Clinical Case Report

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Structural and functional connectivity of ascending reticular activating system in a patient with impaired consciousness after a cardiac arrest

A case report

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Abstract

Rationale: Diffusion tensor imaging (DTI), diffusion tensor tractography (DTT), as well as resting-state-functional magnetic resonance imaging (rsfMRI) are promising methods for assessing patients with disorders of consciousness (DOCs).

Patient concerns: This work describes the main findings using DTI, DTT, and rsfMRI in a patient with a DOC secondary to an anoxic encephalopathy who had a fatal outcome. She was an 85-year-old woman who presented a cardiac arrest and underwent cardiopulmonary resuscitation for 20 minutes then returning to spontaneous circulation. After sedation withdrawal, 2 days after the event, she remained with a Glasgow Coma Scale score of 3/15 and with an absence of brainstem reflexes.

Diagnoses: DOC secondary to an anoxic encephalopathy after cardiovascular resuscitation.

Interventions: A complete brain MRI scan was performed 72 hours after the initial event, including DTI, DTT, and rsfMRI. DTT demonstrated disruption of both ventral and dorsal tegmental tracts bilaterally. DTI showed a reduction of fractional anisotropic level in the mesencephalic nuclei. Moreover, changes in the number of fiber tracts were not evidenced in any portions of the ascending reticular activating system (ARAS). Finally, an increase in the anticorrelated and correlated association among the nuclei in the ARAS and the cortex was evidenced.

Outcomes: Patient deceased.

Lessons: Neuroimaging demonstrated low FA values in the ARAS, destruction of dorsal and ventral tegmental tracts, as well as hyper-connective (highly correlated or anti-correlated) association among ARAS and cortical nuclei compared with 3 healthy control subjects.

Abbreviations: AAN = Arousal Network Atlas, ADC = apparent diffusion coefficient, ARAS = ascending reticular activating system, BOLD = blood-oxygen-level dependent imaging, DIPY = Diffusion Imaging in Python, DOC = disorder of consciousness, DTI = diffusion tensor imaging, DTT = diffusion tensor tractography, DWI = diffusion weighted imaging, FA = fractional anisotropy, FC = functional connectivity, FSL = FMRIB Software Library, ODF = orientation distribution function, ROI = region of interest, rsfMRI = resting-state functional magnetic resonance imaging, TBI = traumatic brain injury.

Keywords: ascending reticular activating system, consciousness, diffusion tensor imaging, arousal, fMRI, tractography

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1. Introduction

Diffuse cerebral hypoxia resulting by the interruption of cerebral blood flow following cardiac arrest is the leading cause of neurological dysfunction.[1] After successful cardiopulmonary resuscitation in this kind of patients, many of them can present disorders of consciousness (DOC).[1] The integrity of neuronal and functional substrates of consciousness, including the ascending reticular activating system (ARAS), after a cerebral hypoxic event in these patients, is critical in their neurological prognosis.[2] The ARAS is a hierarchically organized pathway of neurons sourced in the brainstem which seems to be linked with the wakefulness component of consciousness.[3] Recent neuroimaging techniques such as diffusion tensor imaging (DTI), diffusion tensor tractography (DTT), and resting-state functional magnetic resonance imaging (rsfMRI) have allowed characterization of the integrity of the ARAS in patients with DOCs.[4] These techniques may improve our understanding of the underlying mechanisms of DOCs and may help to characterize the functional and structural features of the ARAS, which could be critical in a clinical setting for determination of suitable treatments or even for a prognosis calculation.[5] This work describes the main findings in the functional and structural characterization of the ARAS using DTI, DTT, and rsfMRI techniques in a patient with a DOC secondary to a hypoxic-ischemic encephalopathy who had a fatal outcome.

2. Case report

2.1. Neuroimaging data acquisition

A 1.5T General Electric resonator was used to collect the images. One hundred eighty multislice T2*-weighted functional images were acquired using axial slice orientation and covering the whole brain (slice thickness = 4.5 mm without free space, matrix = 64 × 64 mm, TR = 3000 ms, TE = 60 ms, flip angle = 90°, and FOV = 288 × 288 mm). The 3 initial volumes were discarded to avoid T1 saturation effects. Moreover, an axial diffusion weighted imaging (DWI) (slice thickness = 2.5 mm without free space, matrix = 100 × 100, TR = 17,000 ms, TE = 96 ms, flip angle = 90°, FOV = 250 × 250 mm, b value = 1000 and gradient directions = 30) was acquired. Finally, a structural axial T1 (slice thickness = 1 mm, GAP = 1 mm, matrix = 256 × 256 mm, TR = 670 ms, TE = 22 ms, flip angle = 20°, and FOV = 250 × 250 mm), and axial T2 (slice thickness = 6 mm, GAP = 1 mm, matrix = 320 × 320 mm, TR = 6.000 ms, TE = 96 ms, flip angle = 90°, and FOV = 220 × 220 mm) images were also acquired for an anatomical reference.

