A Statistical Cerebroarterial Atlas Derived from 700 MRA Datasets

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Summary
Objectives: The cerebroarterial system is a complex network of arteries that supply the brain cells with vitally important nutrients and oxygen. The inter-individual differences of the cerebral arteries, especially at a finer level, are still not understood sufficiently. The aim of this work is to present a statistical cerebroarterial atlas that can be used to overcome this problem.

Methods: Overall, 700 Time-of-Flight (TOF) magnetic resonance angiography (MRA) datasets of healthy subjects were used for atlas generation. Therefore, the cerebral arteries were automatically segmented in each dataset and used for a quantification of the vessel diameters. After this, each TOF MRA dataset as well as the corresponding vessel segmentation and vessel diameter dataset were registered to the MNI brain atlas. Finally, the registered datasets were used to calculate a statistical cerebroarterial atlas that incorporates information about the average TOF intensity, probability for a vessel occurrence and mean vessel diameter for each voxel.

Results: Visual analysis revealed that arteries with a diameter as small as 0.5 mm are well represented in the atlas with quantitative values that are within range of anatomical reference values. Moreover, a highly significant strong positive correlation between the vessel diameter and occurrence probability was found. Furthermore, it was shown that an intensity-based automatic segmentation of cerebral vessels can be considerably improved by incorporating the atlas information leading to results within the range of the inter-observer agreement.

Conclusion: The presented cerebroarterial atlas seems useful for improving the understanding about normal variations of cerebral arteries, initialization of cerebrovascular segmentation methods and may even lay the foundation for a reliable quantification of subtle morphological vascular changes.

1. Introduction

The cerebrovascular system is a very complex network of blood vessels that cross through the whole brain and supply the cells of the brain tissue with vitally important nutrients and oxygen. Although the coarse structure and spatial relationship of the main cerebrovascular arteries are well known, inter-individual differences of the cerebral arteries at a finer level are still not understood sufficiently. More precisely, not much is known about the variability of shape, size and position of the small vessels but it may be assumed that the variability of the cerebral arteries increases with each bifurcation towards the periphery (Figure 1).

Morphological changes of the cerebrovascular system have been associated with age-related alterations of the human brain [1] as well as to several diseases such as hypertension [2] and Alzheimer's disease [3]. However, the differentiation between significant morphological changes and normal variations of cerebral arteries may not be eye-catching and difficult. Thus, an improved understanding of normal inter-individual variations is most important to identify significant structural pathological changes.

Several deterministic atlases of the cerebrovascular system have been generated and are currently available. However, these deterministic cerebrovascular atlases focus mostly on the symbolic description of the cerebrovascular system, which was derived from only one subject in most cases (e.g. [4]). Thus, these atlases are not capable of representing variations of cerebral vessels between different individuals but have rather an educational purpose in

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terms of providing information about the vessel type and name, approximate location, size and course in the 3D space.

To overcome this drawback and enable an analysis of inter-individual differences, many datasets of healthy individuals or patients need to be acquired and post-processed for generating a statistical cerebrovascular atlas. The generation of statistical atlases derived from image datasets from multiple patients or healthy subjects has been in the focus of research for a long time and has been performed for several anatomical structures. Within this context, several statistical brain atlases have been presented in the past, such as the well-known MNI (Montreal Neurological Institute) brain atlas [5]. However, these brain atlases do not incorporate any information about the cerebrovascular system but only about the brain tissue.

So far, cerebrovascular structures have been considered rather seldom for generation of a statistical atlas although they could prove valuable for several purposes in the clinical routine and image-based research projects. Not only that a statistical cerebrovascular atlas enables a definition of normal structural vessel variations between individual humans, it may also prove valuable for improved automatic cerebrovascular segmentation methods in terms of an application within a refinement stage. To our knowledge, only two probabilistic atlases have been presented so far [6, 7].

The main idea of statistical vessel atlases is to determine the probability for a vessel occurrence at each voxel of the brain. The two aforementioned methods for generating a statistical cerebrovascular atlas have in common that the cerebrovascular system is segmented in each dataset and then registered into a defined reference space. The probability for a vessel occurrence can then be determined for each voxel using the registered vessel segmentations by calculating the ratio between the number of segmented voxels and number of cases used for atlas generation. With respect to the expected high variation of small vessels, a high number of datasets is required to obtain results that are sensitive enough for the expected variations. This may be one reason for the limited statistical atlases presented in the past. For example, Cool et al. [6] used only nine datasets while Dufour et al. [7] used 54 datasets for atlas generation, which may not represent a sufficient database for representing the real variations of cerebral arteries to a sufficient extent.

