

Relationship Between Injured Cingulum and Impaired Consciousness in Patients with Hypoxic-Ischemic Brain Injury

SungHO Jang

Yeungnam University Medical Center

YOUSUNG SEO (✉ yousung1008@daum.net)

Daegu Haany University - Samsung Campus: Daegu Haany University <https://orcid.org/0000-0002-7480-3071>

Research Article

Keywords: Cingulum, Consciousness, Diffusion tensor tractography, Hypoxic-ischemic brain injury

Posted Date: December 28th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-1154550/v1>

License:   This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Abstract

Objectives

We investigated the relationship between cingulum injury and impaired consciousness in patients with hypoxic-ischemic brain injury (HI-BI) by using diffusion tensor tractography (DTT).

Methods

We recruited 29 patients with HI-BI and 25 normal control subjects. The patients were classified as intact consciousness (group A, 13 patients) or impaired consciousness (group B, 16 patients). The DTT parameters of fractional anisotropy (FA) and tract volume (TV) were estimated for both cinguli. Glasgow Coma Scale (GCS) and Coma Recovery Scale-Revised (CRS-R) scores were also evaluated.

Results

The FA and TV values of the cinguli in groups A and B were lower than those of the control group ($p < 0.05$), and the FA and TV values of group B were lower than those of group A ($p < 0.05$). The FA and TV values of the cinguli in group A were not significantly correlated with GCS and CRS-R scores ($p > 0.05$); however, regarding the group B, the FA correlations with GCS ($r = 0.457, p < 0.05$) and CRS-R ($r = 0.494, p < 0.05$) and those of TV with GCS ($r = 0.500, p < 0.05$) and CRS-R ($r = 0.491, p < 0.05$) were moderately positive.

Conclusions

We found a significant relationship between injury of the cingulum and impaired consciousness in patients with HI-BI. Our results suggest that an injured cingulum could be an appropriate target for neurointervention or neurorehabilitation in patients with impaired consciousness following HI-BI.

Introduction

Hypoxic-ischemic brain injury (HI-BI) may be caused by strangulation, cardiopulmonary arrest, respiratory failure, carbon monoxide poisoning, etc. Patients with HI-BI exhibit various sequelae, and impaired consciousness is a major sequela that is reported to have a high incidence rate; only 27% of HI-BI patients recover consciousness and the other 73% of patients either exhibit impaired consciousness or die (Lu-Emerson et al., 2010; Heinz et al., 2015). The pathophysiologic mechanisms of impaired consciousness in HI-BI can include abnormal connectivity or dysfunction of the hemispheres or deep structures of the brain, such as the reticular activating system, and the connection between the cingulate cortex and some nuclei of the thalamus (Parvizi et al., 2006; Cauda et al., 2010; Kelly 2001; Huff et al., 2017). However, such mechanisms have not yet been fully elucidated.

Human consciousness is mainly controlled by the actions of the ascending reticular activating system (ARAS) (Paus, 2000; Zeman, 2001; Daube, 1986; Afifi et al., 2005). However, several studies have reported that brain areas other than the ARAS are also involved in human consciousness (Horovitz et al., 2008; Buckner et al., 2008; Greicius et al., 2004; Norton et al., et al., 2012; Vanhaudenhuyse et al., 2010; Qin et al., 2015; Mulert et al., 2005; Jang et al., 2016; Laureys et al., 2000; Zhang et al., 2017; Herbert et al., 2016; Herbert et al., 2014; Guldenmund et al., 2013; Arentz et al., 2014). It includes the corpus callosum, cingulate cortex, medial prefrontal cortex, visual cortex, thalamus, and brain stem (Horovitz et al., 2008; Buckner et al., 2008; Greicius et al., 2004; Norton et al., et al., 2012; Vanhaudenhuyse et al., 2010; Qin et al., 2015; Mulert et al., 2005; Laureys et al., 2000; Zhang et al., 2017; Herbert et al., 2014; Herbert et al., 2016; Guldenmund et al., 2013; Arentz et al., 2014). The cingulum, which is located beneath the cingulate cortex, is reported to have an important role in cognitive function, including attention, learning, memory, emotion, motivation and pain perception (Mufson et al., 2005; Bush et al., 2000; Vogt et al., 1992). Recently, a few studies using diffusion tensor tractography (DTT), which is derived from diffusion tensor imaging (DTI), have reported the possibility that the cingulum might be related with consciousness in patient with HI-BI (Jang et al., 2016; Lee et al., 2012). However, there are no known reports on the relationship between cingulum injury and impaired consciousness in patients with HI-BI (Qin et al., 2015; Mulert et al., 2005; Jang et al., 2016; Laureys et al., 2000; Zhang et al., 2017; Herbert et al., 2016; Herbert et al., 2014)].

