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Longitudinal MRI evaluations of human global cortical thickness over minutes to weeks

Xin Wang[a,b], William Bauer[a], Nicolas Chiaia[a], Michael Dennis[c], Mischka Gerken[a], Jacob Hummel[a], John Kane[d], Cynthia Kenmuir[a], Sadik Khuder[e], Richard Lane[a], Richard Mooney[a], Peter Bazeley[f], Vania Apkarian[g,h], John Wall[a,*]

[a] Department of Neuroscience, University of Toledo Medical Center, Toledo, OH 43614, United States
[b] Department of Psychiatry, University of Toledo Medical Center, Toledo, OH 43614, United States
[c] Department of Radiology, University of Toledo Medical Center, Toledo, OH 43614, United States
[d] Department of Orthopedics, University of Toledo Medical Center, Toledo, OH 43614, United States
[e] Department of Medicine, University of Toledo Medical Center, Toledo, OH 43614, United States
[f] Program in Bioinformatics and Proteomics/Genomics, University of Toledo Medical Center, Toledo, OH 43614, United States
[g] Department of Physiology, Anesthesia, and Surgery, Northwestern University Medical School, Chicago, IL 60611, United States
[h] Neuroscience Institute, Northwestern University Medical School, Chicago, IL 60611, United States

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ABSTRACT

Magnetic resonance imaging (MRI) was used to evaluate within-subject variability in global mean cortical thickness over test–retest intervals of minutes–weeks in five healthy adults. Within-subject measures of global mean thickness were consistent over these intervals. Test–retest assessments of absolute thickness differences and percent thickness differences indicated variations of, respectively, ≤0.05–0.06 mm and ≤±1.9–2.3%. There have been few evaluations of normal within-subject variations in cortical thickness. The present results suggest that within-subject variability in global mean cortical thickness can be low over test–retest intervals of minutes–weeks, and that longitudinal scans can establish useful baseline estimates of variability from which to assess changes due to injury, disease, or other experiences.

Magnetic resonance imaging (MRI) measurements of cortical global mean thickness can be used to supplement regional or other cortical thickness measures and have proven useful for identifying cortical structural changes due to aging and clinical conditions [1,8,10,13,14,16]. Although cross-sectional analyses are appropriate for many studies, longitudinal designs are also being increasingly applied [2,9,11,15,17,18], thus, raising interest in within-subject measurement variability.

Existing data on within-subject test–retest variability of global mean cortical thickness or other thickness biomarkers are limited [3,4,7,17]. A recent study suggested that within-subject global mean cortical thickness measures that were taken at a 2-week interval on the same scanner were highly consistent, but also indicated it was premature to blindly extrapolate these findings to other scanners or study conditions [5]. We are aware of no reports that compare within-subject differences in global mean cortical thickness measures taken over short intervals of minutes, when minimal variability might be expected, to measures taken over longer intervals of weeks, when variability may increase due to different factors.

Working from these perspectives, the present investigation compared global mean cortical thickness measures from five healthy subjects who were longitudinally scanned on the same 3 T scanner over test–retest intervals of minutes to weeks. The question of interest was how variable are within-subject measures of global mean thickness over these time intervals?

MRI scans were made in healthy adults (three females, two males, 24–55 years) as part of studies that received prior approval by the institutional review board and that were conducted in accordance with the Declaration of Helsinki. All subjects gave written consent and had no history of major medical illness.

Imaging was done with a 3T GE Signa scanner using a T1-weighted Inversion Recovery Fast Spoiled Gradient Recall Echo imaging protocol (TE = 3 ms; TI = 650; flip angle = 9°; bandwidth = 31.25 kHz; FOV = 256 mm; resolution 1 mm × 1 mm × 1 mm; 164 continuous axial slices encompassing both hemispheres). Between completion of sets 1 and 2 scans and

* Corresponding author. Tel.: +1 419 383 4027; fax: +1 419 383 3008.
E-mail address: john.wall@utoledo.edu (J. Wall).