2.2. Neuroimaging data preprocessing

rsfMRI data were preprocessed using SPM8 (http://www.fil.ion.ucl.ac.uk/spm/). Preprocessing included: manual realignment, automatic realignment, coregistration of functional onto structural data, segmentation of structural data, normalization into MNI space, and spatial smoothing with a Gaussian kernel of 8 mm. The spurious variance was reduced by regression of nuisance waveforms derived of time series extracted from regions of noninterest white matter and cerebrospinal fluid. Additionally, nuisance regressors included the blood-oxygen-level dependent *imaging* (BOLD) time series averaged over the whole brain.[6] Finally, small head motions were corrected using *ArtRepair* (http://cibsr.stanford.edu/tools/ArtRepair/). DWI was preprocessed using *FMRIB Software Library* (FSL)[7] and *Diffusion Imaging in Python* (DIPY) library.[8] This process included automatic realignment, correction of eddy-current artifacts, reslicing to obtain isotropic voxel size, brain extraction, and improvement of signal-to-noise rate using a Non-Local mean algorithm.

2.3. Location and characterization of the regions of interest

Regions of interest (ROI) to characterize the ARAS were located based on our previous experience.[9] ROIs included the dorsal raphe, mesencephalic reticular formation from Harvard Ascending Arousal Network Atlas (AAN) provided by the Martinos Center for Biomedical Imaging, Charleston, MA,[2] the hypothalamus (bilaterally) from Talairach Atlas, by the Research Imaging Institute of the University of Texas Health Science Center San Antonio,[10] and the intralaminar nuclei of the thalamus (bilaterally) (anterior—rostral: central medial nucleus, central lateral nucleus, and posterior—caudal: centromedian nucleus, parafascicular nucleus), provided by the Morel stereotactic atlas[11] (Fig. 1). These nuclei were linearly (rigid, translation, and affine transformation) and nonlinearly (symmetric diffeomorphic registration[12]) registered with each subject space. Finally, the mean and standard deviation of the fractional anisotropy (FA) values were computed for each ROIs and compared with 3 neurological healthy control values.

2.4. Functional connectivity inside ARAS

Functional connectivity (FC) was estimated using a measure of Pearson correlation among the average filtered time courses of 9

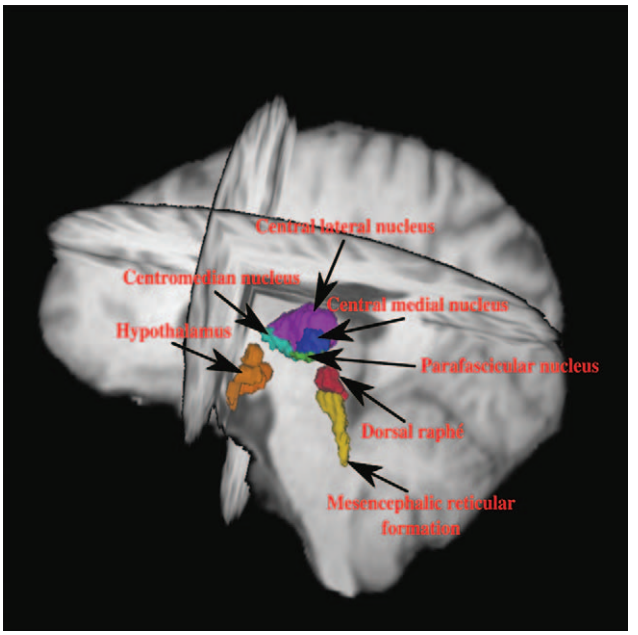

Figure 1. ROIs location of the ARAS. Blue, purple, cyan, and green nucleus (Central medial, central lateral, centromedian, and parafascicular) are the intralaminar thalamic nucleus. Yellow and red nucleus (mesencephalic reticular formation and Dorsal raphe) are the mesencephalic nucleus. Finally, orange ROIs are the hippocampal nucleus. ARAS = ascending reticular activating system, ROI = region of interest.