We hypothesized that there would be a close relationship between injury of the cingulum and impaired consciousness in patients with HI-BI. Thus, in the current study, we investigated the relationship between injury of the cingulum and impaired consciousness in patients with HI-BI by assessing DTT parameters.

Methods

Subjects

Twenty-nine consecutive patients (19 men, 10 women; mean age, 45.9 ± 16.4 years, range, 18–74) were recruited according to the following inclusion criteria: (1) with an obvious HI-BI history (*e.g.*, cardiac arrest, strangulation, CO intoxication, etc.), (2) age at the time of HI-BI: 20–75 years, (3) between 3 weeks and 12 months after the onset of HI-BI, and (4) no previous history of head trauma or neurologic/psychiatric disease. Glasgow Coma Scale (GCS, full score: 15 points) and Coma Recovery Scale-Revised (CRS-R, full score: 23 points) scores were used to evaluate the consciousness of the patients at the time of DTI (Teasdale et al., 1974; Giacino et al., 2004; Schnakers et al., 2009)]. The patients were classified into two groups according to consciousness status: intact consciousness (group A; GCS score ≥ 15 and CRS-R score ≥ 23) and impaired consciousness (group B; GCS score < 15 or CRS-R score < 23). Thirteen patients (8 men, 5 women; mean age 48.3 ± 17.3 years, range 18–66) were assigned to group A and sixteen patients (11 men, 5 women; mean age 47.5 ± 14.5 years, range 18–74) were assigned to group B. Twenty-five age- and sex-matched healthy control subjects (14 men, 11 women; mean age 42.4 ± 13.5 years, range 21–72) were also recruited for the study. The demographic and clinical data of the patient and control groups are summarized in Table 1. No significant differences in age or sex composition were

observed between the patient and control groups or between groups A and B. This study was conducted retrospectively, and written consent was obtained from the control subjects. The institutional review board of a university hospital approved the study protocol.

Table 1
Demographic characteristics of the patient and control groups

	Group A	Group B	Control	<i>p</i> value
Age (years)	48.3 ± 17.3	47.5 ± 14.5	42.4 ± 13.5	0.001
Sex (male:female)	8:5	11:5	14:11	0.001
GCS score	14.7 ± 0.7	8.0 ± 2.9		0.001
CRS-R score	22.8 ± 0.4	8.6 ± 4.7		0.001

Values are presented as numbers or as means ± standard deviation; GCS: Glasgow Coma Scale; CRS-R: Coma Recovery Scale-Revised.

Diffusion Tensor Imaging and Tractography

DTI data were acquired at 6.13 ± 6.46 months after onset by using a 6-channel head coil on a 1.5 T Philips Gyroscan Intera (Philips, Best, Netherlands) with 32 non-collinear diffusion sensitizing gradients by single-shot echo-planar imaging. Imaging parameters were as follows: acquisition matrix = 96×96 , reconstructed to matrix = 192×192 , field of view = 240×240 mm², TR = 0.398 ms, TE = 72 ms, parallel imaging reduction factor = 2, echo-planar imaging factor = 59, b = 1000 s/mm², NEX = 1, slice gap = 0 mm, and slice thickness = 2.5 mm. Each DTI replication was intra-registered to baseline “b0” images for correction of residual eddy-current image distortions and head motion effects by using a diffusion registration package (Philips Medical Systems). Fiber tracking was performed by using the fiber assignment continuous tracking (FACT) algorithm implemented within the DTI task card software. The cinguli were identified by selection of fibers passing through two regions of interest (ROIs). The first ROI was placed on the most posterior coronal slice, and the second ROI was placed on the middle coronal slice. Termination criteria were fractional anisotropy (FA) <0.15 and an angle change of >27° (Malykhin et al., 2008). The FA and tract volume (TV) values were determined for both cinguli in each subject.

