A method for automatic estimation of fractional anisotropy along of cerebral tracts related with the emergency of consciousness

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ABSTRACT

The emergency of consciousness continue to be open challenge the scientific community. Tools such as diffusion-weighted imaging (DWI) and tractography try to settle this debate by showing the processes at the biological level of the a conscious states. Even though many studies have explored structural features in different mental states, the reference values of the brain structures that underlie the emergence of consciousness in healthy subjects are still unknown. Then, this work aims to identify reference values for fractional anisotropy as a structural integrity measurement among white matter pathways involved in emergency of consciousness within a group of 100 healthy subjects from Human Connectome Project. Results showed based on statistical analysis that exists reference values of fraction of anisotropy in healthy subject for the corticothalamic pathway.

Keywords: Consciousness, fractional anisotropy, tractography, bundle segmentation

1. INTRODUCTION

Consciousness is an emergent property derived from a highly complex system such as the human brain.[1] There is not a general definition for consciousness covering all its essential characteristics.[2] However, from the clinical perspective, a pragmatic definition commonly used for diagnosis considers two components: wakefulness and awareness. Wakefulness or level of consciousness is related to the level of alertness (clinically determined, for instance, by the eye-opening). Awareness or content of consciousness is associated with subjective first-person experience (clinically determined, for instance, by the command following or non-reflex motor behavior such as eye-tracking or localized responses to pain).[3,4]

Wakefulness is a necessary but not sufficient property for the emergency of consciousness.[5] However, since wakefulness is a primary function required for conscious processes, several research studies have focused on determining these brain substrates necessary for consciousness. In particular, white matter (WM) fiber pathways ascending along of reticular formation of the brainstem and projected to the cerebral cortex through synaptic relays in the intralaminar thalamic nucleus, hypothalamus, basal forebrain, and several brainstem nuclei were previously characterized as consciousness substrate.[6]

Neuroimages are the primary tool to evaluate brain structure and function in non-invasive ways, e.g., Magnetic Resonance Imaging (MRI). During the last twenty years, several studies have used it to explore the brain structure in healthy and pathological subjects.[7] Diffusion magnetic resonance imaging (dMRI) has been an essential tool for constructing 3D modeling (tractography) used to represent WM nerve tracts. Even though today humanity has at its disposal such an essential tool as dMRI, this is only a tiny part of what there is to know about the

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brain .[8] Despite the significant development of tools and technologies to study the brain, knowledge about the function of this organ remains shallow compared to all there is to know.[8]

Regardless of the recent improvements in the field of neuroimaging, for many years the only method to study brain fibers was through post-mortem dissection.[9,10] However, this method has several downsides such as limitations on the quantity of the dissections that can be conducted, the inability to study brain function, and the fact that this method is often applied to subjects usually belonging to an older age group or with pathologies.[9] These limitations have caused a shift towards new and less invasive technologies to study brain fibers. Studies suggest that neuroimaging techniques, such as tractography, can map fiber connections within the brain correctly when compared to post-mortem dissections.[11,12]

Bundle segmentation is one method to study brain fibers and it can provide information about the anatomical connectivity within different regions.[13] Currently, research is being conducted on studying automatic bundle segmentation with the support of algorithms that aim to minimize errors caused by manual segmentation.[14] There is also a special interest in understanding and comparing how the bundles vary within a group of subjects.[15,16] This has been achieved using artificial intelligence algorithms and brain atlas that propose a gold standard for all existing bundles.[17] Regardless of the extensive research, some issues remain unaddressed. One example is the lack of implementation of modern techniques to study brain fibers in clinical settings. Another example is the lack of reference values to determine criteria for normal brains in terms of fractional anisotropy. This paper aims to propose a viable solution for the second example.

Reference values of the main structures for the emergency of consciousness are significant open challenges. Therefore, this work is focused to perform an automatic strategy to determine reference values of structural integrity (diffusivity) in some primary fiber tracks for the emergency of consciousness. In particular, this work focused on three relevant WM pathways that compose the ascending reticular activating system (ARAS): the corticothalamic pathway (CT), spinothalamic tract (STT), and central tegmental tract (CTT). Results show that reference values of fractional anisotropy exist along these WM pathways; additionally, this estimation is compact and consistent in a large group of healthy subjects.

