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ORIGINAL ARTICLE

Feasibility and reproducibility of diffusion-weighted magnetic resonance imaging of the fetal brain in twin–twin transfusion syndrome

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ABSTRACT

Objective The aim of this study is to test the feasibility and reproducibility of diffusion-weighted magnetic resonance imaging (DW-MRI) evaluations of the fetal brains in cases of twin–twin transfusion syndrome (TTTS).

Method From May 2011 to June 2012, 24 patients with severe TTTS underwent MRI scans for evaluation of the fetal brains. Datasets were analyzed offline on axial DW images and apparent diffusion coefficient (ADC) maps by two radiologists. The subjective evaluation was described as the absence or presence of water diffusion restriction. The objective evaluation was performed by the placement of 20-mm^2 circular regions of interest on the DW image and ADC maps. Subjective interobserver agreement was assessed by the kappa correlation coefficient. Objective intraobserver and interobserver agreements were assessed by proportionate Bland–Altman tests.

Results Seventy-four DW-MRI scans were performed. Sixty of them (81.1%) were considered to be of good quality. Agreement between the radiologists was 100% for the absence or presence of diffusion restriction of water. For both intraobserver and interobserver agreement of ADC measurements, proportionate Bland–Altman tests showed average percentage differences of less than 1.5% and 95% CI of less than 18% for all sites evaluated.

Conclusion Our data demonstrate that DW-MRI evaluation of the fetal brain in TTTS is feasible and reproducible.
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INTRODUCTION

Ultrasonography (US) is the method of choice for the assessment of fetal brain abnormalities, and magnetic resonance imaging (MRI) can improve the diagnosis under specific conditions.[1–6] However, US and T1-/T2-weighted MRI are not appropriate tools for the detection of early fetal brain changes that follow ischemic events.[6] These injuries can result from abrupt episodes of hypotension that may be related to autoimmune or infectious diseases, cardiovascular abnormalities, monochorionic twinning, and fetal interventions.[6–11]

Diffusion-weighted (DW) MRI enables the identification of the initial changes in the brain caused by hypoxic-ischemic events, through subjective and objective evaluations of the microscopic diffusion of water.[6,12–14] An objective evaluation consists of measuring the apparent diffusion coefficient (ADC). The reproducibility of this method in the normal fetal brain in singleton pregnancies was recently demonstrated.[15–17]

Severe twin–twin transfusion syndrome (TTTS) is a condition that exposes the fetus to a higher risk of cerebral damage.[6,10,18–23] Although the pathogenesis of brain injury in TTTS is not clear, the hemodynamic and hematological conditions of the twins before and after the laser ablation of placental vessels, as well as prematurity, are potential threats to the integrity of the brain.[24–26] Therefore, we developed a protocol to evaluate the relationship between fetal brain DW-MRI findings before and after laser surgery, neonatal transfontanellar ultrasound findings, and the clinical neurological outcome of the infant. However, as a first step, the specific objective of the present study was to test the feasibility and reproducibility of DW-MRI evaluations of normal and hypoxic-ischemic twin brain parenchyma in severe cases of TTTS treated with laser.

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METHODS

This study was conducted from May 2011 to June 2012 at the State University of Campinas (UNICAMP) and at Vera Cruz Hospital, Campinas, São Paulo, Brazil. The protocol was approved by the Institutional Review Board of UNICAMP, and all patients who agreed to participate signed an informed consent form prior to enrollment.

The inclusion criteria for this study were as follows: monochorionic diamniotic twin pregnancies with severe TTTS (stages II–IV, according to the classification by Quintero *et al.*[27,28]), no fetal malformations detected by US prior to the laser procedure, a cervical length of 15 mm or greater (the fifth percentile according to the methods of To *et al.*[29]) before the procedure, and no maternal contraindications for the MRI study (metallic implants, pacemakers, or claustrophobia).

