Subdivision of Superior Longitudinal Fasciculus in Human Neonatal Brain

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Abstract

The superior longitudinal fasciculus (SLF) is a complex associative tract comprising of three distinct subdivisions in the fronto-parietal cortex, each presenting different anatomical connectivity and different functional roles. However, the subdivision of SLF was hampered by limitations of data quality and tractography methods, and many studies on white matter development often consider the SLF as a single entity. The exact anatomical trajectory and developmental status of each sub-bundle of the human SLF in neonatal period remain poorly understood. In this work, we investigated the morphological characteristics and maturation degree of SLF each branch using the diffusion MRI (dMRI) data of 40 healthy term neonates from the Developing Human Connectome Project (dHCP) database. An advanced single shell 3-tissue constrained spherical deconvolution (SS3T-CSD) algorithm was used to ensure the successful separation of the SLF three branches (SLF I, SLF II and SLF III). In addition, diffusion tensor imaging (DTI) and neurite orientation dispersion and density imaging (NODDI) parameters values of the three subcomponents of SLF were measured quantitatively. The fiber morphology and connectivity of SLF sub-bundles in neonatal brain were nicely revealed in our study. Furthermore, the comparison results of parameters values supported that the maturation of SLF three segments was heterochronic. Further multiple comparison results indicated that the dorsal SLF II was less mature than the ventral SLF III and the former may involve in higher-level cognitive functions. Our findings can provide new anatomical basis for early diagnosis and treatment of related diseases caused by aberrant development of SLF.

Introduction

The superior longitudinal fasciculus (SLF) is thought to be a long association fiber tract connecting frontal and parietal lobes with the temporo-parietal conjunction area. Based on its distinct anatomical connections in the cerebral lateral hemisphere, SLF can be divided into different subcomponents, each of which has been linked to different cognitive functions, such as language, attention, visuospatial processing and so forth (Thiebaut de Schotten et al. 2011a; Nakajima et al. 2019; Schurr et al. 2020). Previous studies suggested that dysconnectivity or microstructural abnormalities of SLF sub-bundles were correlated to some neurodevelopmental disorders e.g. autism spectrum disorder (ASD) (Fitzgerald et al. 2018) and attention deficit/hyperactivity disorder (ADHD) (Chiang et al. 2020; Hyde et al. 2020). The segmentation study of SLF and the morphological and microstructural exploration of its each sub-bundle using diffusion MRI are helpful for detecting the cryptic white matter injury in neuropsychiatric disorders and facilitating the early diagnosis of related psychosis.

Researchers have found that the fronto-parietal fibers of SLF in human adult and non-human primates can be segmented into three subcomponents (SLF I, II and III) using anatomical and isotope techniques (Petrides and Pandya 1984; Schmahmann and Pandya 2006; Catani and Thiebaut de Schotten 2012). Many advanced tractography methods have been applied in in-vivo studies of human adult enabled the separation and visualization of the SLF three branches (Makris et al. 2005; Thiebaut de Schotten et al. 2011a,2012; Wang et al. 2016; Yagmurlu et al. 2016; Nakajima et al. 2019; Schurr et al. 2020), but the studies of the characteristics of SLF sub-bundles in human fetuses and neonates were still very limited.

Previous diffusion tensor imaging (DTI) tractography studies on the development of fetal and neonatal white matter usually consider the entire SLF as a single bundle (Ouyang et al. 2015,2019; Lynch et al. 2020; Yu et al. 2020). Recently, Horgos et al. found that SLF can be divided into a deep, direct component (arcuate fasciculus, AF) and a more superficial indirect component using the white matter dissection technique between 14 and 35 gestational weeks, which suggests that the DTI tractography results of SLF in fetal and neonatal periods may be not consistent with real anatomical dissection results. There may be a number of complicating factors that contribute to this difference in results. For one thing, the quality of diffusion MRI images of fetuses and neonates was limited by the scanning time, magnetic field intensity and other conditions (Dubois et al. 2020). On the other hand, SLF is one of the slowest maturing white matter tracts with a lower myelination degree and there are many fibers intersecting with it in its running areas (Zhang et al. 2007; Ouyang et al. 2019). All of these factors make the tracking results of SLF not well during the fetal and neonatal periods. Thus, some new technologies should be performed to analyze the high-quality diffusion image data and study the development of SLF sub-bundles in order to offer a new probe for clinical evaluation of neonatal brain development.

