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Research article

The ascending reticular activating system from pontine reticular formation to the hypothalamus in the human brain: A diffusion tensor imaging study

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HIGHLIGHTS

- We identified the ARAS from the pontine RF to the hypothalamus in the normal brain.
- Thirty-one healthy subjects were recruited for study using diffusion tensor imaging.
- Reliability of identification of ARAS by two evaluators was 96.8%.

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ABSTRACT

The ascending reticular activating system (ARAS) is responsible for regulation of consciousness. Precise evaluation of the ARAS is important for diagnosis and management of patients with impaired consciousness. In the current study, we attempted to reconstruct the portion of the ARAS from the pontine reticular formation (RF) to the hypothalamus in normal subjects, using diffusion tensor imaging (DTI). A total of 31 healthy subjects were recruited for this study. DTI scanning was performed using 1.5-T, and the ARAS from the pontine RF to the hypothalamus was reconstructed. Values of fractional anisotropy, mean diffusivity, and tract volume of the ARAS from the pontine RF to the hypothalamus were measured. In all subjects, the ARAS from the pontine RF to the hypothalamus originated from the RF at the level of the midpons, where the trigeminal nerve could be seen, ascended through the periaqueductal gray matter of the midbrain anterolaterally to the anterior commissure level, and then terminated into the hypothalamus. No significant differences in DTI parameters were observed between the left and right hemispheres and between males and females ($p < 0.05$). We identified the ARAS between the pontine RF and the hypothalamus in normal subjects using DTI. We believe that the reconstruction methodology and the results of this study would be useful to clinicians involved in the care of patients with impaired consciousness and researchers in studies of the ARAS.

1. Introduction

Consciousness involves two main components: arousal and awareness of oneself and the environment [25]. The ascending reticular activating system (ARAS) is responsible for regulation of consciousness [17,25,29]. The ARAS is a complicated network which connects a portion of the brainstem reticular formation (RF), nonspecific thalamic nuclei, basal forebrain, hypothalamus, and cerebral cortex [4,17,29]. In detail, the ARAS originates from the RF of the lower midbrain and upper pons, and exerts its influence on the cerebral cortex via three main routes: (1) dorsal pathway; via nonspecific thalamic nuclei, (2) ventral pathway; via hypothalamus and basal forebrain, and (3) direct pathway into the cerebral cortex [4,17,25,29]. Precise evaluation of the ARAS is important for diagnosis and management of patients with impaired consciousness such as vegetative or minimally conscious patients [25,29].

Before development of diffusion tensor imaging (DTI), precise evaluation of the ARAS in the live human brain was limited because the majority of the ARAS is not clearly discriminated with adjacent neural structures. By contrast, DTI enables three dimensional reconstruction and evaluation of the ARAS in the live human brain [7,11,27]. A few studies have demonstrated the usefulness of DTI

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for three-dimensional evaluation of the ARAS in patients with impaired consciousness following brain injury [6,10]. However, in these studies only some parts of the ARAS were reconstructed and no study on the neural pathway from the pontine RF to hypothalamus has been reported. Because the hypothalamus is involved in regulation of sleep and wakefulness as the main timekeeper of consciousness, the reconstruction of the ARAS from the pontine RF to hypothalamus would be useful in research on consciousness in terms of sleep and wakefulness [12,13,21,28].

In the current study, we attempted to reconstruct the portion of the ARAS from the pontine RF to the hypothalamus in normal subjects, using DTI.

2. Subjects and methods

2.1. Subjects

Thirty-one healthy subjects (males: 18, females: 13, mean age: 37.6 ± 10.0 years, range: 22–56 years) with no previous history of neurological, physical, or psychiatric illness were recruited for this study. All subjects understood the purpose of the study and provided written informed consent. The study protocol was approved by our local Institutional Review Board.

2.2. Data acquisition

A 6-channel head coil on a 1.5 T Philips Gyroscan Intera (Philips, Ltd Best, The Netherlands) with single-shot echo-planar imaging (EPI) was used for acquisition of DTI data. For each of the 32 non-collinear, diffusion-sensitizing gradients, we acquired 70 contiguous slices parallel to the anterior commissure-posterior commissure line. Imaging parameters of DTI were as follows: acquisition matrix = 96 × 96; reconstructed to matrix = 192 × 192; field of view = 240 × 240 mm^2; repetition time (TR) = 10,398 ms; echo time (TE) = 72 ms; parallel imaging reduction factor (SENSE factor) = 2; echo-planar imaging (EPI) factor = 59; b = 1000 s/mm^2; number of excitations (NEX) = 1; and a slice thickness of 2.5 mm. (acquired voxel size 1.25 × 1.25 × 2.5 mm^3).