All laser procedures were performed by the same surgeon (C. F. A. P., 7 years of experience in fetoscopic laser surgeries) at the Professor José Aristodemo Pinotti Hospital according to the following technique. First, the chorionic plate vessels of the placenta were mapped endoscopically via the amniotic sac of the recipient fetus. The vascular equator was identified, and a line of ablation of the chorionic plate was created from one edge of the placenta to the other, including the arteriovenous anastomoses and vessels with unknown courses. Caution was taken to preserve the vessels originating from and returning to the same fetus. At the end of the photocoagulation process, redundant amniotic fluid was drained through the fetoscopic sheath such that the deepest amniotic fluid pocket was less than 8 cm deep.

Eligible patients underwent an MRI scan less than 24 h before and after the laser procedure. This was obviously not always possible in all laser cases so that some patients underwent MRI before or after the laser procedure. Fetuses were classified on the MRI and US as either the donor or the recipient. The sites of their umbilical cord insertions on the placental chorionic plate were used as landmarks to avoid mislabeling in subsequent scans and at birth.

All MRI examinations were performed at Centro Radiológico Campinas, Vera Cruz Hospital using a 1.5-T whole-body unit (Signa HDxt – GE Healthcare, Milwaukee, WI, USA) with gradient switching capabilities of 33 mT/m in 276 microseconds (slew rate of 120 T/m/s). Patients fasted for 3 hours prior to the scan, and no maternal or fetal sedation was used. The mother was kept in a supine position, and apnea was only required in specific situations, especially when at least one of the fetuses was in a breech position. An eight-channel phased-array surface cardiac coil was initially positioned over the lower maternal abdomen. First, T2-weighted sequences (single-shot fast spin-echo; echo time, 180 ms; relaxation time, 3000 ms; slice thickness, 5.0 mm; spacing, 0.0 mm; field of view, 380 × 380 mm; matrix, 320 × 224; partial Fourier factor, 0.5 NEX; and bandwidth, 62.5 Hz per pixel) were acquired for the localization and identification of each fetus as the donor or recipient. On the basis of the position of the fetal skulls, the coil was repositioned to optimize the image quality for both twins.

Axial DW sequences of the fetal brains were acquired according to the following protocol: echo time, 95.5 ms; relaxation time, 5100 ms; *b*-values, 0 and 1000 s/mm^2; direction, three; echo planar image; NEX, 4.00; bandwidth direction, right to left; matrix, 192 × 192; field of view, 380 × 380 mm; slice thickness, 4.0 mm; spacing, 0.0 mm. Fat suppression was achieved using a frequency-selective radio frequency pulse. Each DW sequence was acquired over approximately 1 min and 10 s. Apparent diffusion coefficient maps were obtained using *b*-values of 0 and 1000 s/mm^2. During imaging acquisition, if hemorrhage was suspected, T1-weighted sequences were performed (echo time, 4.2 ms; relaxation time, 7.7 ms; inversion time, 774.0 ms; slice thickness, 4.0 mm; spacing, 4.0 mm; field of view, 256 × 256 mm; matrix, 256 × 192; NEX, 1.00). Hemorrhages were detected using the T2-weighted images; *b*-value of 0 obtained from the DWI images and T1-weighted images.

All MRI scans were supervised by the same radiologist (G. E. S., 5 years of experience with fetal neuroradiology). This radiologist determined which datasets were of enough quality on the basis of the sharpness of the image and clear visualization of the brain anatomy [adequate identification of the lobes (frontal, temporal, parietal, insular, and occipital), ventricles, Sylvian fissure, and cerebellum]. If fetal movements prevented the acquisition of a proper dataset, another scan was performed in the next hour. No more than two attempts per patient were made.

