Cerebellum
DOI 10.1007/s12311-013-0473-z

ORIGINAL PAPER

Tractography Demonstrates Dentate-rubro-thalamic Tract Disruption in an Adult with Cerebellar Mutism

Kirsten van Baarsen · Michiel Kleinnijenhuis · Tom Konert · Anne-Marie van Cappellen van Walsum · André Grotenhuis

Abstract A 55-year-old female is presented with transient cerebellar mutism caused by a well-circumscribed left pontine infarction due to postoperative basilar perforator occlusion. Although conventional T2 imaging shows a well-demarcated lesion confined to the pontine region, diffusion tensor imaging shows an asymmetry in fractional anisotropy in the superior cerebellar peduncle. This supports the general hypothesis that cerebellar mutism is caused by functional disruption of the dentate-rubro-thalamic tract. Correlating postoperative anatomic changes to a heterogenic clinical syndrome remains challenging, however.

Keywords Cerebellar mutism · Posterior fossa syndrome (PFS) · Superior cerebellar peduncle (SCP) · Dentate-rubro-thalamic (DRT) tract · Pons · Tractography

K. van Baarsen (✉) · T. Konert · A. Grotenhuis
Department of Neurosurgery, Radboud University Nijmegen Medical Centre, Huispost 636 Neurochirurgie, Postbus 9101, 6500 HB, Nijmegen, The Netherlands
e-mail: k.vanbaarsen@nch.umcn.nl

M. Kleinnijenhuis · T. Konert · A.-M. van Cappellen van Walsum
Department of Anatomy, Radboud University Nijmegen Medical Centre, Huispost 109 Anatomie, Postbus 9101, 6500 HB, Nijmegen, The Netherlands

M. Kleinnijenhuis · A.-M. van Cappellen van Walsum
Radboud University Nijmegen, Donders Institute for Brain, Cognition and Behaviour, Kapittelweg 29, 6525 EN Nijmegen, The Netherlands

A.-M. van Cappellen van Walsum
MIRA Institute for Biomedical Technology and Technical Medicine, University of Twente, Enschede, The Netherlands

Introduction

Mutism, defined as a total inability to speak with intact language comprehension in an otherwise alert patient, has been reported after trauma, epilepsy, tumor, stroke, and psychiatric disorders [1]. Anatomically, lesions to Broca's, anterior opercular, and supplementary motor area have been reported, as well as thalamic, third ventricular, or mesencephalic lesions [2].

Yet, the most well-known cause of mutism is probably posterior fossa surgery in children with a tumor in the cerebellar midline [3, 4]. The total lack of speech typically starts within days after surgery and lasts for 2 to 3 months, evolving in severe dysarthria and frequently persisting motor speech problems [5]. This "cerebellar" mutism may present with other problems such as hypotonia, hemiparesis, cranial nerve deficit, and emotional and cognitive disturbances, called posterior fossa syndrome (PFS) or cerebellar cognitive affective syndrome [6–8].

Currently, the generally accepted hypothesis is that mutism results from bilateral damage to the dentate nucleus or the dentate-rubro-thalamic (DRT) tract within the superior cerebellar peduncle (SCP) [9–11], leading to cerebro–cerebellar diaschisis [7, 12] and lower volumes of frontocerebellar white matter tracts [13]. However, true evidence for a causal relationship is still lacking. Furthermore, the precise pathophysiological mechanism is still a matter of debate [14, 15]. This case report demonstrates a cerebellar pathophysiology for mutism caused by pontine infarction.

Case Report

An otherwise healthy, 55-year-old woman underwent resection of an epidermoid cyst in the left cerebellopontine area at the age of 28. She presented in 2008 with unexplained

Published online: 03 April 2013

vertigo and in 2011 with left hemifacial spasms. At neurological examination, there was a known dysarthric speech due to her congenital hearing impairment with no cranial nerve deficits. Motor and sensory functions of the upper and lower extremities were normal.

MR imaging demonstrated a space-occupying lesion in the left cerebellopontine area, compressing the pons and causing dorsolateral displacement of the seventh and eighth cranial nerves, signal intensities suggesting an epidermoid cyst (Fig. 1). The tumor was extirpated through the preexistent left suboccipital osteoclastic trepanation under continuous cranial nerve monitoring. Two miniscule pieces of tissue that were strongly attached to a perforating artery were left behind to prevent any damage to the perforators.