Statistical analysis

SPSS software (v.15.0; SPSS, Chicago, IL, USA) was used for data analysis. The chi-squared test was used to assess differences in sex composition and an independent t-test was used to assess age differences between groups A and B. Paired *t*-tests were used to assess differences in DTT parameters of the cingulum between groups A and B. The Pearson correlation test was used to identify correlations between DTT parameters of the cingulum and the consciousness data (GCS and CRS-R). Results were considered significant when the *p* value was <0.05. A correlation coefficient of more than 0.60 indicated

strong correlation, a correlation coefficient between 0.40 and 0.59 indicated moderate correlation, while that between 0.20 and 0.39 indicated weak correlation, and one less than 0.19 indicated a very weak correlation (Cohen J, 1988).

Results

A summary of the comparison of DTT parameters of cingulum between subgroup A and subgroup B and control groups is shown in Table 2. The values of FA and TV of the cingulum in the subgroup A and B were significantly different with those of the control group ($p < 0.05$). The values of FA and TV of cingulum were significantly different between the subgroup A and B ($p < 0.05$).

Table 2
Comparison of diffusion tensor tractography parameters of the cingulum in the patient and control groups.

DTT parameters		<i>p</i> value	
	Group A	Control	
FA	0.44 ± 0.05	0.49 ± 0.03	0.001
TV	364.17 ± 208.46	1059.77 ± 318.53	0.001
	Group B	Control	
FA	0.36 ± 0.07	0.49 ± 0.03	0.001
TV	176.31 ± 125.80	1059.77 ± 318.53	0.001
	Group A	Group B	
FA	0.44 ± 0.05	0.36 ± 0.07	0.001
TV	364.17 ± 208.46	176.31 ± 125.80	0.001
DTT: diffusion tensor tractography, FA: fractional anisotropy, TV: tract volume.			
Values represent mean ± standard deviations			
*: significant differences between patient and control groups, $p < 0.05$.			

The correlations between DTT parameters, and GCS and CRS-R scores in the group A and B are shown in Table 3. In the group A, no correlation was observed between DTT parameters and GCS and CRS-R scores ($p > 0.05$). However, regarding the group B, the moderate positive correlation was observed between GCS and the FA of the cingulum ($r = 0.457$, $p < 0.05$), and the TV of the cingulum ($r = 0.500$, $p < 0.05$). In terms of CRS-R, the moderate positive correlation was also observed in the value of FA of the cingulum ($r = 0.494$, $p < 0.05$), and the value of TV of the cingulum ($r = 0.491$, $p < 0.05$).

Table 3

Correlation coefficients for relationships between the duration of cardiopulmonary resuscitation and clinical scores and diffusion tensor tractography parameters.

		GCS	CRS-R
Group A	FA	0.225	0.337
	TV	0.056	0.043
Group B	FA	0.457*	0.494*
	TV	0.500*	0.491*
GCS: Glasgow Soma Scale, CRS-R: Coma Recovery Scale-Revised, FA: fractional anisotropy, TV: tract volume.			
*: significant ($p < 0.05$) correlation coefficient between clinical scores, duration of cardiopulmonary resuscitation and clinical scores and diffusion tensor tractography parameters.			

Discussion

In this study, we investigated the relationship between injury of the cingulum and impaired consciousness in patients with HI-BI. Our results are summarized as follows: 1) the values of FA and TV of the cinguli in patient groups A and B were lower than those of the control group, and the values of FA and TV of group B (impaired consciousness) were lower than those of the group A (intact consciousness), and 2) the values of FA and TV of the cinguli in patient group A were not significantly correlated with GCS or CRS-R scores; however, the values of FA and TV of patient group B had moderate positive correlations with GCS and CRS-R scores.