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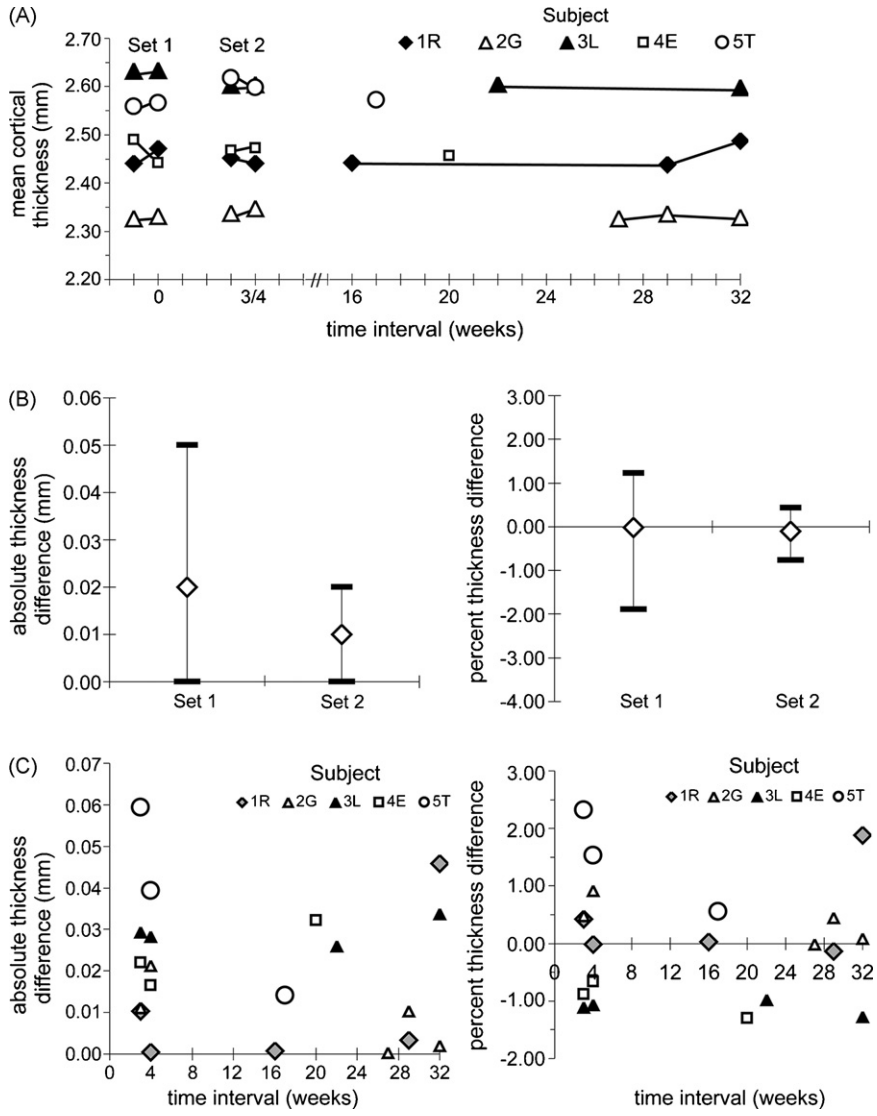

Fig. 1. Longitudinal global mean cortical thickness analyses. (A) Global mean cortical thickness measurements for all scans ($n = 30$) from the five subjects plotted as a function of the time interval between measurements. For set 1 and set 2, a pair of test–retest measurements was made in each subject within minutes of each other. Set 2 measures were made at an interval of 3–4 weeks from set 1 and 1–3 further measures were made at intervals of 16–32 weeks. Coefficients of variation ((standard deviation/mean) × 100) ranged from 24% to 29% for the indicated single scan mean thicknesses. (B) Within-subject differences in global mean thickness measures from pairs of scans that were taken over intervals of minutes in set 1 ($n = 5$ pairs) and set 2 ($n = 5$ pairs). Left: Within-subject means and ranges of absolute thickness differences. Right: Within-subject means and ranges of percent differences in thicknesses. (C) Within-subject differences in cortical thickness measurements for all test–retest measures ($n = 20$) that were taken over intervals of weeks. Left: Absolute thickness differences. Right: percent differences in thickness.

the longer interval scans (see below), the scanner underwent a minor manufacturer upgrade to reduce late echo refocusing which lengthened the TR from 7.5 to 7.8 ms.

Automated cortical thickness measures were made with FreeSurfer programs (http://surfer.nmr.mgh.harvard.edu/fswiki) and a Linux workstation. These programs use intensity and continuity information from MR volumes to reconstruct and measure cortical thickness, and have been shown to provide valid measures at submillimeter resolution [3,6,12,14]. Thickness measures from all cortical locations (vertices) were averaged across both hemispheres to estimate global mean cortical thickness.

Two sets of paired back-to-back scans were made in each subject. Set 1 was taken within a period of about 30 min with removal from the scanner and repositioning between scans. Set 2 was taken within a similar period but without repositioning between the paired scans. Sets 1 and 2 were separated by 3–4 weeks. Each subject also underwent 1–3 further scans that were separated from that subject's set 1 scans by intervals of up to 32 weeks (Fig. 1A).