Postoperatively, there were no more facial spasms. However, the patient had a slight left peripheral and a right central facial nerve palsy, right tongue deviation, and a right upper limb paresis grade 3. Speech was as previously reported until the first postoperative day, when the patient was found to have an additional right-sided hemiparesis, swallowing difficulty, and inability to speak. Language comprehension, facial expression, and body language were, however, normal. Reading and writing were also unimpaired.

MR imaging revealed a wedge-shaped area in the left upper pons with high intensity on T2 and FLAIR images and diffusion restriction on diffusion weighted images, suggesting pontine ischemia by basilar perforator occlusion (Fig. 1). Time of flight images showed normal patency of basilar and superior cerebellar arteries. Within days, mutism developed into a serious dysarthria.

At the 2-month follow-up, there were no more swallowing problems, and according to the family, the patient's speech had normalized to her preexisting dysarthric speech attributed to her congenital hearing impairment. MR imaging at that time showed the large pontine infarction on the left side, containing part of the left medial but not the superior cerebellar peduncle. To look for an anatomical explanation for this patient's mutism, diffusion weighted imaging (DWI) and tractography were performed.

MR Data Acquisition and Processing

Imaging was performed on a 1.5-T scanner (Magnetom Avanto, Siemens Medical Solutions, Erlangen, Germany) with a 32-channel head coil. The protocol included a T1-weighted MPRAGE acquisition (TR/TE/TI=2250/2.58/850 ms; flip angle=15°; matrix=256×256; FOV=256×256 mm; slice thickness=1 mm) and DWI (twice-refocused se-EPI with TR/TE=9,100/98 ms; matrix=80×100; FOV=176×220 mm; slice thickness=2.2 mm; b value=1,000 s/mm^2; 61 directions+7 non-DW). DW images were corrected for eddy currents, cardiac pulsation, movement artifacts, and EPI distortion [16] with the PATCH algorithm [17].

Tractography was performed with MRtrix 0.2.9 (available from http://www.brain.org.au/software/). MRtrix provides a set of tools to perform tractography in a manner that handles crossing fibers, using constrained spherical deconvolution (CSD) [18] and probabilistic tractography. To reconstruct the SCPs, streamlines were initiated from the dentate nuclei (DN) as identified from various data sources (atlases, T1, fractional anisotropy (FA), and CSD maps). Streamlines were discarded unless the following waypoint criteria were met: (1) entering the decussation of the SCP in the mesencephalon, (2) entering the contralateral ventrolateral nucleus of the thalamus (VL; masks for the VLs were obtained by transforming the Oxford Thalamic Connectivity Probability Atlas to the patient's DWI space and thresholding the premotor connectivity probability at 10 %), and (3) *not* crossing the midline outside of the SCP decussation area. Stopping criteria were a fiber orientation distribution (FOD) amplitude <0.1 and radius of curvature >1 mm. Streamlines were initiated until each SCP counted 10,000. Streamlines were transformed to Montreal Neurological Institute (MNI) space and truncated between two planes orthogonal to the local DRT tract direction at MNI coordinates y=−50 mm (in the SCP near the DN) and z=10 mm (at the level of the thalamus). DRT tracts were reduced to 2,000 streamlines. FA and mean diffusivity (MD) were evaluated along the tract by averaging over all streamlines after resampling to 2,000 points.