Among the DTT parameters, the FA and TV have most commonly been used to evaluate the status of neural tracts in patients with brain injury (Assaf et al., 2008; Neil et al., 2008; Jang et al., 2013). The FA value indicates the degree of directionality of water diffusion, and the FA value reflect white matter integrity (*e.g.*, loss of myelination, axon diameter, fiber density, or fiber organization) and a low FA value suggest loss of white matter integrity (Assaf et al., 2008; Neil, 2008). The TV value is determined by the number of voxels included in a neural tract, thereby suggesting the total number of fibers within the tract, and a low TV value reflects a loss of fibers. Therefore, decrements in FA or TV levels in the cinguli of patient groups A and B indicate the presence of cingulum injuries (Jang et al., 2013).

Regarding the correlation between DTT parameters (FA and TV) and GCS and CRS-R scores, we observed that only patient group B showed correlations between DTT parameters and GCS or CRS-R scores. Previous studies have demonstrated that the cingulate cortex, which is connected to other brain areas through the cingulum, is connected to thalamic nuclei, which is an area important for consciousness (Cauda et al., 2010; Assaf et al., 2008). In addition, many studies have demonstrated that the cingulate cortex, which is located above the cingulum, has an important role in consciousness (Horovitz et al.,

2008; Buckner et al., 2008; Greicius et al., 2004; Norton et al., et al., 2012; Vanhaudenhuyse et al., 2010; Qin et al., 2015; Mulert et al., 2005; Jang et al., 2016; Laureys et al., 2000; Zhang et al., 2017; Herbert et al., 2016; Herbert et al., 2014). The results of this study appear to support those in the above-mentioned previous studies (Cauda et al., 2010; Horovitz et al., 2008; Buckner et al., 2008; Greicius et al., 2004; Norton et al., et al., 2012; Vanhaudenhuyse et al., 2010; Qin et al., 2015; Mulert et al., 2005; Jang et al., 2016; Laureys et al., 2000; Zhang et al., 2017; Herbert et al., 2016; Herbert et al., 2014; Assaf et al., 2008)].

After the introduction of DTI, a few studies suggested the relation between the cingulum and consciousness (Jang et al., 2016; Lee et al., 2012). In 2012, Lee et al, reported that the patients (seven) with minimally conscious showed more severe injury of the cinguli that the patients (five) with intact alertness (Lee et al., 2012). In 2016, Jang *et al.* reported on a patient who demonstrated an ARAS change that was concurrent with recovery from a vegetative state to a minimally conscious state in a patient with HI-BI following TBI (Jang et al., 2016). On the serial DTTs, increased neural connectivities to the hypothalamus, basal forebrain, prefrontal cortex, anterior cingulate cortex (including the cingulum), and the parietal cortex were observed in both hemispheres on post-operative DTT compared to those on pre-operative DTT (Jang et al., 2016). To the best of our knowledge, the current study is the first to demonstrate, by using DTT, a relationship between injury of the cingulum and impaired consciousness in a large number of patients with HI-BI. However, some limitations of this study should be considered. First, DTT of the white matter of the brain can produce false negative results due to the presence of crossing fibers and/or the result of the partial volume effect (Parker et al., 2005). Second, this retrospective study included a relatively small number of subjects. Thus, prospective studies including a larger number of subjects should be encouraged.

In conclusion, we found a significant relationship between injury of the cingulum and impaired consciousness in patients with HI-BI. Our results suggest that an injured cingulum should be a target during neurointervention or neurorehabilitation of patients with impaired consciousness following HI-BI.

Declarations

Author contributions

Sung Ho Jang: Study concept and design, Manuscript development and writing, You Sung Seo: Study concept and design, Acquisition and analysis of data, Manuscript authorization

Source of funding

This work was supported by the National Research Foundation(NRF) of Korea Grant funded by the Korean Government(MSIP) (2021R1A2B5B01001386).

Competing interests

The authors reports no competing interests relevant to the manuscript.

Availability of data and materials

The data and materials available if needed.