The aim of this work is to present a statistical atlas of cerebral arterial vascular structures using 700 Time-of-Flight (TOF) magnetic resonance angiography (MRA) datasets that can be used to overcome the problems of previously presented cerebrovascular atlases.

2. Material and Methods

2.1 Patients and MR Protocol

Overall, 782 datasets of healthy subjects were available for generation and first feasibility evaluation of the statistical atlas. The image acquisition was performed within in the large community-based population study SEARCH (Systematic Evaluation and Alteration of Risk Factors for Cognitive Health Study) [8], which focussed on investigating risk factors for cognitive decline in a stroke-free elderly population. Every subject included in the SEARCH study has been screened by a certified radiologist for evident vascular abnormalities and all subjects with visually evident abnormality were excluded a priori. All subjects were between 40 and 85 years and were randomly selected from the population registry of the city of Münster, Germany.

All magnetic resonance imaging (MRI) measurements were performed on a 3T Intera MRI scanner (Philips, Eindhoven, the Netherlands). Among other image sequences, which were not used in this work, a high-resolution time-of-flight magnetic resonance angiography (TOF MRA) and high-resolution anatomical T1 sequence
were acquired for each subject. The TOF MRA imaging was performed without application of contrast agent using a TE of 2.68 ms, a TR of 15.72 ms, a 20° flip angle and a spatial resolution of 0.35 × 0.35 × 0.65 mm³. TOF MRA image sequences offer a good blood-to-background contrast of arteries, which enables a sufficient automatic segmentation of these vascular structures. However, TOF MRA datasets do not display the brain tissue with a high degree of anatomical information, which is required for the registration of the datasets into a reference space. For this reason, the acquired high-resolution structural T1-weighted three-dimensional MR datasets were used in this work in addition to the TOF MRA image sequences. The high-resolution T1-weighted image sequence was acquired using a turbo gradient-echo technique with a TE of 3.40 ms, a TR of 7.00 ms, a 9° flip angle and an isotropic spatial resolution of 1 mm³.

2.2 Preprocessing

For generation of a statistical cerebroarterial atlas, a precise segmentation of the vascular structures from each TOF MRA dataset is required as the basis. Therefore, an in-house developed multi-step segmentation framework was used for extraction of the cerebrovascular structures from the TOF-MRA datasets after intensity non-uniformity correction using the N3 algorithm presented by Sled et al. [9]. More precisely, the first step of this segmentation framework consists of the automatic segmentation of the brain tissue [10]. After this, the vesselness filter [11] is used to enhance bright tubular-like structures in the TOF MRA dataset. The calculated vesselness parameter dataset is then combined voxel-wisely with the TOF MRA dataset using Fuzzy logic [12], which results in a new parameter dataset. This fuzzy parameter dataset, offers an enhanced display of all vessel structures, which are segmented from this parameter dataset using a level-set segmentation approach with anisotropic energy weights [13]. Finally, an automatic detection and correction of gaps [14] is performed in the last segmentation step. This segmentation framework was used due to its ability to extract very small as well as large vessels with high curvature at high precision (Figure 2).

The extracted cerebrovascular segmentations were then used for estimating the diameters of the segmented arteries in a following step using the vessel thickness estimation method proposed Nyström and Smedby [15]. Briefly described, this approach uses a 3D thinning procedure for extracting the 3D skeleton of the cerebrovascular system. The extracted 3D centerline representation is then used for an estimation of the vessel diameters by employing a distance mapping approach. Finally, the closest centerline voxel is determined for each segmented voxel of the cerebrovascular segmentation and used for definition of the corresponding vessel diameter at the given voxel location (Figure 2).

2.3 Atlas Generation

The segmented arteries and corresponding vessel diameter parameter datasets cannot be used directly for the generation of a statistical atlas since the position of the subjects within the scanner may vary considerably. Furthermore, individual head anatomy variations as well as differences regarding the coverage of the head section by the field-of-view of the TOF image sequence may also hamper a direct generation of a statistical vessel atlas. To overcome these problems, all TOF datasets as well as the corresponding segmentations and vessel diameter parameter datasets were registered to the 1 mm³ MNI 152 reference brain atlas, which was used for the definition of a reference space in this work.