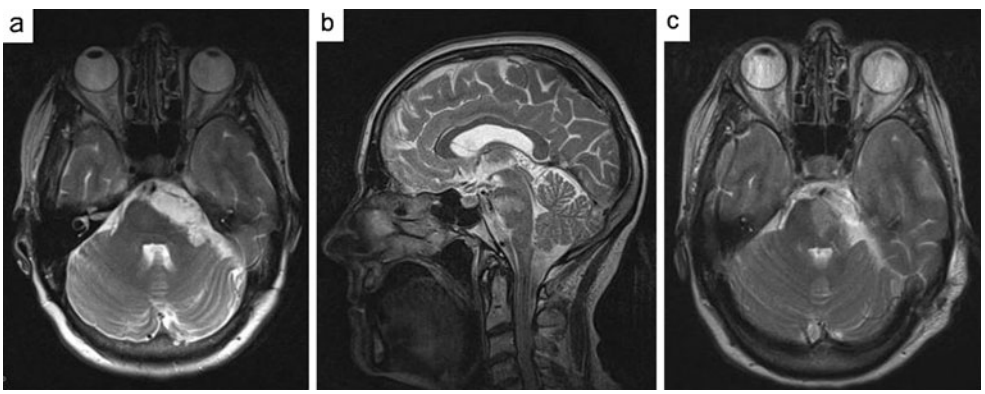

Fig. 1 Pre- and postoperative conventional images. **a** Preoperative T2-weighted image showing a hyperintense lesion in the left cerebellopontine angle compressing the pons and cranial nerves. **b**–**c** Postoperative T2-weighted image showing the wedge-shaped left pontine infarction due to perforator occlusion

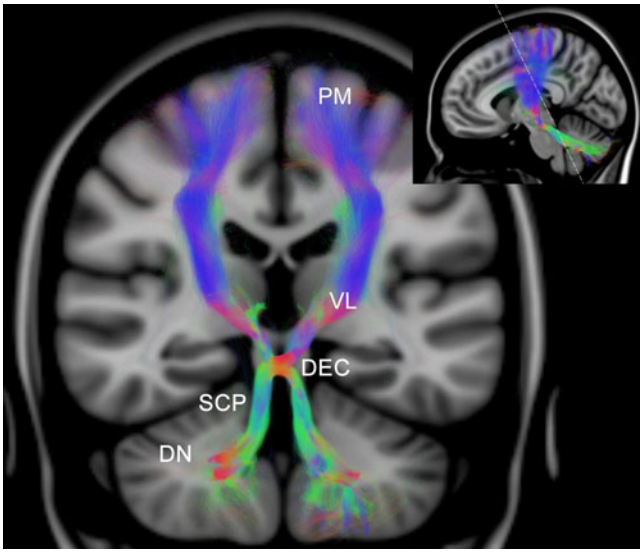

Fig. 2 Reconstruction of the dentate-rubro-thalamic tracts with tractography. From the dentate nucleus (*DN*), the tract runs through the superior cerebellar peduncle (*SCP*) to the decussation of the SCPs in the midbrain (*DEC*). There, the fibers cross the midline and course towards the ventrolateral nucleus of the thalamus (*VL*). This constitutes the dentate-rubro-thalamic tract. From *VL* upward, connections to the premotor areas are visualized which run through the internal capsule and corona radiata. Likewise, downstream from DN, the efferent connections to DN from the cerebellar hemispheres are tracked as an extension of the DRT. Note that, in fact, the cerebro–cerebellar motor loop is polysynaptic with synapses in DN and VL in the return pathway from the cerebellar to premotor cortex. *Background* shows the FSL MNI152 template

Results

A probable course for both dentate-rubro-thalamic tracts could be demonstrated with tractography (Fig. 2). However, the DRT tract starting from the left DN was much more difficult to reconstruct (i.e., it took tenfold more samples to arrive at the specified number of 10,000 streamlines that fit the criteria). Furthermore, the DRT tracts took slightly different courses. This was most evident at the level of the red nuclei (RN). For the tract emanating from the right DN, the highest probability for the tract location was dorsolateral to the left RN, while the most probable pathway from the left DN coursed through the right RN. Within the SCPs, the spatial distribution of the streamlines was narrower for the DRT tract from the left DN. Comparison between left and right SCP in the FA and FOD maps (Fig. 3) indicates some substantial differences in this portion of the DRT tracts (dashed ellipses). In the FOD map, the left SCP appears narrower, and a disruption in the coherent orientation of the left SCP is eminent. Not surprisingly, these left-sided FOD abnormalities coincide with an apparent reduction in FA. This is confirmed in Fig. 4, where the FA and MD of the right (red traces) and left (blue traces) DRT tracts are quantified. The left SCP shows lower FA as compared to the right. Naturally, FA values of both DRT tracts are equal in the area of the decussation. Also, the rubrothalamic portion of the DRT tract from the left DN shows lower FA than contralateral. The high MD values in Fig. 4c indicate an obvious partial volume effect with cerebrospinal fluid surrounding the SCPs. Nevertheless, a substantial difference can be observed in the MD as well. Coinciding with the low FA, a higher MD is seen in the left SCP as compared to the right.