Two neuroradiologists (M. M. and R. C. N., 5 and 6 years of experience with fetal neuroradiology, respectively) also independently rated the appropriateness of each dataset for ADC measurement. The adequacy of the dataset for the acquisition process was defined subjectively on the basis of the sharpness of the image and the ability to clearly evaluate brain structures. If more than one dataset per fetal evaluation was considered to be of good quality by both operators, the first radiologist (G. E. S.) randomly selected one of them for further analysis. If none of the datasets available from a fetal evaluation was judged to be appropriate for the ADC measurements by any of the three radiologists, the evaluation was considered unsuccessful.

The selected datasets were analyzed offline on axial DW images and ADC maps (Advantage Workstation, GE Healthcare, Milwaukee, WI, USA) by M. M. and R. C. N., who were blinded to the following: the evaluation of the other radiologist, their own previous assessment of the same fetus, any information about the mother, the TTTS stage and the time point of the examination (before or after laser surgery), and the phenotypic particularities of each twin (if the fetus was the donor or recipient; Doppler parameters; viability). To guarantee this confidentiality, G. E. S. was responsible for labeling each fetal skull and removing all significant information that could enable their identification. Next, the radiologist zoomed in on the images, and the field of view was set to allow only the fetal brain to be analyzed in the cine mode. For the intraobserver agreement assessment, the interval between the offline evaluations of each fetal brain by both neuroradiologists was at least 15 days, and all images were labeled with different identifiers than those used in the previous evaluation. Only the radiologist who prepared the datasets for analysis was aware of each case and the respective evaluations of the two neuroradiologists.

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Both subjective and objective assessments of the microscopic diffusion of water were performed. The subjective analysis was performed by evaluating the absence or presence of water diffusion restriction and its location (Figures 1 and 2). The objective evaluation was performed by bilaterally placing 20-mm^2 circular regions of interest on the ADC maps at the following sites: frontal (F), thalamic (T), temporoparietal (TP), periventricular (PV), and cerebellar (C) (Figure 1).

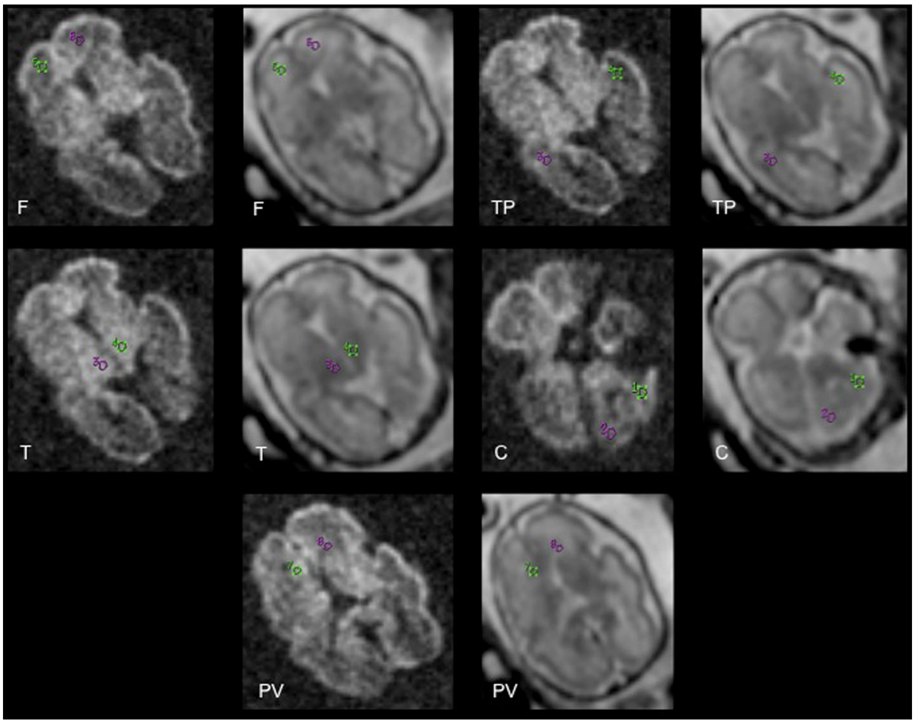

Figure 1 Diffusion-weighted image (left) and apparent diffusion coefficient map (right) of normal fetal brain (gestational age = 26 weeks) and the sites used for the measurements of the apparent diffusion coefficient: frontal (F), thalamic (T), temporoparietal (TP), periventricular (PV), and cerebellar (C)