This registration was realized within a two-step procedure, which is illustrated in Figure 3. The first step consists of the intra-patient rigid registration of each TOF dataset to the corresponding T1-weighted image sequence of the same patient. This registration was performed by maximizing the mutual information [16] between the images. The high-resolution T1-weighted image sequence of a subject was then registered to the MNI standard atlas, which was also derived from T1-weighted image sequences, using an affine transformation and minimization of the mean squared distance. The two calculated transformations were concatenated to a final combined transformation, which was then used to transform each TOF image sequence as well as the corresponding cerebrovascular segmentation and vessel diameter parameter dataset into the MNI reference space.

After registration of all TOF MRA datasets and corresponding vessel segmentation and vessel diameter estimation results to MNI reference space, a statistical cerebroarterial atlas that consists of information about the average TOF intensity, spatial probability for a vessel occurrence and mean vessel diameter at each voxel (Figure 4) was calculated. More precisely, the average TOF MRA signal intensity was calculated over all subjects for each voxel taking into account possible differences re-
3. Evaluation and Results

3.1 Dataset Inclusion for Atlas Generation

The results of the automatic cerebrovascular segmentation as well as those of the two-step registration procedure were visually checked for each dataset by an experienced observer. Overall, 700 of the 782 datasets were included for the generation of the statistical cerebroarterial atlas. The remaining 82 datasets were excluded from the atlas generation due to insufficient segmentation results in n = 48 cases. The reasons for inadequate segmentation results could be ascribed to movement or other TOF MRA acquisition artefacts in all cases. Furthermore, the registration result was not judged sufficient in n = 31 cases, which could be ascribed to artefacts in the high-resolution T1-weighted image sequence. Finally, n = 3 randomly selected datasets were excluded from the atlas generation and only used for quantitative evaluation of the segmentation quality of the automatic segmentation framework used in this work.

For evaluation of the segmentation quality, the cerebrovascular system was manually segmented in each of the three TOF MRA datasets used for evaluation independently by two experienced observers. The manual segmentation was performed using a 3D region growing approach followed by interactive corrections in the orthogonal views using an in-house developed drawing tool. The manual segmentations as well as those obtained by the multi-step segmentation procedure used in this work were quantitatively evaluated using the Dice coefficient:

$$D(A, B) = \frac{2|A \cap B|}{|A| + |B|}$$  \hspace{1cm} (1)

where A and B denote two different segmentation results. Dice coefficients close to 1.0 indicate a good consensus. The Dice coefficient was used for calculation of the inter-observer agreement as well as for quantitative comparison of the automatically extracted segmentation results to the manual gold standard segmentations.

The quantitative results of the segmentation evaluation are given in Table 1. Here, it can be seen that the two observers agreed with a mean Dice-coefficient of 0.673 for the three datasets (ranging from 0.628 to 0.695). Compared to this, the results of the segmentation framework lead to higher mean Dice-coefficients (averaged over both observers) in each of the three cases used for evaluation of the segmentation quality. More precisely, a mean Dice-coefficient of 0.733 compared to the manual segmentations was calculated for the segmentation results of the employed multi-level segmentation framework (ranging from 0.726 to 0.741). Thus, it may be concluded that the segmentation quality of the employed segmentation framework
is suitable for the atlas generation as the results are within the range or even better than the corresponding inter-observer agreement. This finding can also be confirmed visually (▶ Figure 5).

### 3.2 Vessel Probabilities and Diameters in Different Brain Areas

The generated statistical cerebroarterial atlas was visually inspected regarding the feasibility and consistency of the parameter values in the different brain areas with previously reported reference values.

Overall, the visual analysis revealed that arteries as small as 0.5 mm in diameter are well represented in the generated atlas and the corresponding values are well within ranges of validated anatomical references.

The highest probabilistic vessel density is observed in the area of the large cerebral arteries in the skull base. More precisely, probabilities up to 60% for the bilateral internal carotid artery and probabilities up to 40% for the bilateral proximal middle cerebral artery and basilar artery are present in the atlas. The corresponding mean diameter values for these arteries are up to 5.0 mm for the internal carotid artery and up to 4.0 mm for the proximal middle cerebral artery and basilar artery, which is well in accordance with previously reported values that were derived from gold standard angiographic imaging or cadaver studies [17–20].

