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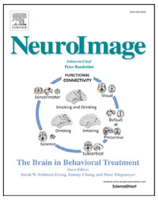

‘Whose atlas I use, his song I sing?’ – The impact of anatomical atlases on fiber tract contributions to cognitive deficits after stroke

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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.

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

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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 Fig. 4 in Thiebaut de Schotten et al., 2011, as well as Fig. 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.

Materials and methods

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.

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.

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 Fig. 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