In this study, we used the diffusion MR images from the first data release of Developing Human Connectome Project (dHCP) to reconstruct the trajectory of SLF subcomponents during the neonatal period. The image quality and acquisition strategy of this multi-shell high angular resolution diffusion imaging (HARDI) data maximized the diffusion MRI (dMRI) tissue contrast (Bastiani et al. 2019), which allowed us to use advanced analysis techniques and do more precise tracking. Some methods based on the constrained spherical deconvolution(CSD) like single-shell 3-tissue CSD (SS3T-CSD) algorithm applied in our work addressed many limitations of DTI and other models, that can estimate the number and orientations of multiple fiber tracts in the same voxel and improve the angular resolution of the results, making the fiber tracking in crossing fiber regions and the grey matter-white matter interfaces more reliable (Tournier et al. 2007; Dhollander and Connelly 2016).

We not only did the segmentation of neonatal SLF in the frontal and parietal areas and performed morphologic observation but also made quantitative measurements. Specifically, we divided the SLF into three parts and did the fiber tracking respectively. Furthermore, we investigated the quantitative microstructural changes of SLF sub-bundles using the more sophisticated diffusion model like Neurite Orientation Dispersion and Density Imaging (NODDI), which can overcome the limitations of the diffusion tensor model and has the specificity to characterize the microstructural features of white matter development (Ouyang et al. 2019; Lynch et al. 2020). The goals of this study were to establish normal reference standards for assessing the development of SLF and provide anatomical basis for early diagnosis and treatment of related diseases caused by abnormal development of SLF in the neonatal period.

Materials And Methods

Diffusion MRI dataset

High quality diffusion MRI data of 40×25 male, 15 female healthy term neonates were selected and downloaded from <http://developingconnectome.org/> (the website address of dHCP). These neonates were medially born at 39.14 (36.14-40.29) and scanned at 39.36 (36.86–44.14) weeks post-menstrual age. All scans from dHCP were conducted on a 3.0 T Philips Achieva MRI scanner equipped with a dedicated neonatal brain imaging system (Hughes et al. 2017). The diffusion MRI data has 4 different b-value shells (0, 400, 1000 and 2600 s/mm²) and 300 diffusion encoding orientations (20,64, 88 and 128 per b-value shell) (Hutter et al. 2018), which already underwent preprocessing by the automated dHCP neonatal diffusion pipeline (Bastiani et al. 2019). The in-plane resolution is 1.5 mm and slice thickness is 3 mm with 1.5 mm slice overlap. More details on the data acquisition and preprocessing can be found in the reference papers (Hutter et al. 2018; Bastiani et al. 2019).

Fiber tracking and segmentation of SLF

The first and most important step before fiber tracking is to obtain an accurate fiber orientation distribution (FOD) image. The white matter fiber orientation distributions (WM-FODs) were computed using the SS3T-CSD algorithm, which succeeded to model WM-like, GM-like and CSF-like signal contributions properly in the dHCP neonatal dataset (Supplementary Material Fig. 1). SS3T-CSD is available in MRtrix3Tissue (<https://3Tissue.github.io>) software, which is a fork of MRtrix3 (Tournier et al. 2019) and requires only one non-zero b-value. We chose the b=1000s/mm² data (+ 20 b=0 images) as a "single-shell" sub-dataset because the data shows a very low signal-to-noise (SNR) at b=2600s/mm² particularly in crossing fiber areas (Dhollander et al. 2019). Next, we performed the global tractography, on the basis of getting an accurate representation of WM-FOD, using a deterministic algorithm: SD_STREAM as implemented in MRtrix (Tournier et al. 2012). Most tractography parameters were set to the default values, except for the following parameters: the maximum angle between successive steps is 45°, the FOD amplitude cut-off is 0.06, and the desired number of streamlines to be selected is 10million.

