Voxel-wise assessment of pathology evolution in articular cartilage based on statistically significant changes of T2

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Introduction: Osteoarthritis (OA) is a degenerative, painful and functionally limiting disease of the joint, which involves progressive loss of articular cartilage. Due to the lack of an effective therapy, OA has a high prevalence and therefore represents an enormous socioeconomic burden. A considerable limitation in the assessment of new therapies and drugs for OA is the absence of robust non-invasive methods for monitoring the progression of joint disease [1]. The articular cartilage is a very important entity in the diagnostic workup of OA since degenerative changes of the collagenous network in the cartilage matrix are considered to be an entry point in the process of irreversible joint degradation. The relaxation time T2 is especially adequate for diagnosis of OA since it is sensitive to the collagen structure of the cartilage matrix [2]. The aim of this work was to develop a method for voxel-wise assessment of pathology evolution in articular cartilage based on statistically significant changes of T2 relaxation.

Methods: In follow-up examinations two image data sets of the same subject acquired at two different time points must be compared. The first step is to register the images to compare the T2 values of the same voxel in the two acquisitions. A rigid 3D registration method with a registration error below 25% of the voxel size was used [3]. After registration, for each voxel there are two T2 values, $T2_1$ and $T2_2$, from the two measurements. To be sure that the two T2 values really represent a significant change in T2, the total errors of T2 must be known. Contributions to the total error of T2 come from SNR, magic-angle effects due to repositioning of the knee between acquisitions, image processing, registration errors...

The total error of T2 was calculated from repeated acquisitions of the tibial cartilage of healthy volunteers (n=24, imaged at three different time points) and OA-diseased patients (n=17, imaged twice) with a multi-slice multi-echo spin-echo sequence (TE/TR = 13.2/3500 ms, echo train length = 8, echo spacing 13.2 ms, FOV = 256×256, in plane resolution = 0.61×0.61 mm, slice thickness = 3 mm). All images of the same volunteer/patient were pairwise registered and the standard deviation of T2 was calculated Based on the T2 values of the healthy volunteers, the 99th percentile was used as a cut-off for pathologic values. With this information, a 2σ-significance map for the follow up is constructed. For each voxel the measured pair of $T2_1$ and $T2_2$ is represented as a point in a 2D plot. 2σ errors around line $T2_1 = T2_2$ represent the region of non-significant changes in T2. The cut-off between healthy and pathological values is represented by two lines in the plot and helps differentiating transition from healthy to diseased T2 (and vice versa). The use of a 2σ-significance map allows significantly (P<0.05) differentiating between 6 possible changes in T2 (Fig 1).

The utility of the 2σ-significance map were tested on 5 patients, which underwent autologous chondrocyte transplantation (ACT). Patients were follow-up examined 6 (baseline), 12, 24 and 52 weeks after intervention. In the baseline examination voxels with T2 larger than the cut-off delineated the baseline lesion. The follow-ups at 12, 24 and 56 weeks were registered to the baseline, and the T2 differences classified according to the regions of the 2σ-significance map. Color-encoded maps of the significant changes of T2 were used to monitor the evolution of the initial lesion.

Results: The result of the calculation of the total error of T2 is represented in Fig. 1A. The high standard deviations at larger T2 values are due to the low number of voxels with high T2 values. The pink line represents the theoretical measurement error calculated from the same SNR and T2 distribution as for the measured data. Differences at high T2 between the theoretical and measured standard deviations are due to partial volume effects with the synovial liquid (T2 around 250 ms). The cut-off between healthy and pathological T2 values was 75 ms. The 2σ-significance map calculated with this data is represented in Fig. 1B. The color encoding of the regions is consistently used in the color maps for the patient in the example of Fig. 1C. In this case the differences in T2 demonstrated significant healing of the lesions located near to the bone-cartilage interface at 12 weeks, and growth of the lesion located at the cartilage surface. Healthy voxels surrounding the surface lesion at baseline turned to be pathological inthe first follow-up. The significant T2 reduction in pathological voxels at the cartilage surface may be an early sign of the healing confirmed by the follow-up at the 24th week.

Conclusions: The method proposed here assesses the pathology evolution in articular cartilage based on detecting statistically significant changes on T2 and offers new information of disease progression, which otherwise could remain hidden. Although the diagnostic relevance of this new information must be still demonstrated in larger patient collectives, the method is a first attempt to deal with the problem of disease progression at a voxel basis.

References:

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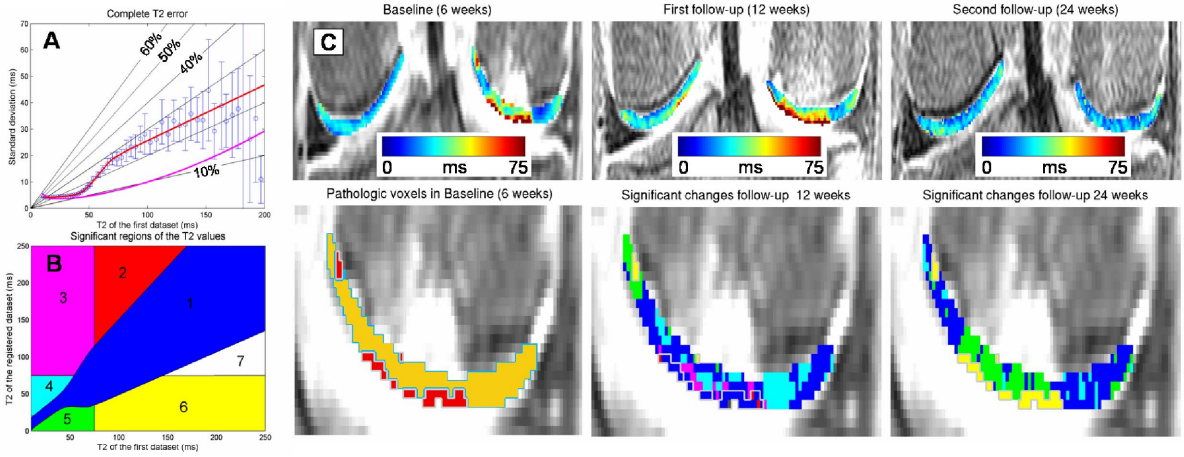

Figure 1. 1A. Calculation of the total error. The red line is a fit of the standard deviations. The pink line is the theoretical measurement error. **1B.** 2σ-significance map calculated from the experimental data differentiating 6 situations: 1. No significant difference. 2. Initially pathological voxel with further increased T2 in follow-up. 3. Initially healthy voxel diseased in follow-up. 4. Initially healthy voxel with increased but still normal T2 in follow-up. 5. Initially healthy voxel with decreased T2 in follow-up. 6. Initially pathological voxel with normalized T2 in follow-up. 7. Initially pathological voxel with decreased but still pathological T2 in follow-up. **1C.First row** T2 maps of examinations at 6, 12 and 24 weeks after intervention (color encode T2 values) **1C.Second row.** Baseline. Detection of the lesion. Follow ups significant changes color-encoded according to 1B.