UNCERTAINTY QUANTIFICATION OF MULTI-SITE T1 MEASUREMENTS WITH POLYVINYLPYRROLIDONE (PVP) PHANTOM AND HUMAN BRAIN USING WILD BOOTSTRAP ANALYSIS

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PURPOSE: T1 value changes in brain tissues have been shown to be related to brain pathological change. However, in multi-center studies variations in T1 measurements are reported from different scanners, even with the same scanning protocol. Therefore, the reliability and stability of T1 mapping from different sites, such as variation of system performance, may hinder further human brain analysis. Due to variability of individual human brain and the imperfect of scanner performance, conventional statistical method based on group analysis often fails to get robust uncertainty estimation for individual samples. As a non-parametric linear model-based resampling technique, wild bootstrap analysis has been used for intra-site T1 uncertainty estimation[1], but not for inter-site study. In this study, T1 mapping of a phantom with different concentration of Polyvinylpyrrolidone (PVP) solutions and a volunteer were acquired in two different 3T scanners using DESPOT1 method[2], and wild bootstrap analysis was used to assess both intra- and inter-site uncertainty of quantitative T1 measurements.

METHODS: DESPOT1 approach used a series of fast low angle shot scans with different flip angles (FA) to fit T1 value. By keeping TR as a constant, the signal S was represented by a linear model: Y=Xb . Because of the unknown noise distribution, the linear model residual ε was added in T1 fitting equation $Y = Xb + \varepsilon$. Wild bootstrap was applied to estimate uncertainty of T1 mapping with the following steps: (1) Acquired data fitting. The solution $\hat{b}$ was fitted by ordinary least square (OLS) fitting method, and then the error was estimated as $\varepsilon = Y - X\hat{b}$. (2) Wild bootstrap samples generation. The error ε was modulated with a heteroskedasticity consistent covariance matrix estimator (HCCME) function: $HCCME = 1/(1-\Omega)$ where $\Omega = diag(X(X^TX)^{-1}X^T)$. Two-point Rademacher function $f = \pm 1$ with equal probability was used to generate the variables. Then one wild bootstrap sample was created by $Y^* = X\hat{b} + \varepsilon^* = X\hat{b} + \varepsilon * HCCME * f$ (3) Wild bootstrap statistics. After 1000 times resamples, b was estimated by generated samples, and the T1 value was calculated from the new b. The uncertainty of T1 measurements was estimated by calculating the standard deviations of all wild bootstrap samples $T1_{wb}$: $\sigma(T1) = \sqrt{\sum_{r=1}^{R}(T1_{wb} - \overline{T1})/(R-1)}$, where R is the number of samples and $\overline{T1}$ is the mean value of wild bootstrap samples.

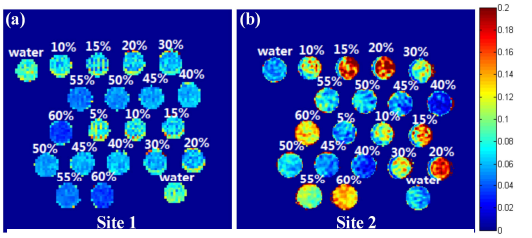

Fig.1. The CV Mapping of Site 1**(a)** and Site 2**(b)**.

Tab.1. The Wild Bootstrap T1 value, CV and Uncertainty of PVP Phantom of two sites.

PVP Phantom	WBT1(ms)		Uncertainty (ms)				CV(%)	
	Site1	Site2	Site1		Site2	Inter-site	Site1	Site2
			Uncert.	Intra-site				
10%	2830	2754	210.84	209.03	298.54	53.74	6.94	10.47
20%	2090	2411	132.21	68.11	416.22	226.98	6.53	17.17
30%	1465	1544	89.73	49.47	159.58	55.86	6.13	11.38
40%	852	672	49.52	22.39	18.42	127.27	5.93	2.69
50%	474	360	24.45	21.24	23.59	80.61	5.11	6.31
60%	218	205	7.33	8.44	26.10	9.21	3.39	3.39