In general, the probability for the spatial occurrence of an artery and corresponding diameters are decreasing towards the periphery with increasing branching degree. The highest order of branching that is resolved by the segmented TOF MRA datasets include the peripheral cortical arteries, such as the M4 segment of the middle cerebral artery. These arteries are represented in the atlas with vessel probabilities below 5%, and average diameters between 1.0 and 2.0 mm. These values can be confirmed by in-vivo reference values measured in living humans (surgical patients). More precisely, it was reported by Peña-Tapia et al. that vessels in the small cortical M4 branches at the end of the sylvian fissure exhibit a mean diameter of 1.5 mm [21]. Furthermore, it was reported in the same study that on average two arteries with mean diameter of 1.3 mm and mean length of 11 mm are visible within an area of a circular surgical borehole (30 mm in diameter). Thus, the mean vessel density of M4 branches within this area amounts to approximately 4%, which corresponds well to the atlas-based probabilistic vessel density in this area (3–5%).

For an analysis of the relation between the average vessel diameter and vessel probability in more detail, the two values were extracted from the generated statistical atlas for each voxel with a vessel probability >1%. The extracted values were then employed for a statistical analysis using Pearson’s correlation coefficient.
Overall, a highly significant (p < 0.001) strong positive relation (probability increases with vessel diameter) was found between these two variables (r = 0.636). Therefore, the lower vessel probability of these peripheral arteries can be explained by the smaller diameter and higher variability in terms of anatomic location in space in comparison to large arteries.

3.3 Initialization of Automatic Vessel Segmentation Methods

Apart from enabling an improved understanding of the variation of the cerebrovascular arteries, it was evaluated in a further experiment if the statistical cerebroarterial atlas is also associated with rather technical benefits in terms of integration in automatic segmentation methods. Therefore, the same three datasets as used for evaluation of the quality of the automatic segmentation results from the employed segmentation framework were also used for this experiment.

For integrating the knowledge about the spatial probability for an occurrence of an artery derived from the atlas within a vessel segmentation method, the corresponding information needs to be transferred to a subject-specific case first. Therefore, the statistical cerebroarterial atlas was registered to each TOF dataset of the three subjects employed for this evaluation using an affine transformation and minimization of the mean squared distance compared to the average TOF intensity information from the atlas. After registration, the vessel probability information is available for each voxel of a subject-specific TOF MRA dataset. The cerebrovascular system was then segmented in each TOF MRA dataset using simple global optimal thresholding. Finally, the resulting cerebrovascular segmentation was refined by rejecting segmented voxels with a vessel probability below 1%. The threshold of 1% was determined analytically by maximizing the mean Dice coefficient compared to the manual segmentations using the three evaluation datasets. The resulting segmentation result of each dataset was quantitatively compared to the corresponding two manual segmentations using the Dice-coefficient.

The results of this quantitative evaluation are also given in Table 1. Here, it can be seen that this simple and intuitive vessel segmentation approach leads to a mean Dice-coefficient of 0.709 (ranging from 0.695 to 0.730), which is not as good as the results of the high-level segmentation framework employed for generation of the statistical atlas but better compared to the inter-observer agreement.

Contrary to this finding, global optimal intensity thresholding of the TOF datasets without integration of the vessel probabilities lead to considerable more over-segmentations, especially of the skull and eye structures (Figure 5). These extensive over-segmentations are also reflected by the Dice-coefficient, which was below 0.1 in all three cases evaluated.

4. Discussion

The main contribution of this work is the generation and first feasibility evaluation of a statistical atlas of cerebral arteries including information about the spatial probability for occurrence of an artery and corresponding mean vessel diameters. This atlas was generated based on 700 datasets of healthy subjects, which exceeds the number of datasets used in previous works by a factor of more than 10. A first evaluation of the atlas revealed that the calculated vessel probabilities and corresponding mean vessel diameters correspond well...
to previously published reference values for different arteries.

The generated statistical cerebrovascular atlas can serve as the basis for an improved understanding of normal variations of the cerebral arteries between humans. Within this context, it has been shown that the probability for spatial occurrence of an artery is decreasing with the number of bifurcations towards the periphery and is strongly correlated with the diameter of an artery. However, the atlas itself does only allow extracting rather general conclusions about the variations of healthy cerebral arteries in human, while no statement about disease-related pathological changes can be made directly based on this atlas.

