and presence or absence of spatial neglect in the Cing and UF of the Jülich atlas was considerably larger. Moreover, these analyses additionally revealed a significant association between the extent of fiber tract damage and presence of spatial neglect in the SLF/AF of the Mori atlas that was not present when we used a continuous variable in our hodological logistic regressions. These results might explain the discrepant results of Karnath et al. (2009) and Thiebaut de Schotten et al. (2014): Whereas Karnath et al. found no significant association between the extent of fiber tract damage and presence or absence of spatial neglect when using a continuous variable to express the individual extent of injury to each fiber tract, Thiebaut de Schotten et al. did find a significant association between the extent of fiber tract damage and presence or absence of spatial neglect when using a binomial variable to express the individual extent of injury to each fiber tract.

In its natural state, the individual extent of injury to each fiber tract variable used in our study and previous studies is a continuous variable, as it depends on two sources of continuous information: the fiber tract probability value and the volume of overlap between the individual lesion map and the fiber tract. Creating a binomial variable to express the individual extent of injury to each fiber tract thus requires the dichotomization of both these sources of continuous information at arbitrary cut-offs. This dichotomization of a continuous variable, however, is known to result in a significant loss of information and thus of statistical power (Cohen, 1983). As mentioned before, this reduced statistical power not only reduces the likelihood of detecting a true effect in the data, but also reduces the likelihood that an observed significant effect reflects a true effect (Button et al., 2013; Ingre, 2013). Moreover, when performing statistical analyses with a dichotomized continuous variable, the results can vary as a function of the cut-off(s) chosen (Altman et al., 1994; Royston et al., 2006; Wainer et al., 2006). For these reasons, statisticians typically advise against the dichotomization of continuous variables. Nevertheless, for the analyses described here, deciding on whether it is

better to use a continuous or a dichotomized binomial variable to express the individual extent of injury to each fiber tract is not entirely straightforward. Our analyses using a continuous variable to express the individual extent of injury to each fiber tract (analogously to the approach taken in Karnath et al., 2009) assume a linear relationship between the continuous extent of fiber tract damage and the severity of the effect of fiber tract damage (impaired transfer of information). However, it is entirely possible that the continuous extent of fiber tract damage has little effect on the transfer of information along the fiber tract until this continuous extent of fiber tract damage exceeds a certain threshold. On the other hand, our analyses using a binomial variable to express the individual extent of injury to each fiber tract (analogously to the approach taken in Thiebaut de Schotten et al., 2014) assume that damage of a single voxel at a location where the probability value of the fiber tract is 50% or higher (i.e. at a location where the fiber tract was found to be present in at least half of the participants) has the same effect on the transfer of information along the fiber tract as damage of 100 or more voxels at locations where the probability value of the fiber tract is 50% or higher. However, it is also possible that the amount of voxels damaged at locations where the probability value of the fiber tract is at least 50% need to exceed a certain threshold before measurable effects on the transfer of information along the fiber tract occur. A final answer to the question which variable used to express the individual extent of injury to each fiber tract – continuous or binomial – most accurately measures the severity of the effect on the transfer of information along the fiber tract is beyond the scope of the present study. Our results here, however, show that the choice made here has the potential to significantly influence the likelihood of finding a significant association between extent of fiber tract damage and severity of cognitive deficit.

4.3 Which white matter atlas is correct?

Our results suggest that conclusions concerning the contribution of long association fiber tract integrity to cognitive function may vary as a function of the white matter atlas used. This raises the question: which white matter atlas should we use to anatomically interpret functional and structural imaging results in cognitive neuroscience, i.e. in which atlas are the white matter fiber tracts most accurately mapped? This question, unfortunately, does not have a straightforward answer.