PVP solutions are stable and non-toxic.[3] The low concentration (20% ~ 30%) PVP solutions are similar to some typical T1 value of brain tissues on 3T, making it convenient to compare with brain tissues. We adopted PVP solutions (K=30) with different concentration levels (10% ~ 60%), and different concentration PVP samples had two (N=2) cells located in different spatial positions for the within-scan validation. PVP phantom data were acquired from two (L=2) different 3T MRI scanners, and 5 (M=5) repeat measurements from these sites. Four of these repeats were in Site 1 and one in another site. Then the inter-site uncertainty were calculated after wild bootstrap analysis estimation[4]: $\sigma(T1)_{inter} = \sqrt{\frac{1}{L-1}\sum_{l=1}^{L}\sum_{m=1}^{M}\sum_{n=1}^{N}\left(\frac{1}{M*N}\sum_{m=1}^{M}\sum_{n=1}^{N}T1_{LMN} - \overline{T1}\right)^2}$, where $T1_{LMN}$ represents the T1 value in Nth cell of Mth acquisition from Lth site, and $\overline{T1}$ is the mean value of all L*M*N measurements. Coefficient of variation (CV) also calculated by $CV=\sigma(T1)/\overline{T1}$ for comparison between different sites. The intra-site uncertainty was calculated by: $\sigma(T1)_{intra} = \sqrt{\frac{1}{M-1}\sum_{l=1}^{L}\sum_{m=1}^{M}\sum_{n=1}^{N}\left(\frac{1}{L*N}\sum_{l=1}^{L}\sum_{n=1}^{N}T1_{LMN} - \overline{T1}\right)^2}$, which described the repeatability of T1 mapping. For PVP phantom, the within-scan variability was calculated: $\sigma(T1)_{within} = \frac{1}{L*M*N}\sum_{l=1}^{L}\sum_{m=1}^{M}\sum_{n=1}^{N}\sigma(T1)_{LMN}$, which indicated the measurement precision for each T1 mapping.

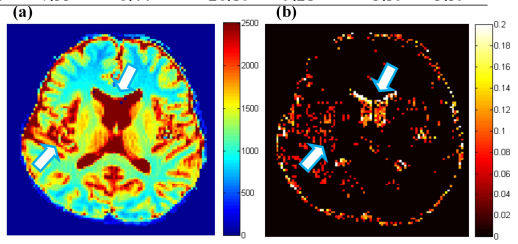

Fig.2. Wild bootstrap T1 mapping of one volunteer **(a)**, the CV mapping on threshold = 0.07**(b)** in Site1.

Tab.2. Wild bootstrap T1 value, CV and uncertainty of different regions showed in Fig.2.

Human ROIs	WBT1(ms)		Uncertainty(ms)			CV(%)	
	Site1	Site2	Site1	Site2	Inter-site	Site1	Site2
CSF	5728	7446	560.51	1559	1214	9.28	50.02
Frontal GM	1595	2063	48.21	381.19	330.93	3.84	13.91
Post GM	1586	1776	45.35	211.59	134.35	3.45	12.45
Thalamus	1657	1562	68.55	131.71	67.18	4.12	10.05
CC WM	1131	1309	33.55	124.25	125.86	2.85	7.92
Post WM	1077	1191	45.81	82.36	80.61	4.12	6.56

For phantom studies, similar configurations were used in two different sites (TR/TE=9/3.48 ms, FOV=180*180 mm^2, slice thickness=4.0 mm, FA=2, 3, 4, 5, 8, 11, 14, 17 degree). In human brain experiment, a healthy volunteer data was acquired in 2 sites and used the same protocol. The Ernst angle of possible T1 value in both phantom and brain tissues were covered in selected FA range.

RESULTS & DISCUSSION: The wild bootstrap analysis results of PVP Phantom measured in two sites was presented in Tab.1. T1 values decreased with increased concentration of PVP solution, and same concentrated PVP samples in different spatial location had stable value with low fluctuation, indicating a good stability of the measurement in this scanner. Both uncertainty and CV decreased while T1 decreased, this tendency was similar in all scanners. Fig.1 showed the CV of T1 Mapping, which represented the inter-site variations. Comparing with the inter-site results, intra-site data was found stable in Site 1, which suggested a better performance of Site 1. In human brain study, the estimated T1 and CV mapping of brain in Site1 was shown in Fig. 3. A display threshold (0.07) was set in CV mapping for highlighting significant variation in specific regions. Some specific regions which had similar T1 value to PVP solutions, were consistent with phantom results acquired in Site 1 (i.e. gray matter compared with 30% PVP solution), which indicated the regions of longer T1 value had higher CV (marked by white arrow). The longer T1 value had lower Ernst angle, and wider FA selection range resulted in higher uncertainty and CV of measurement. The more detailed evaluations of tissues were shown in Tab.2.

CONCLUSION: The consistent results between PVP phantom and *in vivo* human brain data indicated the regions with longer T1 value had higher uncertainty and CV in measurements. The wild bootstrap analysis is helpful for multi-center T1 quantification studies, and the intra- and inter-site uncertainty calculation also provide a robust evaluation for quality assurance and T1 mapping protocols optimization.

REFERENCE: **1.** Polders DL JMR 224 (2012) 53–60; **2.**Deoni SC, et al., MRM, 2003; 49:515-526; **3.**Pierpaoli C, et al., Proc.ISMRM 2009:1414; **4.** Zhu T, et al., Neuroimage, 2011; 56:1398-1411.