2.3. Probabilistic fiber tracking

Analysis of diffusion-weighted imaging data was performed using the Oxford Center for Functional Magnetic Resonance Imaging of the Brain (FMRIB) Software Library (Version 5.0, FSL; www.fmrib.ox.ac.uk/fsl). Head motion effect and image distortion due to eddy current were corrected by affine multi-scale two-dimensional registration. Fiber tracking was performed using a probabilistic tractography method based on a multi-fiber model, and applied in the current study utilizing tractography routines implemented in FMRIB Diffusion with BedpostX method (5000 streamline samples, 0.5 mm step lengths, curvature thresholds = 0.2) [2,3,20]. For skull strip, brain extraction tool was used. The ARAS from the pontine RF to the hypothalamus was determined by selection of fibers passing through two regions of interest (ROIs), the seed ROI and target ROI with option of termination. For identification of the RF as the seed ROI, adjacent structures, that is, the medial lemniscus and rubrospinal tract, were reconstructed and then the seed ROI with option of termination was isolated and drawn at the RF at the mid-pons level where the trigeminal nerve could be seen (Fig. 1A) [14,27]. The target ROI was drawn at the hypothalamus including the mammillary body, which was identified by the optic tract (anterior boundary) and mammillary body (posterior boundary) on the upper midbrain level with a b0 map (Fig. 1A) [5,14]. Out of 5000 samples generated from a seed voxel, results were visualized at the threshold of 2 streamlines through each voxel for analysis. Using MATLAB™ (Matlab R2007b, The Mathworks, Natick, MA, USA), values of fractional anisotropy (FA), mean diffusivity (MD), and tract volume of the reconstructed ARAS from the pontine RF to the hypothalamus were measured. For the reliability, we confirmed the identical course of trajectory of ARAS from the pontine RF to the hypothalamus.

Table 1
Diffusion tensor tractography parameters of the ascending reticular activating system from the pontine reticular formation to the hypothalamus.

		FA	MD	Tract volume
Hemisphere	Right	0.37 (0.03)	1.04 (0.07)	263.45 (94.28)
	Left	0.36 (0.04)	1.07 (0.08)	281.74 (97.08)
	Both	0.36 (0.03)	1.06 (0.08)	272.60 (95.35)
Sex	Male	0.36 (0.03)	1.07 (0.06)	286.03 (92.60)
	Female	0.37 (0.03)	1.04 (0.09)	254.00 (97.77)
	Both	0.36 (0.03)	1.06 (0.08)	272.60 (95.35)

Values represent mean (±standard deviation), FA: fractional anisotropy, MD: mean diffusivity, MD × 10^{-3}(mm^2/s).

2.4. Statistical analysis

SPSS software (v.15.0; SPSS, Chicago, IL) was used for data analysis. An independent t-test was used for determination of variances in the value of FA, MD, and tract volume between the right and left hemispheres and between male and female. In addition, for measurement of intra- and inter-observer reliability, the intraclass correlation coefficient (ICC) was determined by two evaluators (Kwon HG and Seo YS) who were blinded to the other evaluator's data [19]. The significant level of the p value was set at 0.05.

3. Results

In all subjects, the ARAS from the pontine RF to the hypothalamus originated from the RF at the level of the mid-pons where the trigeminal nerve could be seen, ascended through the periaqueductal gray matter of the midbrain anterolaterally to the anterior commissure level, and then terminated into the hypothalamus.

Mean values for FA, MD, and tract volume were 0.36, 1.06, and 272.60, respectively. In terms of FA, MD, and tract volume, no significant differences were observed between the right and left hemispheres and between males and females ($p < 0.05$) (Table 1).

Regarding the reliability, the consistency rates of analyses by two evaluators were identical course of trajectory of ARAS from the pontine RF to the hypothalamus for 60 out of 62 hemispheres (96.8%), and two sets of analyses performed by one analyzer (Kwon HG) were identical course of trajectory of ARAS from the pontine RF to the hypothalamus for 62 out of 62 hemispheres (100%). In addition, results of ICC for two evaluators in FA, MD, and tract volume were 0.93 (excellent reliability), 0.86 (excellent reliability), and 0.91 (excellent reliability), respectively [19]. For two sets of analyses by one evaluator, results of ICC were 0.96 (excellent reliability), 0.88 (excellent reliability), and 0.95 (excellent reliability), respectively [19].

4. Discussion

In the current study, we reconstructed a portion of the ARAS from the pontine RF to the hypothalamus in normal subjects, using DTI. We selected two ROIs for reconstruction of the neural pathway between the pontine RF and the hypothalamus as follows. The seed ROI was placed on the RF of the mid-pons at the level of the trigeminal nerve entry zone with the boundary of the medial lemniscus anteriorly and the rubrospinal tract laterally [1,4]. The target ROI was placed on the hypothalamus with the boundary of the optic tract anterolaterally and the posterior margin of the mammillary