Discussion

Although cerebellar mutism due to brainstem lesions is rare, it has been described before [19–21]. To our knowledge, we are the first to present mutism in a patient with an infarction limited to the pontine region and to demonstrate anatomical–clinical correlations by diffusion tensor tractography.

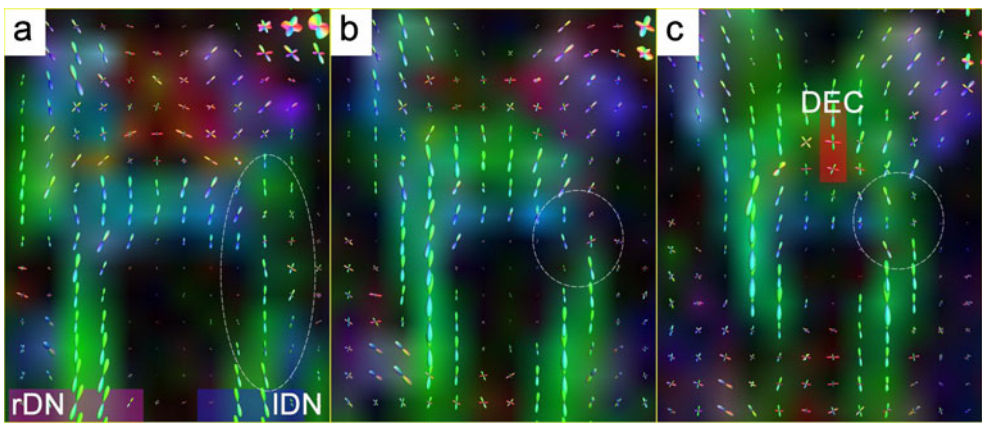

Fig. 3 Fiber orientation distributions (FODs) of the superior cerebellar peduncles. FODs are overlaid on the directionally encoded FA color map; **a**–**c** three consecutive axial slices of the superior cerebellar peduncles. FA in the background image for the left SCP (*dashed ellipses*) appears to be lower when compared to the right SCP. Furthermore, FODs are less coherent in the left SCP compared to the right. Partial tractography ROIs are shown: *rDN*=right dentate nucleus; *lDN* =left dentate nucleus; *DEC*=decussation of the SCPs