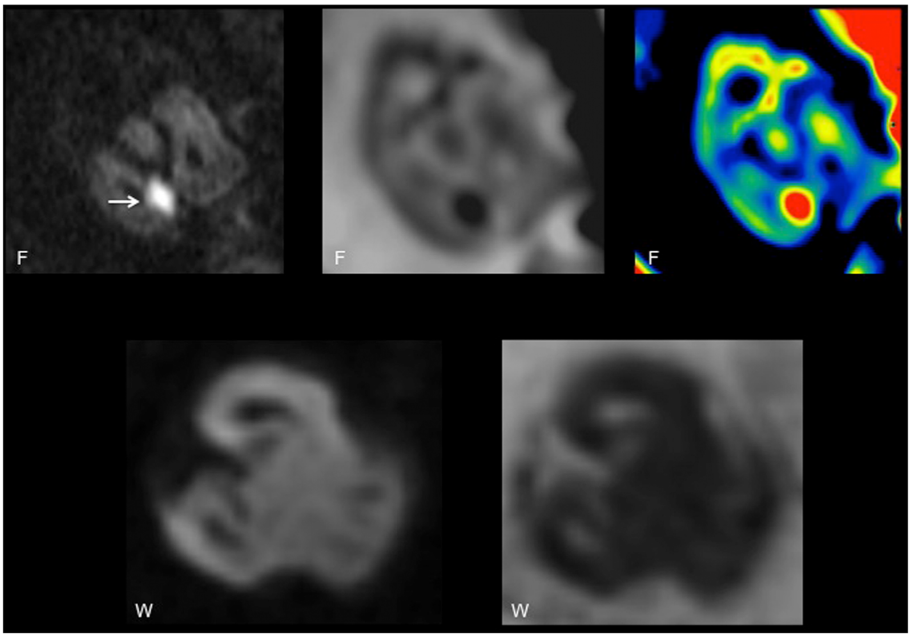

Figure 2 (F) Diffusion-weighted image (left) and apparent diffusion coefficient gray and color maps (right) of one fetus (gestational age = 22 weeks) with a focal hypoxic-ischemic lesion (arrow); (W) diffusion-weighted image (left) and apparent diffusion coefficient map (right) of a dead fetus (gestational age = 21 weeks) after the laser ablation of placental vessels

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Prior to the second or postlaser MRI scan, all patients underwent US to assess viability. The radiologist who prepared the DW-MRI datasets for offline evaluation was the only person aware of this information.

After laser surgery, all patients were examined by US every 2 weeks until delivery. At each evaluation, the fetal brain was scanned for anatomic alterations, which, if found, were described. After birth, surviving neonates underwent transfontanellar ultrasound scans once until the first 3 days of life and every week thereafter until hospital discharge.

The demographic and clinical characteristics of the mothers and neonates were described as medians and ranges for continuous variables and as absolute and relative frequencies for categorical data.

Inter-rater agreement for the subjective evaluation of fetal brain microscopic water diffusion (categorized as normal or abnormal in the entire brain or abnormal in a specific site of the brain) was assessed using Cohen's kappa coefficients.[30]

Because there was an insufficient number of twins with changes in the DW image and the ADC maps, the repeatability (intraobserver variation) and reproducibility (defined in this study as interobserver variation) of the ADC measurements were assessed only in fetuses considered to have normal brains.[31,32] Prior to this evaluation, a preliminary analysis was conducted by separately examining only the first assessments of all datasets by both neuroradiologists. Left and right measurements obtained at each site of the brain (F, T, TP, PV, and C) were compared using the Wilcoxon signed-rank test (datasets acquired before and after the laser were analyzed separately). If no significant difference was found in relation to the side of the brain, the measurements performed on each site before and after the laser were compared using the Mann–Whitney *U* test. If no significant difference between these evaluations was found, no separate analysis of repeatability and reproducibility was performed for datasets acquired before and after the laser, that is, preoperative and postoperative acquisitions were combined as if they were obtained from different fetuses.