Table 1

Fractional anisotropy and number of tracts analysis.

Variable	Patient (n = 1)	Healthy control (n = 3)
FA values for each ROI location (mean ± standard deviation)		
Dorsal raphe	0.294 ± 0.084	0.377 ± 0.095
Midbrain reticular formation	0.235 ± 0.085	0.299 ± 0.094
Thalamus	0.270 ± 0.044	0.247 ± 0.067
Hypothalamus	0.266 ± 0.071	0.185 ± 0.102
Number of tracts for each ARAS portion (mean ± SD)		
Upper	3526	3161 ± 562
Dorsal lower	2168	2336 ± 240
Ventral lower	1396	1550 ± 410

An automatic seeding of regions of interest (ROIs) was performed. The number of tracts, as well as fractional anisotropy values, is demonstrated for each ROI and portion of the ascending reticular activating system.

ARAS nuclei from the AAN Atlas and the 48-cortical nucleus from Harvard-Oxford Atlas provided by Harvard Center for Morphometric Analysis.[13] The filter used in this step was a bandpass Butterworth filter with cut-off frequencies set at 0.005 and 0.1 Hz.[14]

2.5. Structural connectivity inside ARAS

A Constant Solid Angle model was used to obtain the directions from the diffusion imaging.[15] This model estimates the orientation distribution function (ODF) at each voxel. This ODF is a function of the distribution of water movement and its peaks are a suitable estimate for the orientation of track at a voxel. Afterward, a deterministic local fiber tracking algorithm was used just in the white matter,[16] with the following set of parameters: min separation angle = 30°, step size = 1, and number of seed in each voxel = 8. Three parts of the ARAS were reconstructed similarly to.[5] The upper ARAS: fibers passing through intralaminar thalamic nucleus to the cerebral cortex, the dorsal lower ARAS: fibers passing through the mesencephalic reticular formation and dorsal raphe to the intralaminar thalamic nucleus, and the ventral lower ARAS: fibers passing through the hypothalamus. Finally, the structural connectivity was defined as the fiber count in each part of the ARAS.

Authorization was requested to our Institutional Ethics Board to include the information of the patients (case report and 3 controls) in this study, preserving their identity both in the analysis of the information and in the images presented. The family of the patient provided written informed consent for the publication of this case. This is a retrospectively reviewed case report with approval by the Fundación Universitaria de Ciencias de la Salud Review Board.

2.6. Case report

An 85-year-old woman arrived at the emergency room after presenting a cardiac arrest. She underwent cardiopulmonary resuscitation for 20 minutes then returning to spontaneous circulation. At the interrogatory, the family referred that a month before she was treated for a urinary tract infection and that in the last few days she presented left pleuritic pain and cough. She also had a prior history of dementia, arterial hypertension, diabetes mellitus type II, and depression. The initial neurological exam was biased by sedation effects: she showed no brain reflexes and mydriatic pupils at admission. Admission workup demonstrated leukocytosis with neutrophilia, a type II myocardial infarction, and a right basal consolidation in the thoracic x-ray. She was diagnosed with a septic shock of pulmonary origin and with a myocardial infarction. Afterward, the patient was admitted to the intensive care unit, where she remained with antibiotics (piperacillin 4.5 gr QID, clarithromycin 500 mg BID), a vasopressor (norepinephrine), and mechanical ventilator support. A brain CT scan was performed demonstrating a diffuse brain edema with secondary subfalcine and transtentorial herniation. After sedation withdrawal, 2 days after the event, she remained with a Glasgow Coma Scale score of 3/15 and with an absence of brainstem reflexes. A complete brain MRI scan was performed 72 hours after the initial event, including both BOLD signal and DTI acquisitions. After the MRI scan was performed, later the same day the patient presented a second cardiac arrest. An unsuccessful cardiopulmonary resuscitation was intended, but the patient finally deceased.

DTT demonstrated a disruption of both ventral and dorsal tegmental tracts bilaterally (Fig. 2). Changes in the number of fibers were not evidenced in the patient for each portion of the ARAS compared with healthy controls. Additionally, a reduction in the FA values within the mesencephalic nuclei was shown (Table 1). Finally, FC among the ARAS and cortical nuclei seems to be more hyperconnected in this patient compared with control subjects. In particular, more anticorrelated (superior parietal lobule, supramarginal gyrus, angular gyrus, cingulate gyrus, central opercular cortex) and correlated (insular cortex, temporal pole, temporal gyrus, parahippocampal gyrus, parietal operculum cortex) brain regions associations with ARAS nucleus were found (Fig. 3).