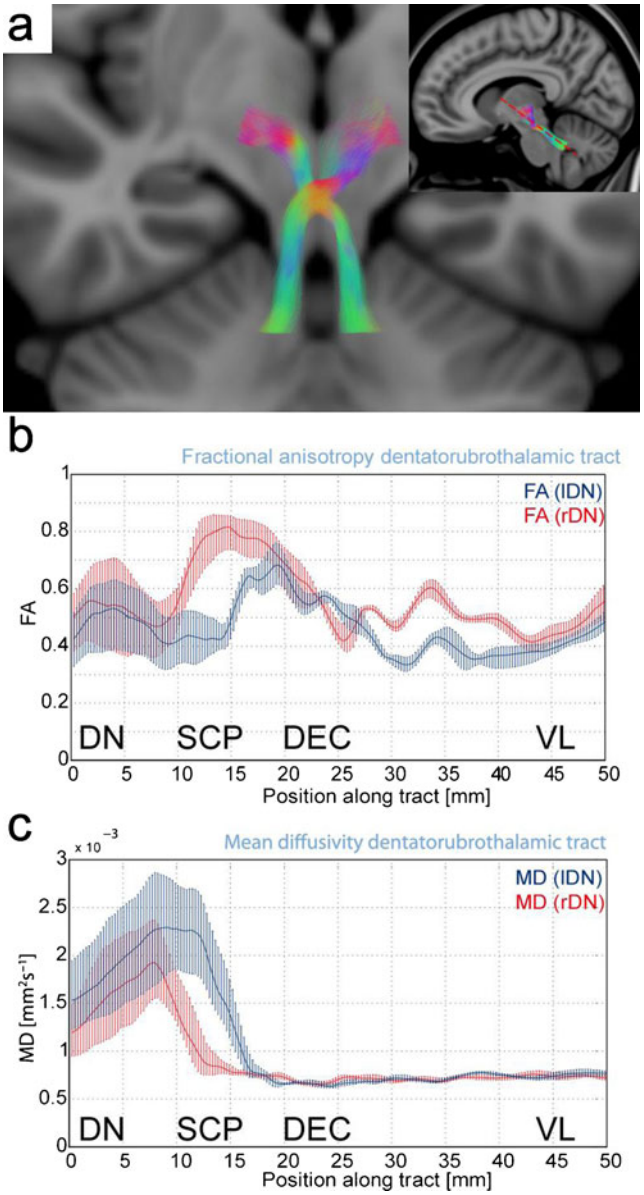

Fig. 4 Diffusion tensor metrics in the dentate-rubro-thalamic tracts. **a** Tractography results truncated to the DRT tracts. Background shows the FSL MNI152 template. **b** Median FA values and **c** median MD values over the DRT tracts from the right (*red traces*) and left (*blue traces*) DN. Note the prominent differences between left and right SCP in x=[10 20] mm. *Error bars* show quartiles

Our patient was diagnosed with postoperative mutism, oropharyngeal apraxia, hemiparesis, and cranial nerve deficit due to a well-circumscribed pontine infarction. Although at conventional T2 imaging the superior cerebellar peduncle seemed unharmed, functional disruption was demonstrated by a unilateral decrease in FA. FA and hemispheric FA asymmetry are well-known parameters to investigate tract integrity [22]. Our study therefore confirms the generally accepted hypothesis that the DRT tract is involved in the cerebellar mutism syndrome.

Morris et al. [10] were the first to use diffusion tensor imaging in patients with posterior fossa syndrome. In their series of ten patients with PFS compared to 12 controls after posterior fossa surgery, it appeared that the FA value in both superior cerebellar peduncles was significantly lower in the PFS patients. Although it is unclear to what extent speech was affected in their patients, the findings do suggest damage to the superior cerebellar peduncles as the primary cause of cerebellar mutism. Our study confirms this finding; however, this implicates that unilateral peduncle involvement may be equally devastating.

Apart from the superior cerebellar peduncle, Morris' PFS patients also showed significantly more damage to the mesencephalon and pons on conventional T2 weighed images, as was the case in our patient. Our study therefore supports the alternative hypothesis that functional disruption of brain stem nuclei may attribute to the cerebellar mutism syndrome. This correlation between brain stem damage and cerebellar mutism has been described before [23, 24].

Although diffusion imaging provides valuable anatomical and functional information, pathophysiological questions are still to be resolved [14]. Based on the onset of cerebellar mutism several days after the initial trauma, edema may be proposed as the primary cause [25]. However, the natural course of neurological deterioration caused by edema is much shorter than seen in cerebellar mutism. Another hypothesis is the transient decrease in cerebellar blood flow due to reversible vasoconstriction of small vessels [4]. In addition, SPECT functional imaging reveals frontal cortical hypoperfusion during cerebellar mutism [7, 12], suggesting cerebro–cerebellar diaschisis due to disruption of unmatured connections between cerebellar and cerebral structures [4].

Conclusions from this single-case study are still premature. First of all, the reliability of tractography itself is debatable and needs to be validated for cerebellar white matter. The slightly different courses of the left and right DRT tracts might stem from limitations of the tractography technique or noisy voxels in the diffusion data. While this may have influenced the DT metrics sampled in the rubrothalamic portion of the tract, we do not believe that the FA differences observed in the SCPs can be explained by limitations in diffusion imaging. Secondly, there is no preoperative tractography to compare with, for the mutism in this patient was not foreseen. In addition, our patient might not be representative of the general population because of her congenital hearing impairment. Hypothetically, her language neuronal network might be less well developed and therefore more vulnerable compared to age-matched controls. In patients with a congenital hearing impairment, tractography studies have revealed both gray and white matter changes in the bilateral superior temporal gyrus, Heschl's gyrus, planum polare, and splenium of the corpus callosum [26, 27]. An association with white matter