The final analysis of intraobserver and interobserver agreement was conducted as follows. Shapiro–Wilk tests were used to assess the distributions of the percentage differences between two measurements [(measurement 1 − measurement 2)/(average of measurements 1 and 2) × 100]. Proportionate Bland and Altman analyses were performed to determine the agreement between measurements performed in each side of the brain (for all sites evaluated: F, T, TP, PV, and C), by the same operator (repeatability) and by different operators (reproducibility). Bias was defined as the average of the percentage differences between two measurements, and the limits of agreement were defined as 1.96 multiplied by the standard deviation of the mean percentage difference.[31,32] Percentage differences between two measurements were further compared with zero using the one-sided *t*-test. Differences were considered statistically significant if the *p*-value was less than 0.05.

To assess repeatability, if no discrepancy was found between measurements performed on each side of the brain (for each of the abovementioned sites), the left and right ADC values from the first evaluation were combined for comparison with the left and right measurements performed in the second assessment. If a difference between sides was detected, the left and right ADC values of the first and second evaluations were compared separately.

For the assessment of reproducibility, the averages of the first and second evaluations of both operators were compared.

The data were analyzed using the statistical software SPSS for Macintosh 21.0 (IBM Corp., Chicago, IL, USA) and Excel for Macintosh 2011 (Microsoft Corp., Redmond, WA, USA).

RESULTS

Twenty-four patients (48 twins) met the entry criteria for the study. The median (range) maternal and gestational ages at laser surgery and the median (range) gestational age at birth were 29 years (18–39), 22 weeks (18–26), and 32 weeks (21–37), respectively. Eight patients (33.3%) were treated at stage II of TTTS, 11 patients (45.8%) were treated at stage III, and 5 (20.8%) were treated at stage IV.

On the day after the laser procedure, 40 of the 48 twins (83.3%) were still alive. The overall survival rate, survival of at least one twin, and survival of both twins at the time of hospital discharge were 54.2% (26/48), 66.7% (16/24), and 41.7% (10/24), respectively.

Because of maternal clinical conditions and MRI scanner availability (MRI scans were performed in a different hospital than the hospital in which the patients were treated), it was not possible to perform prelaser evaluations in four cases and postlaser evaluations in seven. Therefore, only 74 out of a possible 96 datasets were obtained. Of these, 60 (60/74 = 81.1%) were considered by all three radiologists to be of sufficient quality to assess the microscopic diffusion of water.

The agreement between the two neuroradiologists was 100% for the absence (55/60 = 91.7%) or presence of diffusion restriction of water and corresponding sites (5/60 = 8.3%: whole brain in four dead fetuses after the laser; focal occipital lesion in one donor fetus before the laser). Ultrasound scans performed prior to the MRI examinations showed normal brains in all but two fetuses (2/60 = 3.3%) that died after the laser. In these two cases, a slight increase in the echogenicity of the periventricular white matter was noted.

For fetuses considered to have normal brains in the DW image and the ADC maps ($n = 55$), the analysis using only the first assessments by both neuroradiologists showed no difference between the left and right measurements. In addition, no significant differences between the measurements performed before and after the laser were identified. Therefore, to analyze repeatability and reproducibility, the preoperative and postoperative acquisitions were combined as if they were obtained from different fetuses.