2. MATERIALS

In this work, we employ 100 brain MRI from the Human Connectome Project (HCP)[18] dataset, 54 of them belonging to females and 46 to males. All of the subjects in this set were between the ages of 22 to 36 years old. Bundle segmentation was implemented using the HARDI atlas, which contains segmentation for 79 lateralized bundles throughout the brain.[18] However, for the purpose of this article, only 3 bundles were used. These bundles were chosen regarding their relevance to the emergency of consciousness. All of the procedures were performed on a computer with standard specifications.

3. METHODOLOGY

This paper proposes an automatic method to characterize the brain bundles as substrate of the consciousness using fractional anisotropy (FA) as a diffusivity metric in a group of healthy subjects. The methodological workflow was divided into five steps, as shown in Figure 1. All steps are described in detail as follows.

3.1 Pre-processing

First, Eddy currents were corrected in each DWI image to improve distortions caused by moving patients while taking DWI. Subsequently, a reslicing step was performed to have an isotropic voxel size. Next, the non-local means filter was applied to improve the signal-to-noise ratio by modeling the noise as Rician noise.[19] Finally, a segmented brain image and a binary brain mask were computed on each b_0 image using an Otsu median filter, where the median radius was 4 pixels, and the filter was applied four times, as suggested by Garyfallidis et al. 2014.[20]