pathways in the cerebellum has never been demonstrated, even when searched for [28]. There is insufficient proof for a functional or anatomical alteration of cerebellar white matter pathways in patients with congenital hearing problems. Nevertheless, indirect pathways between the auditory cortex and the cerebro–cerebellar circuitry may be altered and may make these patients more vulnerable for the cerebellar mutism syndrome. Consequently, it would be inaccurate to extrapolate the findings in this study to the general population.

Lastly, at the time of postoperative diffusion tensor imaging, the mutism had already resolved. The tractography results thus do not necessarily indicate a causal relationship between clinical results and anatomical changes. They rather demonstrate the residual changes after clinical improvement. This phenomenon is actually of particular pathophysiological interest. Apparently, fractional anisotropy is far behind on regain of function. Its clinical implication in terms of pathophysiological mechanisms needs to be further evaluated.

Conclusion

This case report supports the general hypothesis that cerebellar mutism is caused by functional disruption of the dentate-rubro-thalamic tract, even when primary damage is confined to the pontine region.

Informed Consent

Written informed consent was obtained from the patient for performing diffusion tensor imaging and publishing clinical data and images.

Acknowledgments We would like to thank Dr. F.J. Meyer, radiologist of the Radboud University Nijmegen Medical Centre, for providing conventional MR images.

Conflict of Interest The authors declare that there is no conflict of interest.

References

1. Crutchfield JS, Sawaya R, Meyers CA, Moore III BD. Postoperative mutism in neurosurgery. Report of two cases. J Neurosurg. 1994;81(1):115–21.
2. Dailey AT, McKhann GM, Berger MS. The pathophysiology of oral pharyngeal apraxia and mutism following posterior fossa tumor resection in children. J Neurosurg. 1995;83(3):467–75.
3. Gelabert-Gonzalez M, Fernandez-Villa J. Mutism after posterior fossa surgery. Review of the literature. Clin Neurol Neurosurg. 2001;103(2):111–4.
4. Ildan F, Tuna M, Erman T, Gocer AI, Zeren M, Cetinalp E. The evaluation and comparison of cerebellar mutism in children and adults after posterior fossa surgery: report of two adult cases and review of the literature. Acta Neurochir (Wien). 2002;144(5):463–73.
5. De Smet HJ, Baillieux H, Catsman-Berrevoets C, De Deyn PP, Marien P, Paquier PF. Postoperative motor speech production in children with the syndrome of 'cerebellar' mutism and subsequent dysarthria: a critical review of the literature. Eur J Paediatr Neurol. 2007;11(4):193–207.
6. Doxey D, Bruce D, Sklar F, Swift D, Shapiro K. Posterior fossa syndrome: identifiable risk factors and irreversible complications. Pediatr Neurosurg. 1999;31(3):131–6.
7. De Smet HJ, Baillieux H, Wackenier P, De PM, Engelborghs S, Paquier PF, et al. Long-term cognitive deficits following posterior fossa tumor resection: a neuropsychological and functional neuroimaging follow-up study. Neuropsychology. 2009;23(6):694–704.
8. Levisohn L, Cronin-Golomb A, Schmahmann JD. Neuropsychological consequences of cerebellar tumour resection in children: cerebellar cognitive affective syndrome in a paediatric population. Brain. 2000;123(Pt 5):1041–50.
9. Pollack IF, Polinko P, Albright AL, Towbin R, Fitz C. Mutism and pseudobulbar symptoms after resection of posterior fossa tumors in children: incidence and pathophysiology. Neurosurgery. 1995;37(5):885–93.
10. Morris EB, Phillips NS, Laningham FH, Patay Z, Gajjar A, Wallace D, et al. Proximal dentatothalamocortical tract involvement in posterior fossa syndrome. Brain. 2009;132(Pt 11):3087–95.
11. Law N, Greenberg M, Bouffet E, Taylor MD, Laughlin S, Strother D, et al. Clinical and neuroanatomical predictors of cerebellar mutism syndrome. Neuro Oncol. 2012;14(10):1294–303.
12. Miller NG, Reddick WE, Kocak M, Glass JO, Lobel U, Morris B, et al. Cerebellocerebral diaschisis is the likely mechanism of postsurgical posterior fossa syndrome in pediatric patients with midline cerebellar tumors. AJNR Am J Neuroradiol. 2010;31(2):288–94.
13. Soelva V, Hernaiz DP, Abbushi A, Rueckriegel S, Bruhn H, Eisner W, et al. Fronto-cerebellar fiber tractography in pediatric patients following posterior fossa tumor surgery. Childs Nerv Syst. 2013;29:597–607.
14. Frassanito P, Massimi L, Caldarelli M, Di RC. Cerebellar mutism after spontaneous intratumoral bleeding involving the upper cerebellar vermis: a contribution to the physiopathogenic interpretation. Childs Nerv Syst. 2009;25(1):7–11.
15. Gudrunardottir T, Sehested A, Juhler M, Schmiegelow K. Cerebellar mutism: review of the literature. Childs Nerv Syst. 2011;27(3):355–63.
16. Visser E, Poser BA, Barth M, Zwiers MP. Reference-free unwarping of EPI data using dynamic off-resonance correction with multiecho acquisition (DOCMA). Magn Reson Med. 2012;68(4):1247–54.
17. Zwiers MP. Patching cardiac and head motion artefacts in diffusion-weighted images. NeuroImage. 2010;53(2):565–75.
18. Tournier JD, Calamante F, Gadian DG, Connelly A. Direct estimation of the fiber orientation density function from diffusion-weighted MRI data using spherical deconvolution. NeuroImage. 2004;23(3):1176–85.
19. Frim DM, Goumnerova LC. Telemetric intraventricular pressure measurements after third ventriculocisternostomy in a patient with noncommunicating hydrocephalus. Neurosurgery. 1997;41(6):1425–8.
20. Nishikawa M, Komiyama M, Sakamoto H, Yasui T, Nakajima H. Cerebellar mutism after basilar artery occlusion–case report. Neurol Med Chir (Tokyo). 1998;38(9):569–73.
21. Miyakita Y, Taguchi Y, Sakakibara Y, Matsuzawa M, Kitagawa H. Transient mutism resolving into cerebellar speech after brain stem