For both operators, the percentage difference between the ADC measurements performed on each side of the brain and between the first and second assessments (repeatability) for all sites evaluated (F, T, TP, PV, and C) were not significantly different from zero (the bias and 95% CI for these comparisons are presented in Table 1 and Figure 3). Similarly, the mean percentage differences between the averages of the first and

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Table 1 Proportionate Bland and Altman analyses for assessment of the agreement between apparent diffusion coefficient measurements performed in each side of the normal twin brain and between the first and second evaluations (repeatability) performed by two operators

	Operator 1				Operator 2			
	$n = 110$		$n = 110$		$n = 110$		$n = 110$	
Site	Left/right bias (95% CI)	p	Repeatability bias (95% CI)	p	Left/right bias (95% CI)	p	Repeatability bias (95% CI)	p
F	0.450 (−11.7–12.6)	0.448	−1.197 (−14.6–12.2)	0.069	0.240 (−11.7–12.2)	0.807	−0.298 (−12.7–12.1)	0.636
T	−0.009 (−9.32–9.30)	0.818	−0.794 (−11.5–9.89)	0.100	−0.459 (−10.5–9.6)	0.416	0.829 (−10.4–12.1)	0.173
TP	0.054 (−16.5–16.6)	0.947	−1.190 (−18.1–15.7)	0.151	−0.352 (−16.0–15.4)	0.658	−0.104 (−16.4–16.2)	0.896
PV	0.214 (−12.9–13.4)	0.739	−0.104 (−17.3–17.1)	0.901	−0.141 (−11.7–11.4)	0.762	−0.580 (−13.7–12.5)	0.375
C	−0.930 (−11.2–9.3)	0.065	−0.938 (−11.7–9.79)	0.075	0.179 (−13–13.4)	0.781	−0.709 (−10.8–10.1)	0.179

n is the number of compared measurements.
Bias is average of percentage differences between two measurements.
95% CI is the 95% confidence interval (limits of agreement).
p is the p-value obtained by one-sample t-test (percentage differences of measurements compared with zero).
F, frontal; T, thalamic; TP, temporoparietal; PV, periventricular; C, cerebellar.