Finally, the region of interests (ROIs) were manually drawn on the FOD image and the SLF was segmented into three parts: SLF I, SLF II and SLF III. Before defining the ROIs for each fiber bundle, it is critical to find the approximate anatomical locations of the three branches of SLF. Some adult SLF studies have found that SLF I is located above the cingulum (Komaitis et al. 2019), and it runs parallel to the cingulum. Therefore, we defined the anatomical location of SLF I by determining the location of the cingulum in the sagittal position. As shown in the Fig. 1, we placed eight ROIs in the left SLF I running areas, all of which were drawn on the coronal position of the WM-FOD map by ITK-SNAP (www.itksnap.org/) software (Yushkevich et al. 2006). We carefully observed the fiber distribution in the sagittal and axial positions while drawing the ROIs in the coronal position. Then we carefully located the running areas of SLF I and distinguished the hybrid fiber bundles adjacent to or crossing it. In most cases, only after repeated tracking and verification can the height of ROI in each sagittal position and the width in each axial position be finally determined. On the axial position below SLF I, we could see that SLF II was located outside of SLF I (Fig. 2) and there were some projection fibers known as corona radiata between them (Komaitis et al. 2019). The same is true for ROI drawing of SLF II and SLF III. On the sagittal position lateral to SLF II, we found that SLF III was located ventral to the SLF II. In order to

separate the two fiber branches, we regarded the more dorsal fiber tracts as SLF II and the remaining ventral fibers as SLF III (Fig. 3, Fig. 4). In general, our protocol of delineating ROIs for isolating the three components of SLF was mainly inspired by the previous work of Thiebaut de Schotten et al. (Thiebaut de Schotten et al. 2011a). These multiple ROIs we labeled can be split into two categories: one is delineated around the white matter of the superior, middle and inferior/precentral frontal gyri, and another is around the white matter of the parietal lobe. While the former served as key ROIs to classify SLF into three different sub-bundles, and another type of ROIs in parietal lobe areas constrained the trajectories of fiber bundles.

Defining the cortical ROIs based on the newborn AAL template

Shen et al. used advanced MR image segmentation techniques to create infant brain atlases from neonates to children up to 2 years (Shi et al. 2011). They divided the newborn brain into 90 regions of interest, all of which were defined based on the location of sulci as well as gyri and thus have important anatomical significance. We registered the neonatal atlases published by Shen et al. to the space of diffusion MRI data of 40 newborns respectively using the Advanced Normalization Tools (ANTs, <http://stnava.github.io/ANTs/>) software, which combines affine with diffeomorphic deformations (Avants et al. 2007), thus dividing each newborn individual's brain into 90 anatomical regions (see Supplementary Material Fig. 2).

Measurements of DTI and NODDI parameters values

The FSL (<https://fsl.fmrib.ox.ac.uk/fsl>) software was used to get whole-brain DTI metrics (Fractional Anisotropy [FA], Mean Diffusivity [MD], Axial Diffusivity [AD] and Radial Diffusivity [RD]) values of 40 term neonates. For further quantitative analysis, we also calculated the NODDI metrics (Neurite Density Index [NDI], Orientation Dispersion Index [ODI]) values of whole brain in each individual through the NODDI Matlab Toolbox (https://www.nitrc.org/projects/noddi_toolbox) software (Zhang et al. 2012), see Supplementary Material Fig. 3.

Combined with the results of fiber tracking as well as DTI and NODDI parameters values, we used the “tcksample” command in MRtrix (<https://www.mrtrix.org/>) to obtain the DTI and NODDI parameters values of sampling points in SLF each branch. Finally, we used in-house python script to calculate the average value of metric values of all sampling points in each fiber bundle.