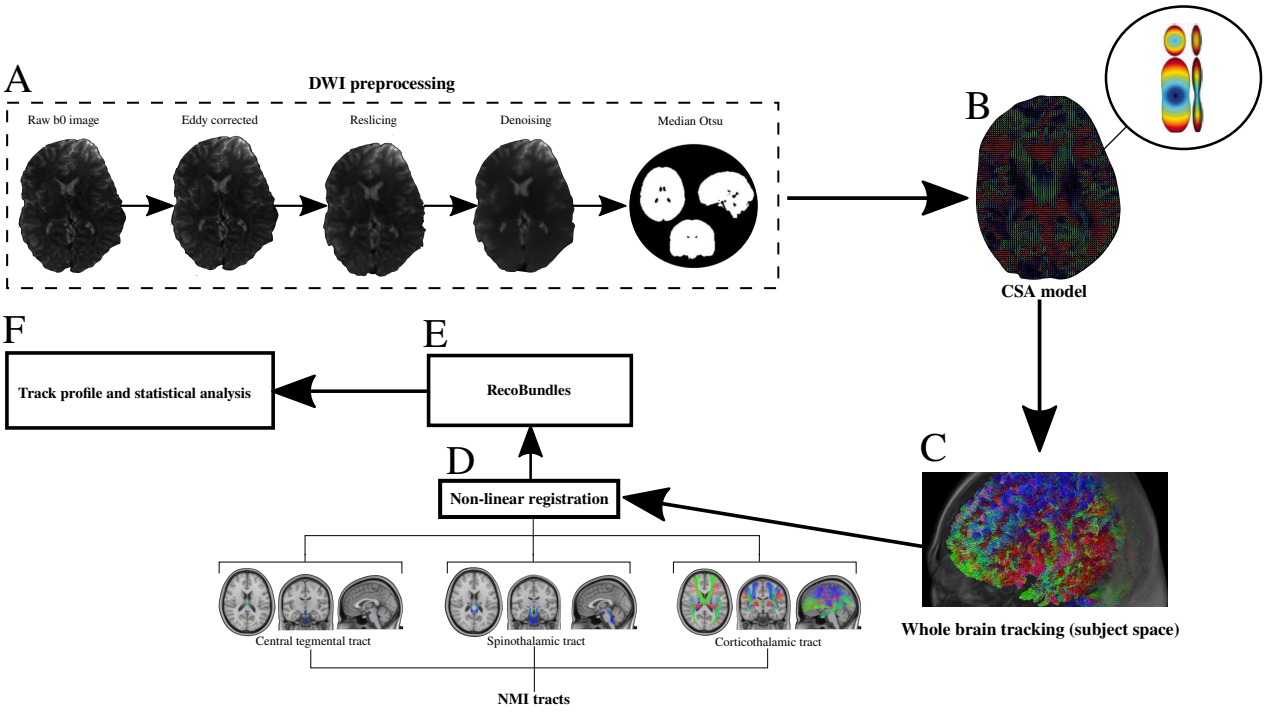


Figure 1: In the first step, all images were preprocessed (A) to subsequently perform the reconstruction of the orientation distribution function from DWI (B). Next, the whole brain tractography was computed (C). In the fourth step, the Hardy whole brain tractography was warped to subjects space (D). Later, beams were segmented according to the HARDI beam atlas (E). Finally, based on fractional anisotropy, a tract profile was estimated in each beam, and similarity metrics were implemented to validate the hypothesis (F).

3.2 Constant Solid Angle Model Construction (Q-Ball)

The Constant Solid Angle (CSA) Model was used to calculate the orientation Distribution Function (ODF) peaks in the DWI using the solid angle factor to return a dimensionless and normalized ODF. This solid angle factor is namely Q-Ball.[21] The probability (P) of water diffusion in the direction $\widehat{s}$ through the solid angle $d\alpha$ is calculated by integrating the movement probabilities for all magnitude m; the ODF calculation are demonstrated as follows :

$$ODF(\widehat{s})d\alpha = \int_{m=0}^{m=\infty} P(m\widehat{s})m^2 dm d\alpha \tag{1}$$

For doing so, the first stage consists of calculating a gradient table using the b-values and B-vectors; this table is used to initialize the CSA model, and the spherical harmonic order is set in 6. Later, the CSA model calculated is implemented to compute the ODF peaks. In addition, the relative peak threshold was set at 0.8, the minimum separation angle at 45, and the subject's brain mask was also required.

3.3 Tractography

To build the tractography based on the streamlines, first, a stop criterion was configured where a restricted with a white matter threshold at 0.2. in addition, the generalized map of fractional anisotropy was used. To sow the seeds the brain mask where was used with a 2^3 seeds grid per voxel. Moreover, the ODF peaks from CSA model also are needed, and the streamlines are generated from local tracking where EuDX algorithm[22] is used.

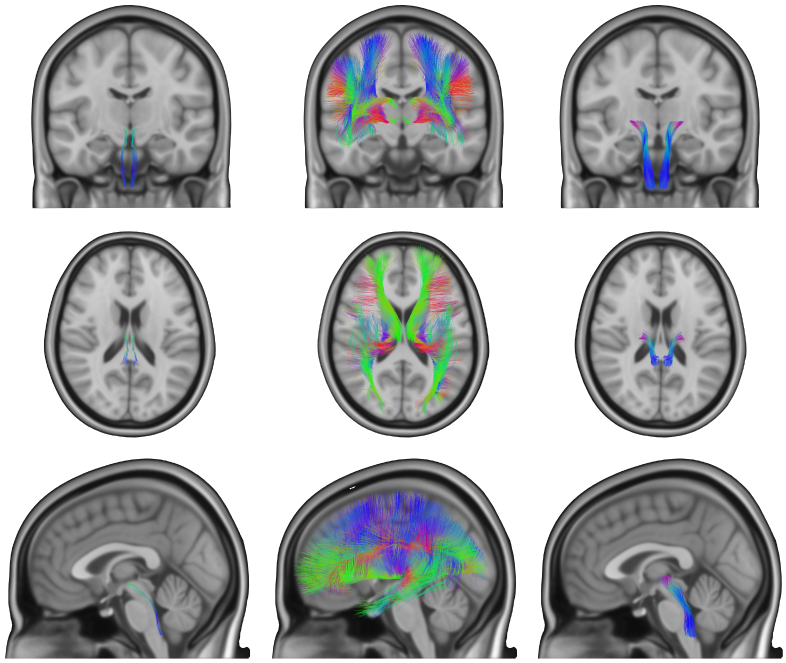


Figure 2: Bundles that compose the ascending reticular activating system

3.4 Bundles Segmentation

The first stage of bundle segmentation is tractography registration. Registration is required because the whole-brain Hardi atlas tractography is warped from MNI space to each subject's tractography space. To tackle this, stream-linear registration was applied, i.e., the Hardi atlas streamlines move linearly from MNI space152 to each subject tractography space. The stream-linear registration method minimizes the cost function containing streamlines' lengths and neighborhoods information. This registration method is described in the work of Garifaldis et. al. 2015.[23]