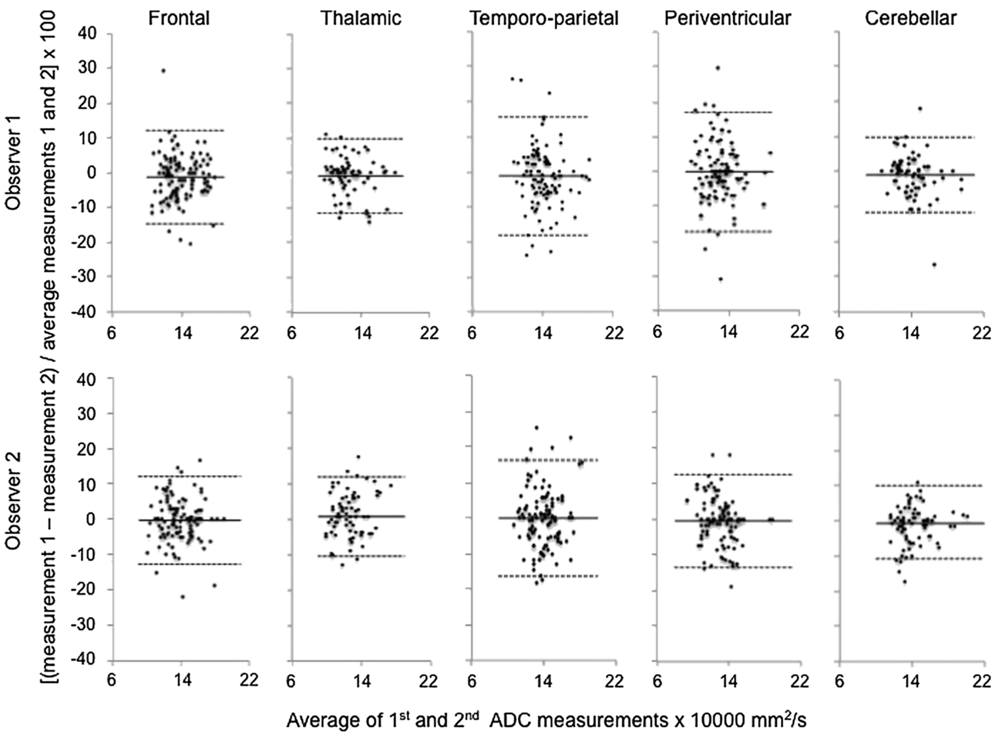

Figure 3 Bland and Altman plots for the analysis of repeatability (intraobserver variation) of apparent diffusion coefficient [apparent diffusion coefficient (ADC)] measurements performed by observers one and two in different sites of the normal twin brain. The continuous line represents the bias (average percentage difference) and the dotted lines represent the 95% limits of agreement

second measurements performed by the two operators (reproducibility) for each site of the brain were not significantly different from zero (the bias and 95% CI for these comparisons are presented in Table 2 and Figure 4).

All fetuses with normal ADC measurements demonstrated normal subsequent brain ultrasound evaluations until delivery. All neonates born alive demonstrated normal transfontanellar ultrasound scans until the first 3 days of life.

DISCUSSION

This study demonstrated that DW-MRI evaluation of the fetal brain in cases of severe TTTS treated with fetoscopic laser is feasible and reproducible.

Several authors have described the use of DW-MRI for the evaluation of normal and abnormal fetal brains.[6,13–16] Boyer et al.[17] recently demonstrated that the measurement of the ADC in normal brains of singleton fetuses is reproducible.

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Table 2 Proportionate Bland and Altman analyses for assessment of the agreement between the averages of the first and second apparent diffusion coefficient measurements of normal twin brains performed by the two operators (reproducibility) for each site

Site	Operator 1 $n = 110$ A: Average (SD) of first and second measurements	Operator 2 $n = 110$ B: Average (SD) of first and second measurements	C: Average of A and B (SD) $n = 110$	Reproducibility bias (95% CI) $n = 110$	p
F	0.00139 (0.000183)	0.00138 (0.000189)	0.00139 (0.000180)	1.240 (−12.7–15.2)	0.07
T	0.00128 (0.000195)	0.00127 (0.000171)	0.00128 (0.000178)	0.733 (−13.9–15.4)	0.31
TP	0.00140 (0.000174)	0.00140 (0.000159)	0.00140 (0.00157)	0.900 (−13.8–15.6)	0.67
PV	0.00129 (0.000171)	0.00130 (0.000164)	0.00130 (0.000157)	−0.814 (−18.8–17.1)	0.35
C	0.00140 (0.000170)	0.00140 (0.000181)	0.00140 (0.000170)	−0.045 (−12.0–11.9)	0.94

Average (SD) is the average (standard deviation) of two measurements of apparent diffusion coefficient, expressed in mm^2/s.
n is the number of compared measurements.
Reproducibility: C (bias) + 1.96 SD of C (95% confidence interval/limits of agreement of C).
p is p-value obtained by one-sample t-test (C compared with zero).
F, frontal; T, thalamic; TP, temporoparietal; PV, periventricular; C, cerebellar.