This drawback can be overcome by registering the statistical cerebroarterial atlas to subject-specific or patient-specific TOF MRA datasets. After automatic registration of the statistical atlas, the vessel probability and diameter information can be mapped to a specific case and evaluated visually or quantitatively for the whole cerebroarterial system or only for single branches. Within this context, it should be highlighted that no T1-weighted image sequence, as needed and used for atlas generation, is required for this purpose as the average TOF intensity information can be used directly for this purpose, which is another benefit of the generated atlas. Figure 6 exemplarily demonstrates the main idea of this procedure. After registration of the statistical cerebrovascular atlas, a single vessel branch or the whole cerebroarterial system of a patient can be analyzed regarding the probability for a vessel occurrence derived from healthy subjects. Furthermore, the mean atlas vessel diameters can be compared to the calculated "real" subject-specific vessel diameters. In doing so, it may be possible to quantify pathologic deviations from the population norm, even if subtle and not apparent to the human eye without the need of manual measurements, which are time-consuming and error-prone. This aspect may be particularly relevant for extraction of reliable physiological parameters to quantify silent or subclinical target organ damage, which is, for example, essential for cardiovascular risk stratification and proper management of patients with hypertension [22, 23]. For instance, MR imaging of the brain allows an assessment of silent lacunar infarcts, white matter lesions, and microbleeds as markers for end organ damage. Likewise, the presented atlas could prove valuable for a reliable and objective assessment of new cerebroarterial imaging features that may be relevant for evaluating brain damage in hypertensive patients or other cerebrovascular diseases in general. It is conceivable, that the location and degree of elongation and caliber changes of cerebral arteries, which is common in hypertensive patients, may relate to a distinctive feature pattern (i.e. lower vessel probabilities or increased vessel diameters) that is different from the normally distributed vascular features in a healthy population. Likewise, further arterial diseases, such as inflammatory vasculopathies exhibiting multifocal areas of stenosis alternating with dilated segments may be captured and objectively characterized by atlas-based imaging features.

However, the ability to quantify such subtle changes and variations exceeding the normal variation using the generated statistical cerebrovascular atlas needs to be evaluated in further experiments, e.g. using TOF MRA datasets from other community-based population studies such as SHIP (Study of Health in Pomerania) [24]. Within this context, it seems valuable to extent the current atlas by additional information about the standard deviation of the vessel diameters from healthy subjects at each voxel. This would, for example, allow calculating Z-scores for each voxel or vessel branch of a specific case, which could be used statistical analyses in terms of group comparisons.

Apart from this, the presented atlas could be also used for generating hypotheses. Within this context, a large database could be divided in two groups (e.g. high blood pressure vs. low blood pressure). The datasets of each group could then be used to generate group-specific atlases that can be compared with each other to identify possible differences between the groups, which can then be analyzed in more detail in a second step.

Beyond the benefits of the presented atlas regarding clinical applications, the atlas also appears useful for initialization of automatic cerebrovascular segmentation methods as it allows an intuitive and fast
segmentation of cerebroarterial vessel structures from TOF MRA datasets. However, it has to be pointed out that this benefit may be counterbalanced by the inability to segment malformed vessel structures, such as giant aneurysms, which may exhibit parts of low vessel occurrence probabilities in the presented atlas.

The presented statistical atlas offers several possibilities for further extensions, which may also prove valuable for an atlas-based analysis of imaging features of the cerebral arterial vasculature. Within this context, it is planned to extend the presented statistical atlas with information about the degree and location of branching patterns as well as information about the vessel direction in 3D space, which can, for example, be derived from the vesselness filter [11].

It has to be emphasized that although every subject included in the SEARCH study has been screened by a certified radiologist for evident vascular abnormalities, some potential abnormalities, which were not eye-catching, may have been missed. However, we believe that this problem can be neglected due to the large population used in this work.

Another important limitation of the presented atlas is that it does not include any information about venous vessel structures as these vessels are not visible in TOF MRA datasets, which were acquired without contrast agent. Furthermore, susceptibility weighted MR imaging (SWI) that are capable of displaying venous vessel structures were also not available in the database used for generation of the presented atlas. However, the same methods as described in this work could be applied to SWI datasets with only minor adaptations in case venous structures are also of clinical interest.  

5. Conclusion

In conclusion, the presented statistical cerebroarterial atlas seems useful for improving the understanding about normal variations of cerebral arteries, initialization or refinement of cerebrovascular segmentation methods and may lay the foundation for a reliable quantification of subtle morphological vascular changes that are not eye-catching.

References