Within-subject thickness variations were assessed using global mean thickness measures from each scan. Magnitudes of within-subject variations were assessed as absolute thickness differences (in mm) and percent thickness differences between global mean thicknesses from scans at different time intervals.

To assess magnitudes of absolute thickness differences over time intervals of minutes, the absolute difference in millimeters between the mean thicknesses for the 2nd and 1st scans in set 1 was determined in each subject using the 1st scan as the reference (2nd − 1st scan), and a mean and range for these within-subject differences was then calculated. Similar calculations were made for the pairs of set 2 scans to provide a second estimate over time intervals of minutes. To assess magnitudes of absolute thickness differences over time intervals of weeks, each subject's 1st scan in set 1 was again used as a reference, and absolute thickness differences were

determined between each of the week interval scans and this reference. In each subject, this provided two measures at 3–4 weeks (one measure for each of the set 2 scans) and 1–3 further measures over periods of 16–32 weeks. A within-subject mean absolute thickness difference was calculated across these week interval differences. Within-subject absolute thickness differences at week intervals were compared to the within-subject absolute thickness differences seen in set 1, which used the same 1st scan as a reference.

To assess magnitudes of percent thickness differences over time intervals of minutes, the percent thickness difference between the mean thicknesses for the 2nd and 1st scans in set 1 was determined in each subject using the 1st scan as the reference ($((2\text{nd} - 1\text{st})/1\text{st}) \times 100$), and a within-subject mean and range for set 1 differences was calculated. Similar calculations were made for the pairs of set 2 scans to provide a second estimate over time intervals of minutes. To assess magnitudes of percent thickness differences over time intervals of weeks, each subject's 1st scan in set 1 was again used as a reference, and percent thickness differences were determined between each of the week interval scans and this reference. In each subject, this provided two measures at 3–4 weeks (one measure for each of the set 2 scans) and 1–3 further measures over periods of 16–32 weeks. A within-subject mean percent difference was calculated across these week interval differences. Within-subject percent thickness differences at week intervals were compared to the within-subject percent thickness differences seen in set 1, which used the same 1st scan as a reference.

Global mean thickness measures were statistically analyzed with SPSS correlation and ANOVA tests as described below.

Global mean cortical thicknesses from all scans in each subject were charted as a function of time interval between scans (Fig. 1A). Set 1 and set 2 pairs of scans were used to evaluate measurement variability over minutes, and scans over intervals of up to 32 weeks were used to evaluate variability over weeks (Fig. 1A).

Cortical thickness measures from the scan pairs in set 1 and set 2 provided two independent evaluations of within-subject variability for measures that were taken over intervals of minutes. Pearson's correlation coefficients indicated paired measures within each set were highly positively correlated (set 1 correlation = +0.970, $p = 0.006$; set 2 correlation = +0.996, $p = 0.0001$). In addition, intraclass correlation coefficients (ICC) to test agreement in set 1 and set 2 measures revealed high consistency in each set (set 1 ICC = 0.988 (95% confidence interval = 0.882–0.999); set 2 ICC = 0.997 (95% confidence interval = 0.979–1.000)).

These results suggest that within-subject global mean thickness measures closely coincided over intervals of minutes. To further characterize measurement variability over minutes, within-subject differences in paired set 1 and set 2 measures were assessed in terms of absolute thickness (in mm) differences and percent thickness differences. The within-subject means and ranges of absolute thickness differences between 2nd and 1st scans were 0.02 mm (0–0.05 mm) for set 1, and 0.01 mm (0–0.02 mm) for set 2 (Fig. 1B, left). Evaluations of percent differences between 2nd and 1st scans revealed within-subject mean percent differences of −0.02% for set 1 and −0.10% for set 2, with the range of the differences for set 2 completely encompassed in the range of set 1 differences (Fig. 1B, right). For set 1, the maximal within-subject ± percent difference was 1.9%. These results suggest within-subject global mean thickness measures that were taken over intervals of minutes were consistent and had absolute thickness and percent thickness variations of, respectively, ≤0.05 mm and ≤±1.9%.

Variations in global mean thickness measures were also assessed for test–retest intervals of weeks, and compared to the above variations for intervals of minutes. Within-subject profiles of global mean thickness measures across all week intervals appeared relatively flat (Fig. 1A). To assess within-subject variations, a general linear model ANOVA compared mean cortical thicknesses across five scans in each subject: (1) 1st scan of set 1 as a beginning scan, (2) 2nd scan of set 1 to represent a test–retest interval of minutes from (1), (3) 1st scan of set 2, (4) 2nd scan of set 2, both of which represented test–retest intervals of 3–4 weeks from (1), and (5) the final scan to represent each subject's longest test–retest interval (17–32 weeks) from (1). There was no overall statistical difference in cortical thicknesses across scans 1–5 ($p = 0.980$); in addition, there were no differences between measures of scans 2 versus 1 ($p = 0.961$), 3 versus 1 ($p = 0.727$), 4 versus 1 ($p = 0.816$), or 5 versus 1 ($p = 0.961$).