Statistical analysis

SPSS software, Version 22.0 (IBM, Armonk, NewYork) was used for statistical analysis. Firstly, the differences between parameters values of SLF left and right branches in the hemispheres were compared using the Paired-Samples t-Test. We also used Wilcoxon Rank-Sum Test instead when the data were not normally distributed. Secondly, we used the Analysis of Covariance to test the sex differences. For data that do not meet the requirements of “covariance analysis” but satisfy the normal distribution and homogeneity of variance, independent sample T-test was adopted. For non-normally distributed data, we

used the non-parametric Mann-Whitney U test. Thirdly, general linear regression analysis was performed for each diffusion metric to provide data reference in evaluating the development status of each fiber bundle. Gestational age was entered as the independent variable and diffusion metrics values were entered as the dependent variable. Fourth, we compared the parameters values of the three fiber branches were same or not by using one-way analysis of variance (ANOVA) test, and Bonferroni correction method was used for further multiple-comparison. We used the non-parametric Friedman's rank test when the data was not normally distributed or heterogeneity of variance. $P \leq 0.05$ was considered statistically significant.

Results

Trajectory of SLF in the human neonatal brain

We conducted whole-brain fiber tracking for 40 neonates aged from 36.86 weeks to 44.14 weeks, and then got three segments of SLF (Fig. 5) through manually delineating ROIs on the WM-FOD map.

Combined with the registered AAL atlases of neonates, we found that the fiber morphology and connected cortical regions of SLF each branch in neonates were similar to those of adults. Fig. 6 shows that SLF I and cingulum run parallel to each other. The former is located on the superior and lateral side of the cingulum and sometimes close to each other. SLF I appeared "S" shape connecting some critical cortical areas like the superior parietal lobule, supplementary motor area, paracentral lobule and precuneus as well as the superior frontal gyrus. SLF II located more laterally and inferiorly originating from angular gyrus to middle frontal gyrus and precentral gyrus as compared to the SLF I. At the slightly lower level of SLF II, the superior fronto-occipital fasciculus appeared medial to it. These two fiber tracts connected some same cortical regions, sometimes can be distinguished by the fibers of internal capsule (Fig. 7). As for SLF III, Fig. 8 shows that it is located on the ventral side of SLF II. In the sagittal planes where SLF II and SLF III exist simultaneously, the fiber bundles running with a more dorsal direction were regarded as SLF II, while the remaining fibers with a more ventral direction were regarded as SLF III.

Quantitative analysis of SLF subcomponents

According to statistical results, there were no side and sex differences in three SLF fiber branches. Therefore, we took the average values of left and right parameters values as the final parameters values of fiber bundles to do the linear regression analysis with gestational age. As shown in the Fig. 9, with the increase of gestational age, the FA and NDI values of SLF I, SLF II and SLF III increased linearly, while the MD and RD values of them decreased linearly. Different from the above metrics, the ODI values of SLF I and SLF III changed non-linearly with the increase of gestational age. Although the ODI values of SLF II showed a linear decrease, the P value of the slope had reached 0.047. The AD values of SLF II changed non-linearly, but the decrease of AD in SLF I and SLF III was linear with the increase of gestational age. In addition, we also compared the differences of DTI and NODDI parameters values in the SLF three fiber branches (Fig. 10). Our statistical results showed that SLF III had the highest FA value and the lowest ODI value among the three fiber branches. On the contrary, the FA value of SLF II was the lowest, but the ODI

value of it was the highest. The FA and ODI values of SLF I were in the middle of the three. Besides, the differences of NDI, MD and RD values among the three branches can be detected, and the differences were statistically significant. But further multiple comparison results indicated that only the differences of parameters values between SLF II and SLF III were statistically significant, showing the NDI value of SLF III was greater than the SLF II as well as the MD and RD values of SLF II were greater than SLF III.