Consent to publish

The authors agreed to publication

Consent to participate

The participants(or their family) agreed to publication

References

1. Afifi AK, Bergman RA (2005). Functional neuroanatomy : Text and atlas. New York: Lange Medical Books/McGraw-Hill.
2. Arenth PM, Russell KC, Scanlon JM, Kessler LJ, Ricker JH (2014). Corpus callosum integrity and neuropsychological performance after traumatic brain injury: a diffusion tensor imaging study. *J Head Trauma Rehabil*,29,E1-E10.
3. Assaf Y, Pasternak O (2008) Diffusion tensor imaging (DTI)-based white matter mapping in brain research: a review. *J Mol Neurosci*,34,51-61.
4. Buckner RL, Andrews-Hanna JR, Schacter DL (2008). The brain's default network: anatomy, function, and relevance to disease. *Ann N Y Acad Sci*,1124,1-38.
5. Bush G, Luu P, Posner MI: Cognitive and emotional influences in anterior cingulate cortex (2000). *Trends Cogn Sci*,4,215-222.
6. Cauda F, Geminiani G, D'Agata F, Sacco K, Duca S, Bagshaw AP, Cavanna AE (2010). Functional connectivity of the posteromedial cortex. *PLoS One*,5(9),e13107
7. Cohen J. Statistical power analysis for the behavioral sciences (1988). 2nd ed. Hillsdale, N.J.: L. Erlbaum Associates.
8. Daube JR (1986). Medical neurosciences: an approach to anatomy, pathology, and physiology by systems and levels. 2nd ed. Boston: Brown and Co.
9. Greicius MD, Srivastava G, Reiss AL, Menon V (2004). Default-mode network activity distinguishes Alzheimer's disease from healthy aging: evidence from functional MRI. *Proc Natl Acad Sci U S A*,101,4637-4642.
10. Giacino JT, Kalmar K, Whyte J (2004). The JFK Coma Recovery Scale-Revised: measurement characteristics and diagnostic utility. *Arch Phys Med Rehabil*,85,2020-2029.
11. Guldenmund P, Demertzi A, Boveroux P, Boly M, Vanhaudenhuyse A, Bruno MA, Gosseries O, Noirhomme Q, Brichant JF, Bonhomme V, Laureys S, Soddu A (2013). Thalamus, brainstem and salience network connectivity changes during propofol-induced sedation and unconsciousness. *Brain Connect*,3,273-285.