3. Discussion

Cases reporting ARAS reconstruction using DTT in patients with DOCs secondary to cardiac arrest have demonstrated affection of the ARAS either by thinning of the fibers or absence of fiber projections to certain regions.[17,18] Previously, DTI has shown changes in the free diffusion values measured using FA in the ARAS nucleus in patients with DOC compared with control subjects.[2,9,17–19] As far as we know, rsfMRI has not been used to estimate the integrity of ARAS in these patients; therefore, this case report shows a novel approach in this context.

3.1. Structural connectivity of the ARAS

A meta-analysis recently demonstrated that FA correlates better with consciousness levels compared with other MRI tools like apparent diffusion coefficient (ADC) in patients with traumatic brain injury (TBI).[20] However, it also showed that the degree of

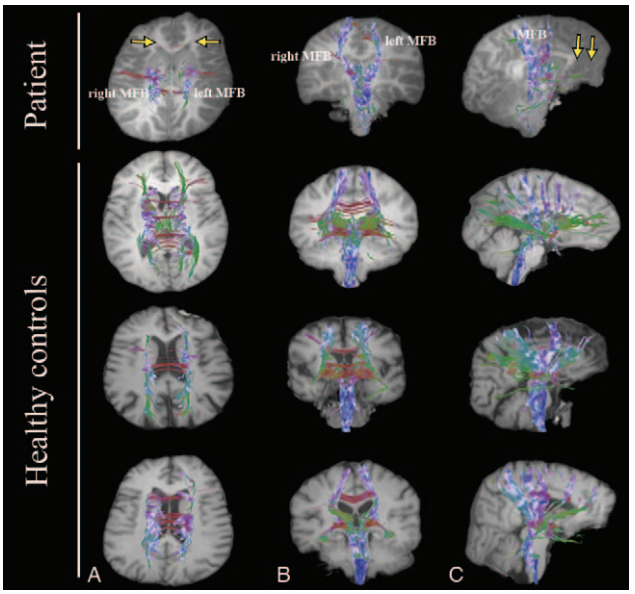

Figure 2. Tractography reconstruction of the ascending reticular activating system. (A) Superior, (B) anterior, and (C) lateral views of tractography of the ARAS are demonstrated in the patient, as well as in healthy controls. The fibers coming upward from brainstem to the intrathalamic complex are demonstrated, represented by the median and dorsal raphe fibers, which remain intact. The posterior fibers that extend to the posterior frontal cortex remain intact bilaterally as well, which represent the medial forebrain bundle (MFB). Both the dorsal and ventral tegmental tracts are disrupted bilaterally (arrows). ARAS = ascending reticular activating system.

correlation varies among brain regions. Multiple manual and automatic protocols have been reported for the reconstruction of the ARAS with DTT aiming to correlate radiological findings with the level of consciousness after a TBI or stroke.[2,9,17–19] Descriptions among these reports reflect a wide variety within the grade and localization of injury in ARAS pathways. Mean FA in healthy subjects has been reported to be around 0.4.[17] In this report, we described the majority of FA values in healthy controls below this reported normality threshold, being the lowest value at the hypothalamus bilaterally (0.185) (Table 1). Also, a considerable decrease in FA value was noted in the midbrain reticular formation and dorsal raphS ROIs, compared with healthy control subjects mean FA values. Additionally, visual 3-dimensional reconstruction of tractography consequently demonstrated a disruption in the reconstruction of both ventral and dorsal tegmental tracts bilaterally (Fig. 2). Disruption of this connection between the brainstem and the basal frontal cortex may represent a dysfunction in the ARAS measured by the number of fiber tracts among them. However, the severity of affection of the consciousness is not well understood. A severe affection of the consciousness was present in this patient, followed by a fatal outcome. Information regarding long-term neurological outcomes is missing. A correlation between this damage and clinical outcome is still a matter of study.