Discussion

Trajectory of SLF in the human neonatal brain

In this study, we used the SS3T-CSD algorithm proposed by Dhollander et al. to calculate the WM-FOD images meeting the tracking requirements and then successfully divided SLF into SLF I, SLF II and SLF III in the neonatal brain. This is different from the previous results of many newborn DTI studies. Huang et al. used DTI technique to conduct deterministic fiber tracking of the fetal brain in the second trimester, third trimester and neonatal period respectively. Their results indicated that SLF could not be tracked in the second trimester and only part of SLF (mainly refer to AF) could be detectable in the third trimester as well as neonatal period. Therefore, they speculated that SLF might emerge in the third trimester (Huang et al. 2006; Ouyang et al. 2015,2019). In fact, such DTI fiber tracking results are likely to be incomplete. From the perspective of the developmental characteristics of SLF, as one of advanced association fibers, it matures later than other fiber tracts and has a low degree of myelination in the fetal and neonatal periods (Kulikova et al. 2015). In addition, there are corpus callosum, corticospinal tracts and multiple fiber tracts in the running regions of SLF crossing with it. While DTI is limited by the model algorithm and can simply estimates the only one major fiber distribution direction in a single voxel (Jeurissen et al. 2019). All these factors will greatly interfere with the DTI tracking results of SLF. With the development of MR sequences, more advanced diffusion MRI techniques, such as high angular resolution diffusion imaging (HARDI) and diffusion spectrum imaging (DSI) based on probability density function, have been widely applied and popularized (Tuch et al. 2002; Wedeen et al. 2005,2008). They effectively make up for the deficiencies of DTI algorithm and present more abundant and real fiber bundle direction as well as connection information, so as to fully display the fiber bundles with more complex structures such as crossing and bifurcation. However, these advanced MRI methods still not be widely applied in the neonates due to the limitation of scanning time. Recently, Hutter et al. proposed a highly optimized HARDI MRI protocol that can control the scanning time within the tolerated range of the newborns (20 minutes) (Hutter et al. 2018). This protocol helped dHCP to collect enough high-quality neonatal diffusion data. Besides, SS3T-CSD was proposed and shown to be performed well in the dHCP data (Dhollander et al. 2019). The most prominent advantage of SS3T-CSD is that it can model 3 tissue compartments well using single-shell data and thus there is no need to segment newborn brain tissue into white matter, gray matter, and cerebrospinal fluid, which avoids the segmentation difficulties of neonatal brain tissue.

Although SS3T-CSD algorithm helped us obtain the optimized WM-FOD image and high-quality whole-brain fiber tracking map, we still need to complete the delineation of ROI in order to get the final SLF segmentation results. Some researchers performed DSI-based tractography to get the adult SLF and its

three branches selecting the cortical ROIs in parietal and frontal regions (Wang et al. 2016; Nakajima et al. 2019). In view of this, we also used parietal cortical ROIs to track SLF in neonatal brain, but we found that fibers from parietal lobe to the frontal lobe were interrupted, and we could not get the three branches of SLF in the prefrontal areas. Similarly, the fibers in posterior parietal regions could not be tracked using the cortical ROIs of the frontal lobe. After have ruled out many factors such as unreasonable tracking parameters (step size, angle, FOD amplitude) that may lead to fiber interruption, we found that there were many U-shaped fibers (short association fibers) in the SLF branches during the neonatal period and fiber tracking was prone to be interrupted in connection areas of adjacent U-shaped fibers. Although it has been reported that adult SLF was mainly composed of short association fibers connecting neighboring cortical regions (Catani and Thiebaut de Schotten 2012; Yagmurlu et al. 2016), we speculated that the main reason for the two different tracking results between adults and neonates may be related to the immature fiber structure of SLF in neonatal period. Axonal pruning, myelination and other maturation processes which have finished in human adult period may be conducive to fiber tracking results. In order to reduce or even avoid interruptions in the tracking process, we adopted the whole-brain fiber tracking method and got the three branches of SLF by manually plotting multiple ROIs in the white matter regions along the fibers.