The histological Jülich atlas uses a modified Heidenhain-Woelcke technique to simultaneously stain all myelinated axons in the brain (Bürgel et al., 1997). This staining

technique not only enhances the contrast between myelinated fiber tracts and the surrounding non-myelinated white matter, but also produces a graded reduction in myelin staining on fiber tracts proportional to the degree of myelination of the tracts. This allows the differentiation of different fiber tracts according to their respective degrees of myelination and thus a precise microscopical identification of the course, location and extent of each individual white matter fiber tract, even for poorly-myelinated long association fiber tracts. As such, the Jülich atlas should theoretically map the white matter fiber tract anatomy with perfect accuracy. However, the coronal cutting plane of the histological sections used for the atlas makes it more difficult to follow long association fiber tracts that run in the anterior-posterior direction, in contrast to those fiber tracts which run in medio-lateral and dorso-ventral directions. In combination with the fact that the precise cortical source and end points are not fully known for long association fiber tracts, this might have led to an underestimation of the length of long association fiber tracts in the Jülich atlas (Bürgel et al., 2006). Moreover, as histology is very labour-intensive and time-consuming, the Jülich atlas is based on a comparatively "small" sample of ten post-mortem brains. This number represents an enormous step forward compared to previous histological atlases, for the first time allowing a probabilistic approach to human brain anatomy. Nevertheless, the sample size might limit the representativeness.

The Mori and Catani atlases both use DTI tractography to delineate the location and extent of individual white matter fiber tracts. DTI tractography takes advantage of the fact that water molecules diffuse more readily along white matter fiber tracts than perpendicular to them and that thus the diffusion direction of these water molecules can be used to map the course, location and extent of individual white matter fiber tracts (Basser et al., 2000; Conturo et al., 1999; Jones et al., 1999; Mori et al., 1999). The main advantage of DTI tractography is that it can be performed in vivo (as opposed to histology), and that thus large subject samples can be collected, improving the representativeness of these atlases. DTI tractography, however, also has several weaknesses (see e.g. Dick and Tremblay, 2012; Assaf and Pasternak, 2008). Firstly, DTI tractography requires the selection of a seed region from which to start the fiber tracking. As a consequence, DTI tractography typically relies heavily on a priori hypotheses about fiber tract pathways, which may or may not be correct. Secondly, DTI tractography rests on the assumption that each voxel can be characterised by a single diffusion direction. This assumption does, however, not hold in voxels that contain both white matter and grey matter or cerebrospinal fluid, or in voxels where fiber tracts merge, branch or cross each

other. In these situations, DTI tractography can lead to incorrect conclusions concerning the course, location and extent of individual white matter fiber tracts. These problems associated with DTI tractography have been confirmed in validation studies where the results from DTI tractography were quantitatively compared to the results from neuronal tract tracing within the same minipigs (Dyrby et al., 2007) or macaques (Dauguet et al., 2007). While these studies found an overall acceptable overlap between these techniques, they also found that DTI tractography both failed to correctly identify some (parts of) fiber tracts and falsely identified non-existing (parts of) fiber tracts (see also Thomas et al., 2014).

A final answer to the question which atlas – the histology-based Jülich atlas or the tractography-based Mori and Catani atlases − contains the most accurate mapping of the white matter fiber tracts is beyond the scope of the present experiment. Investigations are required that address this question directly. Nevertheless, at the moment the existing literature suggests that while both the histological Jülich atlas and the Mori and Catani DTI atlases might fail to correctly identify some (parts of) fiber tracts, the DTI atlases might additionally falsely identify non-existing (parts of) fiber tracts. Ultimately, atlases based on novel techniques such as 3D-polarized light imaging (Axer et al., 2011) might allow a more precise mapping of the course, location and extent of white matter fiber tracts than either histology or DTI tractography.

5 Conclusions

Our results suggest that, for topological analyses, the conclusions concerning the contribution of long association fiber tract integrity to cognitive function vary as a function of the anatomical atlas used. Studies that use the tractography-based Mori or Catani atlases to anatomically interpret their statistical results appear to be more likely to conclude that white matter integrity is critical for a cognitive function than studies that use the histological Jülich atlas. For hodological analyses on the other hand, our results suggest that the conclusions concerning the overall importance of long association fiber tract integrity to cognitive function do not necessarily depend on the white matter atlas used, but conclusions may vary as a function of atlas used at the level of individual fiber tracts. Moreover, these conclusions may vary as a function of whether the individual extent of injury to each fiber tract is expressed as a continuous or as a binomial variable. Specifically, our results suggest that

hodological studies that express the individual extent of injury to each fiber tract as a binomial variable are more likely to conclude that white matter integrity is critical for a cognitive function than studies that express the individual extent of injury to each fiber tract as a continuous variable.