3.2. Functional connectivity of the ARAS

Recently, rsfMRI has been used to characterize the brain dynamics in patients with DOCs.[21] Main findings showed a

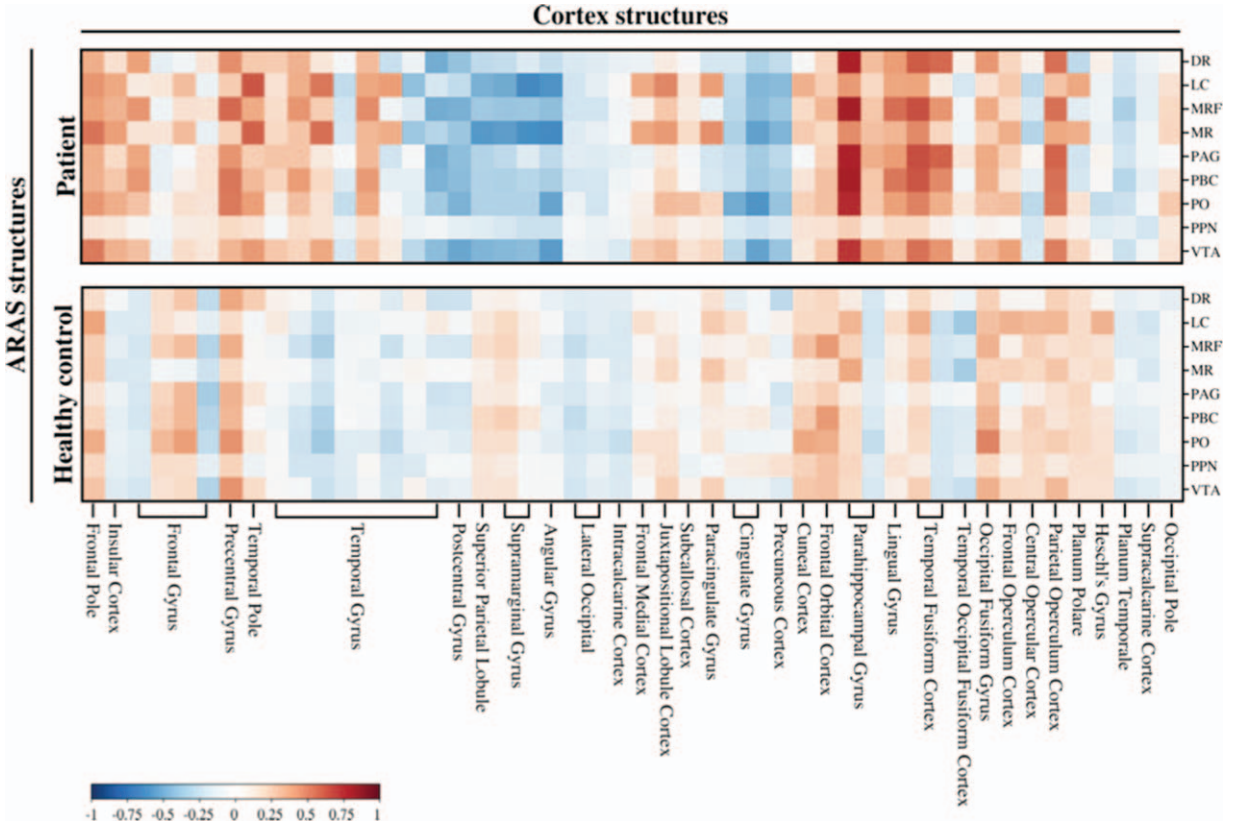

Figure 3. Average functional connectivity between ascending reticular activating system and cortical nuclei. The direction of associative connection is represented in colors between anatomical structures. Correlated and anticorrelated associations between cortical and ARAS nuclei are represented. ARAS = ascending reticular activating system.

hyperconnective (highly correlated or anticorrelated) association among resting state networks, similarly to our results for these patients.[21,22] Our results showed an increased level of integration among the ARAS and cortical nuclei. This hyperconnectivity level could produce a reduction of segregation level in the functions linked with the consciousness. In consequence, it may possibly trigger a breakdown of brain functional modularity. Recent computational models suggest that too much integration between brain systems, which are normally segregated, may facilitate the abnormal propagation of information across the brain,[23] resulting in a reduction of the functional specialization and abnormal cerebral activity.[24] A similar result was shown in the beta band connectivity using electroencephalography during the transitions into and from unconsciousness based on propofol sedation.[25] Additional information regarding the correlation of these findings with further clinical changes in follow-ups is required.

4. Conclusions

The DTI, DTT, and rsfMRI analysis of the ARAS were performed in a patient with a DOC secondary to a hypoxic-ischemic encephalopathy after a cardiac arrest. Neuroimaging demonstrated low FA values in the ARAS, destruction of dorsal and ventral tegmental tracts, as well as hyperconnective (highly correlated or anticorrelated) association among ARAS and cortical nuclei compared with 3 healthy control subjects.

Author contributions

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