From the segmentation results of SLF, we found that the cortical regions connected by SLF three branches in the human neonatal brain were similar to those of adults, which to some extent verified the accuracy of our segmentation. Actually, there are still some controversies about segmentation of SLF three branches at present. For example, several studies have questioned the existence of SLF I (De Benedictis et al. 2016; Wang et al. 2016; Nakajima et al. 2019; Schurr et al. 2020). Some researchers believe that SLF I has many similarities with the cingulum in anatomical structures and functions, so SLF I belongs to the cingulum fiber system (Wang et al. 2016; Nakajima et al. 2019). In contrast, Yagmurlu et al. demonstrated that SLF I was an independent fiber bundle using both DSI fiber tracking and microanatomical dissection technique (Yagmurlu et al. 2016). Besides, Komaitis et al. successfully separated SLF I and cingulum on human adult specimens, likewise, proving that they were independent fiber systems (Komaitis et al. 2019). Our results also showed that SLF I was located above the cingulum and the two fiber tracts were clearly separated by the corpus callosum on the three-dimensional fiber tracking map, although SLF I and the cingulum were close to each other in the cross-section planes. In addition, it is occasionally difficult to separate SLF II and SLF III on the axial planes (Makris et al. 2005). Combined with a lot of relevant literatures, we summarized our own segmentation principles. That is in the sagittal planes where SLF II and SLF III exist simultaneously, the fiber bundles running with a more dorsal direction were regarded as SLF II, while the remaining fibers with a more ventral direction were regarded as SLF III (Wang et al. 2016).

Quantitative analysis of SLF subcomponents

After obtaining the fiber tracking results of SLF three branches in 40 neonates, we measured the DTI and NODDI parameters values of each branch and conducted quantitative analysis on their maturation degree.

Our statistical results showed that there were no side and sex differences of parameters values in the SLF three branches. Earlier DTI studies on development of SLF also got the same results (Liu et al. 2010, 2011). While many studies have reported that the SLF of human during the adult period shows obvious lateralization and asymmetry (Makris et al. 2005; Thiebaut de Schotten et al. 2011b; Budisavljevic et al. 2017; Nakajima et al. 2019). Therefore, we predicted that the side and gender differences of SLF were not obvious or present in the newborn period. With the development and maturity of fiber function, these differences may gradually show up during the later period.

We also performed linear regression analysis of DTI and NODDI parameters values in relation to gestational age. Among these parameters, FA is one of the most commonly used metrics to evaluate the maturity of fiber tracts (Qiu et al. 2015; Feng et al. 2019), which reflects the degree of fractional anisotropy of fiber bundles (Pierpaoli and Basser 1996). Our results showed that the FA values of SLF I, SLF II and SLF III all increased linearly with the increase of gestational age. This indicated that the fractional anisotropy of the SLF three branches enhanced in neonatal period. However, from the point of view of biophysical properties, the increase of fractional anisotropy is closely related to the changes of many white matter microstructure characteristics, such as axonal density, axonal diameter, cell membrane permeability, myelination degree, axonal orientation distribution, etc. (Jones et al. 2013). Any variations of these factors can cause the change of FA value. In order to further explain the reason for the increase of FA value of fiber tracts, we also observed the changes of NODDI parameters values. The NDI value represents the neurite density, while the ODI value represents the neurite orientation dispersion, especially the degree of fiber coherence (Dean et al. 2017; Genc et al. 2017). Therefore, the increase of NDI value or the decrease of ODI value can lead to the increase of FA value (Chang et al. 2015). Our results showed that with the increase of gestational age, the NDI values of SLF I, SLF II and SLF III all increased linearly. While the ODI values of SLF II decreased linearly, and the ODI values of SLF I and SLF III changed nonlinearly. In view of this, we speculated that the increase in FA values of SLF I and SLF III during the neonatal period was mainly due to the increase of axonal density, with little influence by the change of axonal orientation dispersion. The increase of FA value of SLF II was influenced both by the increase of axonal density and the decrease of axonal orientation dispersion in this period. Our further analysis of NODDI parameters values revealed two key factors that may lead to the changes in the FA values of SLF three branches, thus improving the biological specificity of the FA value. Besides, other DTI parameters (RD, AD, MD) also changed differently in the three fiber branches: with the increase of gestational age, the MD, RD, and AD values of SLF I as well as SLF III decreased linearly. The MD and RD values of SLF II also decreased linearly, but the AD values of it changed nonlinearly. Among these parameters, in the biological sense, AD value can reflect the degree of axonal arrangement, while RD value represents the degree of myelination and the growth of oligodendrocyte (Song et al. 2005; Dubois et al. 2008). The results from our studies clearly showed that, with the increase of gestational age, the degree of axonal packing and the number of oligodendrocytes around the axons of SLF I and SLF III increased during this period. This led to the decrease of longitudinal and transverse diffusivity of SLF I and SLF III and finally caused the reduce of mean diffusivity. However, SLF II was different. The decrease

of mean diffusivity of it was mainly caused by the decrease of transverse diffusivity, which means that the number of oligodendrocytes around the axon increased.