The second step consists of the bundle extraction from the subject brain tractography. Where the bundle was morphologically similar with the bundle standard in the Hardi atlas. For this purpose, all atlas streamlines were selected fixing the model cluster threshold in 0.01mm. Subsequently, each bundle atlas shape was found looking at the neighboring region in the subject tractography, this neighboring reduction threshold was set at 30mm. Later, the following step consists in filtering the streamlines that the distance to the atlas bundle is greater than 12mm (pruning threshold). Finally, the minimum direct-flip distance was set in reduction distance and pruning distance parameters. An example of CT (center), STT (right), and CTT (left) bundles can be observed in Figure 2 .

3.5 Track profile and statistical analysis

During the last step of the process, the track profile for each bundle was computed. This information was used to perform statistical analyses to compare the similarity regarding fractional anisotropy among the subjects.

3.5.1 Track profile

Tract profiles are the statistics computed from a brain bundle using the coordinates along their length. However, some streamlines may have a significant deviation from the directions of the rest of the streamlines within the bundle. To handle this issue, a weight for each streamline is calculated according to their bundle contribution and the distance to the streamline, which is in the bundle centroid.[24] Thus, the first step in the track profiling stage was to orient all streamlines per subject bundle with respect to the centroid streamline direction of each atlas bundle. Then, with those orientations computed, each bundle is resampled to 100 points using the mean Euclidean distance between the points. Later, the FA map per subject is loaded, and the weights

are calculated for each bundle. Finally, the FA tract profile was calculated at each point in the streamlined package sample using the FA map, the calculated orientations, and the computed weights.

3.5.2 Statistical analysis

Using the data obtained in the tract profile, a statistical analysis was executed in three parts. The first part consists of knowing if the used data have a normal distribution using a Shapiro-Wilk test (W). The test will take a value between zero and one, where one is a perfectly normal distribution.[25]

The second part described the average, standard deviation, minimum, maximum, and quarterlies 1 and 3 for each point of 100 sampled in every bundle per subject. The result of this analysis was 6 matrices, one for every bundle lateralized. To understand how bundles vary between subjects, the data previously mentioned was used to calculate the coefficient of variation (C_v).

The coefficient of variation is a standard dispersion metric from a probability distribution. In the same direction, this coefficient allows measuring how much the data oscillate using a relation between the deviation standard and the mean.[26] Equation 2 shows the C_v definition. The resulting coefficient is between 0 and 1, with the standard deviation of a sample being smaller than the mean when the coefficient approaches zero.[26]

$$C_v = \frac{\sigma}{\overline{x}} \tag{2}$$

The third part of the analysis focused on calculating the distance correlation between subjects per bundle. The distance correlation is a dependency metric between two random vectors.[27] Furthermore, the correlation coefficient is zero if the vectors are independent and one if the vectors are dependent.[28] The mathematical definition is shown in equation 3, where a and b are the evaluated vectors, the co-variance between a and b is Cov, and $sDev$ is the standard deviation of each sample.

$$dCor(a,b) = \frac{Cov(a,b)}{\sqrt{sDev(a) * sDev(b)}} \tag{3}$$

This portion was achieved by comparing all possible pairs of subjects in complete FA tract profiles per bundle. Once all of the distance correlations are calculated, the resulting matrix is simplified by averaging all values and obtaining the mean distance in every bundle.