12. Herbet G, Lafargue G, de Champfleury NM, Moritz-Gasser S, le Bars E, Bonnetblanc F, Duffau H (2014). Disrupting posterior cingulate connectivity disconnects consciousness from the external environment. *Neuropsychologia*,56,239-244.
13. Herbet G, Lafargue G, Duffau H (2016). The dorsal cingulate cortex as a critical gateway in the network supporting conscious awareness. *Brain*,139,e23.
14. Horovitz SG, Fukunaga M, de Zwart JA, van Gelderen P, Fulton SC, Balkin TJ, Duyn JH (2008). Low frequency BOLD fluctuations during resting wakefulness and light sleep: a simultaneous EEG-fMRI study. *Hum Brain Mapp*,29,671-682.
15. Huff JS, Dulebohn S (2017): Coma. Treasure Island (FL): StatPearls Publishing.
16. Jang SH, Chang CH, Lee J, Kim CS, Seo JP, Yeo SS (2013). Functional role of the corticoreticular pathway in chronic stroke patients. *Stroke*,44,1099-1104.
17. Jang SH, Kim SH, Lee HD (2016). Recovery From Vegetative State to Minimally Conscious State: A Case Report. *Am J Phys Med Rehabil*,95,e63-66.
18. Kelly JP (2001). Loss of Consciousness: Pathophysiology and Implications in Grading and Safe Return to Play. *J Athl Train*,36,249-252.
19. Laureys S, Faymonville ME, Luxen A, Lamy M, Franck G, Maquet P (2000). Restoration of thalamocortical connectivity after recovery from persistent vegetative state. *Lancet*,355,1790-1791.
20. Lee AY, Shin DG, Park JS, Hong GR, Chang PH, Seo JP, Jang SH (2012). Neural tracts injuries in patients with hypoxic ischemic brain injury: diffusion tensor imaging study. *Neurosci Lett*,528,16-21.
21. Lu-Emerson C, Khot S (2010). Neurological sequelae of hypoxic-ischemic brain injury. *NeuroRehabilitation*,26,35-45.
22. Malykhin N, Concha L, Seres P, Beaulieu C, Coupland NJ (2008). Diffusion tensor imaging tractography and reliability analysis for limbic and paralimbic white matter tracts. *Psychiatry Res*,164,132-142.
23. Mufson EJ, Pandya DN (2005). Some observations on the course and composition of the cingulum bundle in the rhesus monkey. *The Journal of Comparative Neurology*,225,31-43.
24. Mulert C, Menzinger E, Leicht G, Pogarell O, Hegerl U (2005). Evidence for a close relationship between conscious effort and anterior cingulate cortex activity. *Int J Psychophysiol*,56,65-80.
25. Neil JJ (2008). Diffusion imaging concepts for clinicians. *J Magn Reson Imaging*,27,1-7.
26. Norton L, Hutchison RM, Young GB, Lee DH, Sharpe MD, Mirsattari SM (2012). Disruptions of functional connectivity in the default mode network of comatose patients. *Neurology*,78,175-181.
27. Parker GJ, Alexander DC (2005). Probabilistic anatomical connectivity derived from the microscopic persistent angular structure of cerebral tissue. *Philos Trans R Soc Lond B Biol Sci*,360,893-902.
28. Parvizi J, Van Hoesen GW, Buckwalter J, Damasio A (2006). Neural connections of the posteromedial cortex in the macaque. *Proc Natl Acad Sci U S A*,103,1563-1568.
29. Paus T (2000). Functional anatomy of arousal and attention systems in the human brain. *Prog Brain Res*,126,65-77.

30. Qin PM, Wu XH, Huang ZR, Duncan NW, Tang WJ, Wolff A, Hu J, Gao L, Jin Y, Wu X, Zhang JF, Lu L, Wu CP, Qu XY, Mao Y, Weng XC, Zhang J, Northoff G (2015). How Are Different Neural Networks Related to Consciousness?. *Ann Neurol*,78,594-605.
31. Schnakers C, Vanhaudenhuyse A, Giacino J, Ventura M, Boly M, Majerus S, Moonen G, Laureys S (2009). Diagnostic accuracy of the vegetative and minimally conscious state: clinical consensus versus standardized neurobehavioral assessment. *BMC Neurol*,9,35.
32. Teasdale G, Jennett B (1974). Assessment of coma and impaired consciousness. A practical scale. *Lancet*,2,81-84.
33. Vanhaudenhuyse A, Noirhomme Q, Tshibanda LJ, Bruno MA, Boveroux P, Schnakers C, Soddu A, Perlberg V, Ledoux D, Brichant JF, Moonen G, Maquet P, Greicius MD, Laureys S, Boly M (2010). Default network connectivity reflects the level of consciousness in non-communicative brain-damaged patients. *Brain*,133,161-171.
34. Vogt BA, Finch DM, Olson CR (1992). Functional heterogeneity in cingulate cortex: the anterior executive and posterior evaluative regions. *Cereb Cortex*,2,435-443.
35. Zeman A (2001). Consciousness. *Brain*,124,1263-1289.
36. Zhang HS, Dai R, Qin PM, Tang WJ, Hu J, Weng XC, Wu X, Mao Y, Wu XH, Northoff G (2017). Posterior cingulate cross-hemispheric functional connectivity predicts the level of consciousness in traumatic brain injury. *Sci Rep*,7,387.