Moreover, the parameters values of SLF three branches have significant differences by statistical analysis. Our results showed that, among the three fiber branches, SLF III had the highest FA value, followed by SLF I, and SLF II had the lowest FA value. On the contrary, SLF II had the highest ODI value and SLF III had the lowest ODI value. In addition, the differences of NDI, MD and RD values among the three fiber branches were statistically significant. However, further multiple comparisons showed that only the parameters values differences between SLF II and SLF III were statistically significant, which showed that the NDI values of SLF III were greater than SLF II, and the MD values as well as RD values of SLF II were both higher than SLF III. According to the differences of parameters values of these fiber branches and the biological significance represented by them, we speculated that the three branches of SLF had different maturity degree. One of the hallmarks of white matter maturation after birth is retraction and myelination of the axonal pathways (LaMantia and Rakic 1990; Kunz et al. 2014), which means the decrease of the axonal orientation distribution and increase in the number of oligodendrocytes, corresponding to the increase of NDI values and decrease of ODI and RD values. The increase of NDI and the decrease of ODI led to the increase of FA, and the decrease of RD also led to the decrease of MD. Therefore, we speculated that SLF III with the highest FA values and the lowest ODI values had the highest maturity degree, while SLF II with the lowest FA value and the highest ODI value had the lowest maturity degree. The study of Horgos and colleagues also confirmed our findings. They used anatomical dissection technique to investigate the development of white matter tracts in human fetal brain aged between 13 and 35 gestational weeks. Their results showed that the periinsular portion of SLF, corresponding to our SLF III segment and AF, can be identified by dissection at 14 weeks. Then the newer fibers always emerge in more superficial positions with the gestational age increasing and formed a more superficial component of SLF (Horgos et al. 2020), corresponding to our SLF II segment. The sequence of development in periinsular area from ventral to the dorsal direction supported our quantitative analysis results, that is, ventral SLF III is more mature than dorsal SLF II in human neonatal period.

The general sequence of development is from the simple to the complex as well as from the lower to the higher, and the differences in the maturity status of these three fiber branches may be related to their different levels of brain functions. Parlatini et al. found that the functions of the human frontal and parietal regions can be divided into dorsal spatial/motor and ventral non-spatial/motor networks, corresponding to SLF I and SLF III functional networks respectively. Whereas, SLF II is associated with a network of multimodal region at the intersection between the dorsal and ventral networks. There may be many neurons with very flexible response characteristics in the regions connected by SLF II, reflecting the function of human conscious processing (Parlatini et al. 2017). In addition, some studies suggested that SLF I mainly connect the core areas of the dorsal attention network (DAN), and the SLF III mainly connect the areas of ventral attention network (VAN). While the middle SLF II, however, is reported to directly connect the DAN and the VAN, which may provide critical anatomical communication for the two attention systems (Thiebaut de Schotten et al. 2011a; Sani et al. 2019; Suo et al. 2021). Therefore, the

later development tracts such as the SLF II may contribute more to higher-level brain functions especially in mediating between the SLF I and SLF III.

Limitations and future directions

We segmented the neonatal SLF into three branches and assessed quantitatively the maturation status of each branch using diffusion MRI technique. None of this has been deeply explored before. However, one of the limitations in our study is that the definition of each individual cortical ROIs was based on the registered newborn AAL atlases, whose precision and accuracy need to be further improved. In addition, although diffusion MRI tractography is currently the only non-invasive detection method of the white matter structure in vivo, our results still need to be histologically verified for the widely acknowledged limitations of tractography. And we will supplement and confirm our studies in the future through the fiber dissection technique of newborn specimens.