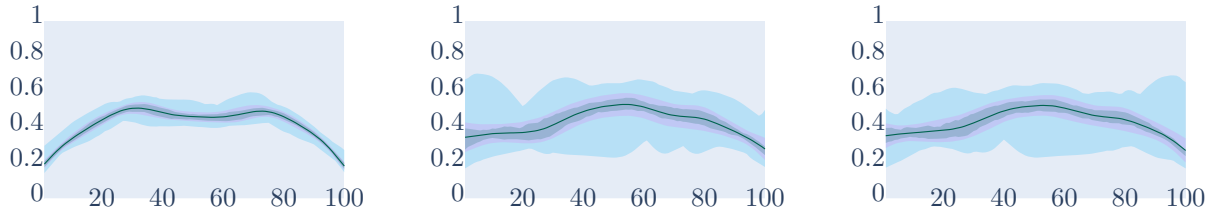
4. RESULTS

After the Shapiro-Wilk test, the FA track profiles demonstrate a normal distribution for all bundles. The CTL bundle presents a low W value with $W = 0.911$. the high value is for $STTR$ with $W = 0.993$. Consequently, the average, standard deviation, minimum, maximum, and quarterlies 1 and 3 for each point of 100 sampled in each track profile are shown in Figure 3 where the solid green line is the FA average per point sampled between all subjects. The green shade shows quartiles one and three. The pink shade is the ± standard deviation, and the maximums and minimums are represented in the blue shade.

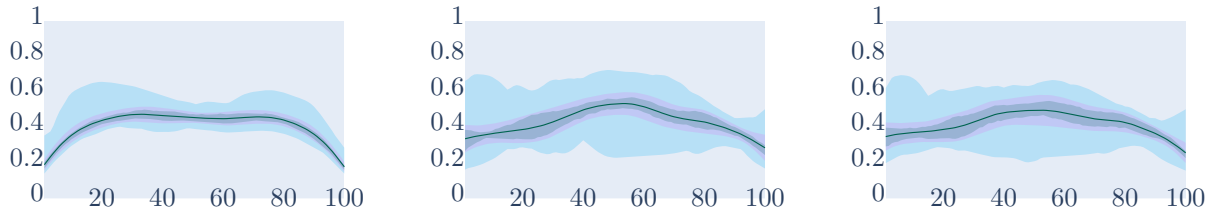
The C_v was computed for every sampled point in each tract profile to understand how bundles vary between subjects. These results are presented in Table 1. The Spinothalamic Tract Right had the highest average coefficient of variation with only 16%. The bundle with the least average coefficient variation was Corticothalamic Pathway Left with only 6.9%. These results suggest that the standard deviation variability with respect to the average is lower than others selected bundles.

On the other experiment, the distance correlation coefficient in each pair of tract profiles across subjects was computed. Figure 4 illustrates the heatmaps in each selected bundle and the best performance was in the Corticothalamic Pathway .

In addition, the detailed results of this process are shown in Figure 5. All the bundles were above 0.64 when the average was calculated per bundle. In the distance correlation average, the best coefficients were the Corticothalamic Pathway left(CT L) with 0.93, the standard deviation for this bundle was ±0.048, the $sCor$ maximum 0.996, and a $dCor$ minimum of 0.601. In the Corticothalamic Pathway right (CT R), the average



(a) CT L **(b)** CTT L **(c)** STT L



(d) CT R **(e)** CTT R **(f)** STT R

Figure 3: Statistical analysis for track profile per bundle

Table 1: Coefficient of variation to fractional anisotropy

Bundle	C_v Mean	C_v Max.	C_v Min.
Corticothalamic Pathway Left	0.069	0.123	0.050
Corticothalamic Pathway Right	0.094	0.170	0.063
Central Tegmental Tract Left	0.146	0.242	0.110
Central Tegmental Tract Right	0.151	0.255	0.100
Spinothalamic Tract Left	0.142	0.250	0.108
Spinothalamic Tract Right	0.159	0.226	0.108