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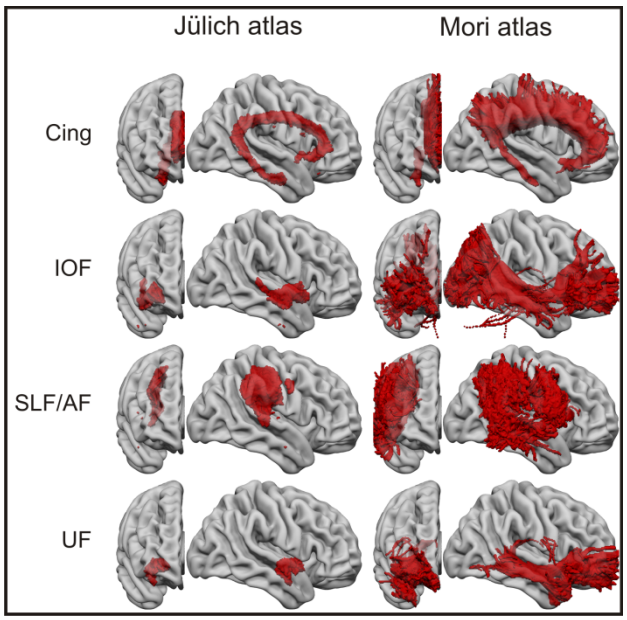
Supplementary Materials



Supplementary Figure 1: The 4 long association fiber tracts used from the Jülich and Mori atlases. All voxels where the fiber tract probability value was higher than 0% are shown for each fiber tract and atlas. For each fiber tract from each atlas, a coronal (left) and sagittal (right) view is shown. All images are shown in neurological orientation. Surface rendering of both fiber tracts and brain were performed with SurfIce (https://www.nitrc.org/projects/surfice/). The resulting images thus display a transparent view of the fiber tracts within the brain. Abbreviations: Cing = cingulum, IOF = inferior occipital fasciculus, SLF = superior longitudinal fasciculus, AF = arcuate fasciculus, UF = uncinate fasciculus.

Supplementary Table 1: The 4 long association fiber tracts used from each atlas and the total volume (in cc/ml) of each fiber tract. Volumes are given both for the entire fiber tract (all tract probabilities) and for the part of the fiber tract where fiber tract probability was higher than 50%

	All tract probabilities		**Tract probabilities > 50%**		
	Jülich atlas	**Mori atlas**	**Jülich atlas**	**Mori atlas**	**Catani atlas**
Cing	15.38	43.07 *CGC: 41.37* *CGH: 1.71*	1.85	8.55 *CGC: 6.84* *CGH: 1.71*	12.19
IOF	15.19	62.29	0.40	4.10	3.99
SLF/AF	9.54	87.99 *FT: 32.53* *FP: 48.56* *PT: 41.80*	0.58	2.47 *FT: 0.94* *FP: 3.40* *PT: 2.40*	3.32 *ANT: 1.97* *LONG: 0.11* *POST: 1.31*
UF	3.06	27.80	0.16	2.80	2.83

Abbreviations: Cing = cingulum (CGC = cingulum in the cingulate gyrus, CGH = cingulum in the hippocampal regions), IOF = inferior occipital fasciculus, SLF = superior longitudinal fasciculus (FP = fronto-temporal segment, FT = fronto-parietal segment, PT = parieto-temporal segment), AF = arcuate fasciculus (ANT = anterior segment, LONG = long segment, POST = posterior segment), UF = uncinate fasciculus. For the cingulum from the Mori atlas and the SLF/AF from the Mori and Catani atlases, we report both the volume of the maximum probability summary map and the volumes of the constituent sub-tracts.