infarction following a traumatic injury of the vertebral artery in a child. Acta Neurochir (Wien). 1999;141(2):209–13.
22. Borich MR, Wadden KP, Boyd LA. Establishing the reproducibility of two approaches to quantify white matter tract integrity in stroke. NeuroImage. 2012;59(3):2393–400.
23. Robertson PL, Muraszko KM, Holmes EJ, Sposto R, Packer RJ, Gajjar A, et al. Incidence and severity of postoperative cerebellar mutism syndrome in children with medulloblastoma: a prospective study by the Children's Oncology Group. J Neurosurg. 2006;105(6 Suppl):444–51.
24. McMillan HJ, Keene DL, Matzinger MA, Vassilyadi M, Nzau M, Ventureyra EC. Brainstem compression: a predictor of postoperative cerebellar mutism. Childs Nerv Syst. 2009;25 (6):677–81.
25. Wells EM, Khademian ZP, Walsh KS, Vezina G, Sposto R, Keating RF, et al. Postoperative cerebellar mutism syndrome following treatment of medulloblastoma: neuroradiographic features and origin. J Neurosurg Pediatr. 2010;5(4):329–34.
26. Miao W, Li J, Tang M, Xian J, Li W, Liu Z, et al. Altered white matter integrity in adolescents with prelingual deafness: a high-resolution tract-based spatial statistics imaging study. AJNR Am J Neuroradiol 2012 (in press).
27. Li Y, Ding G, Booth JR, Huang R, Lv Y, Zang Y, et al. Sensitive period for white-matter connectivity of superior temporal cortex in deaf people. Hum Brain Mapp. 2012;33(2):349–59.
28. Boyen K, Langers DR, de Kleine E, van Dijk P. Gray matter in the brain: differences associated with tinnitus and hearing loss. Hear Res. 2013;295:67–78.