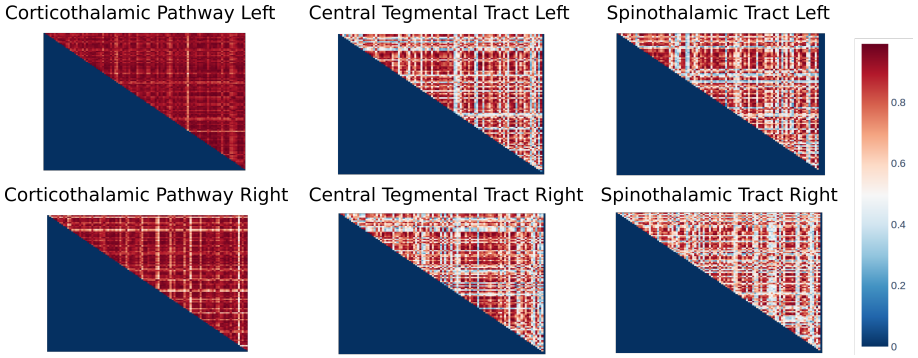


Figure 4: Distance correlation per bundle

was 0.88, the standard deviation ±0.099, the distance correlation maximum 0.996 for this bundle, and the *sCor* minimum was 0.428. To the Central Tegmental Tract Left, the average distance correlation was 0.688, the standard deviation for this bundle was ±0.214, the maximum value was 0.991, and the minimum was 0.183. For the same bundle but in the right brain hemisphere, the average value was 0.674, ±0.212 was the standard deviation, the minimum was 0.168, and the maximum 0.997 respectively. Furthermore, the lower mean distance

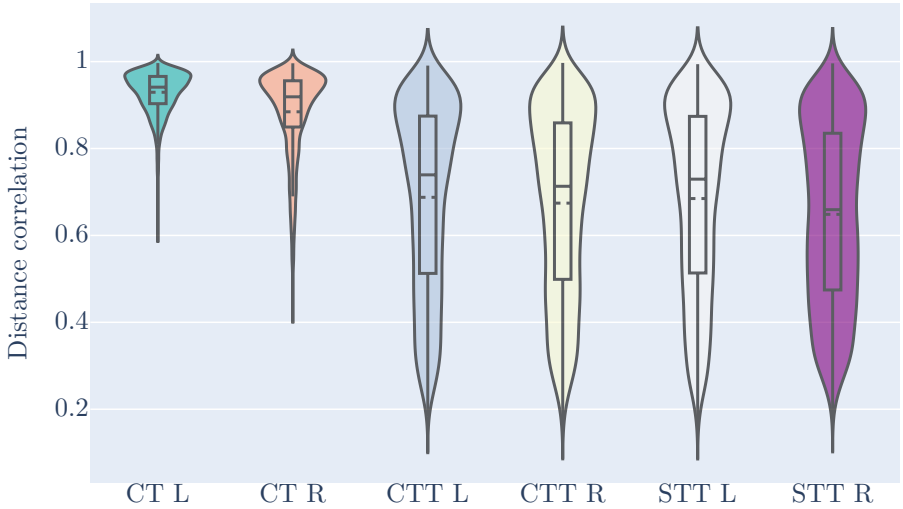


Figure 5: Distance correlation in pair of possible subjects combinations.

correlation was in Spinothalamic Tract for both hemispheres. The left side had an average of 0.685 and the right bundle 0.648; the standard deviation was ± 0.214 for $STTL$ and ± 0.207 for $STTR$, the maximum $dCor$ for the left bundle was 0.994, and 0.996 for the right bundle. Finally, the $dCor$ minimum for $STTL$ bundle was 0.169 and 0.182 for $STTR$.

5. DISCUSSION AND CONCLUSIONS

Three interesting findings were shown in the results section of this work. First, the FA profile seems to have bilateral behaviors to the three characterized tracts. This finding is consistent with previous evidence as shown by[29] in which structural properties like FA evidenced symmetric structural behaviors along brain hemispheres. Second, average FA values for each tract (CT, CTT, STT) showed consistent values compared to focal FA inside dorsal raphe, midbrain reticular formation, thalamus, and hypothalamus.[30] Even if, this analysis was focused on tract analysis in three main tracts of ARAS and[30] performed a subcortical FA analysis, both approaches can be compared given represented structural properties of the same anatomy brain structure. Finally, both CTT and STT show high variability across subjects. Then, we hypothesized that these brain structures can be high anatomical variables across subjects or our methodological approach is not capable to identify consistently. Complementary analyses are required to confirm it. However, the CT tract shows an FA profile highly consistent across the healthy subjects. Then, this paramount finding can represent a new reference value for healthy brain subjects, and it can be used as a comparative approach concerning brain pathological conditions. Future work necessary must be directed to identify the same references value for the altered state of consciousness.

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