Figures

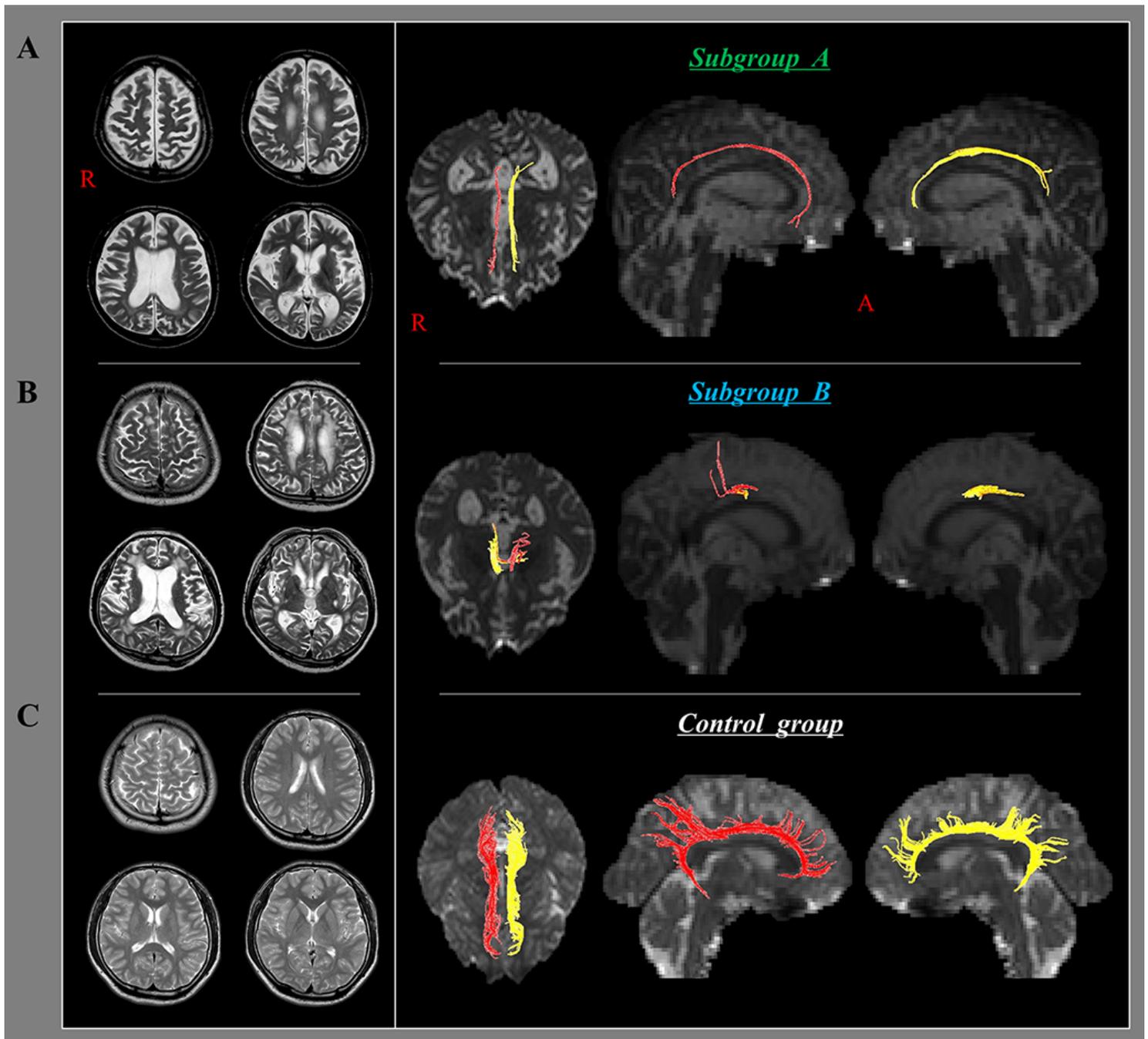


Figure 1

Results from T2-weighted brain magnetic resonance images and diffusion tensor tractography (DTT) for the cingulum in representative patients from patient groups A and B and the control group. (A) Narrowing of both cinguli in a representative patient of group A (intact consciousness, 53-year-old male); however, the anterior and posterior portions of the cinguli are intact. (B) Non-reconstruction of the anterior and posterior portions of the cinguli in a representative patient of group B (impaired consciousness, 47-year-old male). (C) Images showing the normal cinguli in a representative subject of the control group (46-year old male).

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [STROBEchecklistv4combined.docx](#)