Declarations

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Conflicts of interest/Competing interests

We declare that there is no conflict of interest in the submission of this manuscript.

Availability of data and material

The data used in this paper were provided by Developing Human Connectome Project (dHCP) and can be downloaded from <http://developingconnectome.org/> (the website address of dHCP).

Code availability

Our python script developed for calculating the average value of metric values will be made available on request from any qualified investigator who provides a practicable proposal, or for the purpose of replicating procedures and results presented in our study.

Authors' contributions

Wenjia Liang: Conception and design, Methodology, Formal analysis, Writing-original draft. **Qiaowen Yu:** Conception and design, Writing-editing. **Wenjun Wang:** Methodology, Writing-editing. **Thijs Dhollander:** Methodology, Software. **Emmanuel Suluba, Zhuoran Li, Feifei Xu, Yang Hu:** Writing-editing. **Yuchun Tang:**

Writing-editing, Funding acquisition. **Shuwei Liu:** Conception and design, Writing-review, Supervision, Funding acquisition.

Ethics approval

Data of this study were acquired from the Developing Human Connectome Project (dHCP). The research of dHCP was approved by the UK Health Research Authority (Research Ethics Committee reference number: 14/LO/1169).

Consent to participate and consent for publication

Written parental consent have been obtained in every case for imaging and data release in the Developing Human Connectome Project.

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Figures

Figure 1

The placement of left SLF I ROI masks. (A) Sagittal view of WM-FOD map, and eight ROIs (a-h) were placed in the walking areas of the left SLF I. (B) The seven ROIs (b-h) were shown in a cross-sectional position. (C-D) The two ROIs (b and f) were shown in a coronal position

Figure 2

The placement of left SLF II ROI masks. (A) Sagittal view of WM-FOD map, and six ROIs (a-f) were placed in the walking areas of the left SLF II. (B) The four ROIs (b-e) were shown in a cross-sectional position. (C-D) The two ROIs (b and d) were shown in a coronal position

Figure 3

The placement of left SLF III ROI masks. (A) Sagittal view of WM-FOD map, and four ROIs (a-d) were placed in the walking areas of the left SLF III. (B) The four ROIs (a-d) were shown in a cross-sectional position. (C-D) The two ROIs (a and c) were shown in a coronal position

Figure 4

The placement of left SLF II and SLF III ROI masks. (A) Sagittal view of WM-FOD map, and different colorful masks (a-f) represent the ROIs of different SLF branches. Green ROIs were put in the left SLF II running areas, while red ROIs were put in the left SLF III running areas. (B) Coronal view of WM-FOD map, which is also the coronal plane of mask “d” in Figure (A). The yellow, green and red masks represent ROI regions of SLF I, SLF II and SLF III respectively

Figure 5

a three-dimensional view of SLF three branches

Figure 6

The tracking results of SLF I. (a-b) a sagittal view of the left SLF I (yellow) and left cingulum (green). (c-d) the cortical regions that SLF I connected. SFGmed medial superior frontal gyrus, SFGdor dorsal superior frontal gyrus, SMA supplementary motor area, PCL paracentral lobule, PCUN precuneus, SPG superior parietal gyrus

Figure 7

The tracking results of SLF II. (a-b) a sagittal view of the left SLF II (green) and left superior fronto-occipital fasciculus (yellow). (c-d) the cortical regions that SLF II connected. SFOF superior fronto-occipital fasciculus, MFG middle frontal gyrus, PreCG precentral gyrus, IPL inferior parietal lobule, ANG angular gyrus

Figure 8

The tracking results of SLF III. (a-b) a sagittal view of the left SLF II (green) and SLF III (red). (c-d) the cortical regions that SLF III connected. IFGtriang inferior frontal gyrus (triangular), IFGoperc inferior frontal gyrus (opercular), PreCG precentral gyrus, SMG supramarginal gyrus

Figure 9

The scatter plot of tract-specific microstructural indices (DTI and NODDI parameters) varying with gestational age

Figure 10

The DTI and NODDI parameters values of SLF three branches. Asterisks indicate that the differences of parameters values among the branches of SLF were statistically significant, $p < 0.05$

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