The above results suggest there were no significant differences in within-subject global mean thickness measures that were taken over intervals of minutes or weeks. To further characterize within-subject variability over weeks, absolute and percent thickness differences were assessed for all week interval scans, using the 1st scan in set 1 as a reference. This also allowed comparison to data from set 1. The within-subject mean absolute thickness difference across all week interval scans was 0.02 mm (range = 0–0.06 mm) (Fig. 1C, left). This is similar to the above within-subject absolute thickness variability seen in set 1 (compare Fig. 1C, left, to set 1 in Fig. 1B, left). With respect to within-subject percent differences across all week intervals, the mean difference was 0.04% and the maximal ± percent difference was 2.3% (Fig. 1C, right). This is similar to the above within-subject percent difference variability seen in set 1. These results suggest that within-subject global mean thickness measures that were taken over test–retest intervals of weeks were consistent and, similar to test–retest measures over minutes, had absolute thickness and percent thickness variations of, respectively, ≤0.06 mm and ≤±2.3%.

The present findings suggest that within-subject global mean cortical thickness measures that were taken over intervals of minutes–weeks were consistent and had absolute thickness and percent thickness variations of, respectively, ≤0.05–0.06 mm and ≤±1.9–2.3%. To our knowledge, there have been no previous comparisons of within-subject global mean thickness over test–retest time intervals of minutes and weeks.

Existing data on within-subject variability in cortical thickness measures are limited, and often difficult to directly relate to the present findings. As part of a study on developmental changes in cortical thickness, test–retest cortical thickness measurements were taken in three adults at about a 5 min interval [17]. Average absolute differences at cortical measurement points ranged between 0 and 1.4 mm but variability in global mean thickness was not indicated. As part of an interest in using scan averaging to produce higher resolution images and to analyze measurement precision and power, another study analyzed 19 scans taken over 3 months in one subject [7]. Different cortical thickness metrics were compared, and normalized standard deviations of these metrics ranged up to 0.11 but differences in global mean thickness from one scan to the next were not indicated in terms of absolute thickness or percent thickness variations. As part of another study that compared three computational methods for assessing global mean cortical thickness [4], 10 subjects underwent test–retest measurements (with intervening head repositioning) of global mean cortical thickness. Across the three methods, group differences in test versus retest mean thicknesses were 0.06–0.11 mm. These results were derived from scans using 2 mm slices and the discussion raised the idea that thickness measures would generally improve with smaller slice thickness.

In another recent study, within-subject test–retest measures of global mean thicknesses were made 2 weeks apart, using a 1.5 T scanner [5]. Global mean thickness measures at both times were similar in each subject, with absolute thickness differences

averaging 0.03 mm. These results are similar to the present findings and appear to hold despite differences in variables across the two studies (e.g., previous study [5]: 1.5 T field strength, Siemens scanner, MPRAGE pulse sequence with 1 mm × 1 mm × 1.3 mm resolution, subject age range 66–81 years old, 2 weeks test–retest interval, versus present study: 3 T field strength, GE scanner, IRFSPGR pulse sequence with 1 mm × 1 mm × 1 mm resolution, subject age range 24–55 years old, minutes or weeks test–retest intervals). This previous study also analyzed differences in global mean cortical thicknesses for measures from 1.5 T versus 3 T scanners, and found within-subject absolute thickness differences increased to 0.11 mm when scans from 1.5 T versus 3 T scanners were compared. In these analyses, the within-subject comparisons were between test measures made with a 1.5 T scanner, and retest measures made with a 3 T scanner. In contrast, in the present study within-subject comparisons were done between test and retest measures from the same 3 T scanner. As indicated above, the resulting absolute differences for the present test–retest measures, and the absolute differences for the above test–retest measures that were made with one 1.5 T scanner, were similar. Thus, within-subject test–retest variability is similar for scans that are made on at least some 1.5 and 3 T scanners provided test–retest measures are both made with a constant field strength and scanner. This issue deserves further attention in larger samples.

The present results indicate that within-subject variability in global mean thickness of the studied healthy adults was low over periods of minutes to weeks. This suggests that longitudinal measurements can provide useful empirical estimates of variability from which to assess global thickness changes due to injury, disease, or other experience-related factors.

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