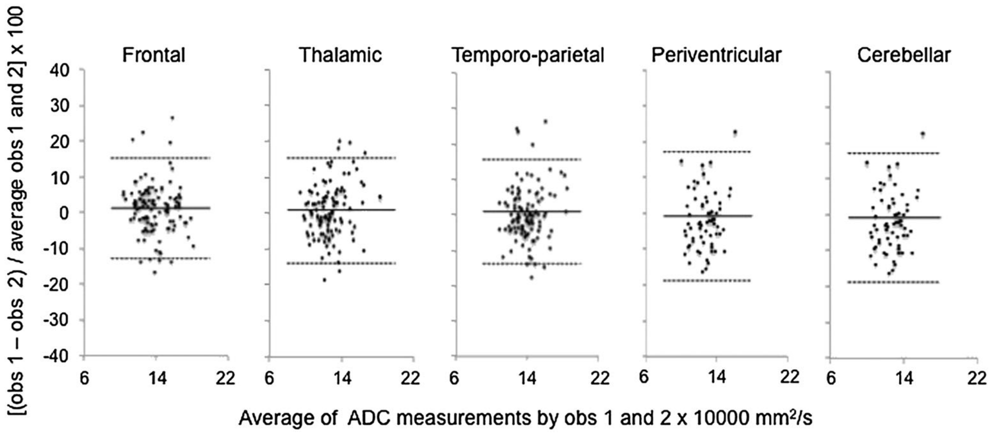

Figure 4 Bland and Altman plots in the analysis of reproducibility (interobserver variation) of apparent diffusion coefficient [apparent diffusion coefficient (ADC)] measurements performed by two observers in the different sites of the normal twin brain. The continuous line represents the bias (average percentage difference) and the dotted lines represent the 95% limits of agreement. Obs 1: average of the first and second ADC measurements performed by observer 1 in the intraobserver analysis; Obs 2: average of the first and second ADC measurements performed by observer 2 in the intraobserver analysis

Of the different conditions associated with an increased risk of fetal brain damage, severe TTTS deserves special consideration. TTTS occurs in approximately 15% of monochorionic twin pregnancies. The pathophysiology itself, which is characterized by an unbalanced blood flow between twins mainly over arteriovenous anastomoses, predisposes to brain injuries.[6,18–21] In addition, laser may worsen or cause brain lesions because of the abrupt hemodynamic changes imposed on the fetuses during the coagulation process or because of accidental bleeding.[24–26] A detailed evaluation of the fetal brain could help physicians counsel parents about the possibilities of neurodevelopmental compromise in their infant. As a first step before performing DW-MRI evaluation of the fetal brain in this disease, the feasibility and reproducibility of the aforementioned method should be tested.

Without maternal sedation, MRI evaluation of the fetus in a polyhydramnious sac can often be a challenging task. Moreover, because not all twins survive fetoscopic laser surgery, this approach enables the assessment of the reproducibility of the evaluation of normal and hypoxic-ischemic fetal brain parenchyma. Despite the efforts made during the acquisition process, some images in the current study were considered inadequate for the evaluation of water diffusion restriction. Most inappropriate datasets were obtained during the evaluation of the recipient twin prior to the laser procedure. Maternal sedation could have helped to overcome this difficulty, but sedation was not an option in our protocol.

In the present study, we did not have a sufficient number of cases with hypoxic-ischemic brain injuries for a subanalysis of the reproducibility of ADC measurements. Although the

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agreement between the two observers in identifying poorly perfused tissues was high, the reproducibility of ADC measurements in what has been confirmed hypoxic-ischemic twin brain parenchyma warrants further testing.

The observation that all of our twins with normal brains on both prenatal examinations also had normal transfontanellar ultrasound scans reinforces the prenatal US and MRI findings.

CONCLUSION

Our data demonstrate that DW-MRI evaluation of the fetal brain in TTTS is feasible and reproducible. Therefore, this method may represent a useful tool for further evaluation of neurological outcome of infants following laser surgery.

WHAT'S ALREADY KNOWN ABOUT THIS TOPIC?

- Twin–twin transfusion syndrome exposes the fetus to a high risk of brain injury.
- Diffusion-weighted magnetic resonance imaging enables the detection of acute hypoxic-ischemic events in the brain.
- Diffusion-weighted magnetic resonance imaging evaluation of the normal fetal brain in singleton pregnancies is reproducible.

WHAT DOES THIS STUDY ADD?

- Diffusion-weighted magnetic resonance imaging evaluation of the fetal brain in cases of twin–twin transfusion syndrome treated with laser ablation of placental vessels is feasible and reproducible.

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