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A web-based system for neural network based classification in temporomandibular joint osteoarthritis

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ABSTRACT

Objective: The purpose of this study is to describe the methodological innovations of a web-based system for storage, integration and computation of biomedical data, using a training imaging dataset to remotely compute a deep neural network classifier of temporomandibular joint osteoarthritis (TMJOA).

Methods: This study imaging dataset consisted of three-dimensional (3D) surface meshes of mandibular condyles constructed from cone beam computed tomography (CBCT) scans. The training dataset consisted of 259 condyles, 105 from control subjects and 154 from patients with diagnosis of TMJ OA. For the image analysis classification, 34 right and left condyles from 17 patients (39.9 ± 11.7 years), who experienced signs and symptoms of the disease for less than 5 years, were included as the testing dataset. For the integrative statistical model of clinical, biological and imaging markers, the sample consisted of the same 17 test OA subjects and 17 age and sex matched control subjects (39.4 ± 15.4 years), who did not show any sign or symptom of OA. For these 34 subjects, a standardized clinical questionnaire, blood and saliva samples were also collected. The technological methodologies in this study include a deep neural network classifier of 3D condylar morphology (ShapeVariationAnalyzer, SVA), and a flexible web-based system for data storage, computation and integration (DSCI) of high dimensional imaging, clinical, and biological data.

Results: The DSCI system trained and tested the neural network, indicating 5 stages of structural degenerative changes in condylar morphology in the TMJ with 91% close agreement between the clinician consensus and the SVA classifier. The DSCI remotely ran with a novel application of a statistical analysis, the Multivariate Functional Shape Data Analysis, that computed high dimensional correlations between shape 3D coordinates, clinical pain levels and levels of biological markers, and then graphically displayed the computation results.

Conclusions: The findings of this study demonstrate a comprehensive phenotypic characterization of TMJ health and disease at clinical, imaging and biological levels, using novel flexible and versatile open-source tools for a web-based system that provides advanced shape statistical analysis and a neural network based classification of temporomandibular joint osteoarthritis.

1. Introduction

No proven disease-modifying therapy exists for osteoarthritis (OA) and current treatment options for chronic arthritic pain are insufficient (Hunter et al., 2013). The NIH-funded categorization of OA includes imaging, clinical and molecular markers of inflammation, angiogenesis and bone resorption in arthritis initiation and progression. Variation in disease progression requires biomarkers that can reflect morphological

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and pathological changes in joints, beginning in the earliest stages of OA development and throughout the course of the disease. Biochemical markers may reflect ultrastructural changes in joint tissue metabolism very early in the disease process prior to any apparent change in imaging appearance. Not only local proteins in the synovial fluid, but also circulating levels of proteins, may play a role in the cross-talk among the different joint tissues. The ascertainment of variations between health and disease is essential information for detecting inflammatory and degenerative conditions of the tissues affected (Abramson and Attur, 2009).

Patient data in clinical research on Temporo-Mandibular Joint Osteoarthritis often includes large amounts of structured information, such as imaging data, biological marker levels, and clinical variables. The present study proposes improvement in the precision of the subjective radiological interpretation of morphological variability described in Su et al., (2014) the unsupervised statistical classification proposed by Gomes et al., (2015), and the shape statistical models proposed by Paniagua et al., (2017). Given the various sources of information, computerized methods can be a great help to clinicians to discover hidden patterns in the data. The computerized methods often employ data mining and machine learning algorithms, lending themselves as the computer-aided diagnosis tool that assists clinicians in making diagnostic decisions. State-of-the art methods to classify morphological variations include extreme learning machine, sparse representation-based classification and neural network deep learning (Ashinsky et al., 2017; Li, 2018). Neural network applications in computer-aided diagnosis represent the main stream of computational intelligence in medical imaging (Qian et al., 2007). Their application is generalizable to most medical problems due the adaptive and flexible nature of learning directly from input information. Given a suitable learning algorithm, the neural network can improve the algorithm performance in accordance with the variety and the change of input datasets. Neural networks have the capability of optimizing the relationship between the input and output via distributed computing, training, and processing, leading to reliable solutions to a specific clinical question. Diagnosis often relies on visual inspection of scans, and 3D imaging provides a most important tool for facilitating such inspection and visualization. Surpassing human-level performance on certain image recognition tasks, neural networks enable the incorporation of large training data sets, as well as the use of different shape analysis features within the same classification (Jiang et al., 2010).

The neural network deep learning proposed in this manuscript to classify morphological variability extract features from the mandibular condyle morphology to describe each patient 3D mesh. There is a compelling need for such more efficient software tools that facilitate the analyses of clinical, biological and imaging data of the complex heterogeneous conditions in TMJ OA. To answer the diagnostic and assessment of treatment effectiveness challenges, our innovative solutions include the development of a web-based system, which implements a broad set of statistics and an advanced neural network classifier that supports the analysis of shape variability based on a training dataset. Our DSCI (Data Storage for Computation and Integration) web system provides useful features for integrating databases, performing data quality control and sample selection. The purpose of this study is to describe the DSCI system methodological innovations in functionality and efficiency, using a training imaging data set to remotely compute a neural network classifier of temporomandibular joint osteoarthritis.

2. Materials and methods

2.1. Materials

Data used in the preparation of this article were obtained from the Dental and Craniofacial Bionetwork of Image Analysis database (DCBIA). The DCBIA has performed an observational clinical study that collected imaging, biological, and clinical data to characterize TMJ OA. This study is in concordance with STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) guidelines for observational studies. The University of Michigan Institutional Review Board approved the data acquisition and analysis in this study.

This study included imaging, clinical and biological datasets. Three-dimensional (3D) surface representation (meshes) for 293 condyles were constructed from CBCT scans. The training dataset consisted of 259 condyles, 105 from control subjects and 154 from patients with diagnosis of TMJ OA. For the image analysis classification, 34 right and left condyles from 17 patients (39.9 ± 11.7 years), who experienced signs and symptoms of the disease for less than 5 years, were included as the testing dataset. For the integrative statistical model of clinical, biological and imaging markers, the sample consisted of the same 17 test OA subjects and 17 age and sex matched control subjects (39.4 ± 15.4 years), who did not show any sign or symptom of OA. For these 34 subjects, a standardized clinical questionnaire, blood and saliva samples were also collected. Subjects recruited from the university clinic and through advertisement, underwent a clinical exam by an orofacial pain specialist using the research diagnostic criteria for temporomandibular disorders (RDC/TMD) guidelines (Ahmad et al., 2009). Following clinical diagnosis of TMJ osteoarthritis or health, a Cone beam CT (CBCT) scan was taken on all participants, with 0.08 mm isotropic voxel size and 4 cm × 4 cm field of view, using the 3D Accuitomo 170, Morita Corp. Blood and saliva samples were collected on the same day by an experienced nurse at the Department of Oral and Maxillofacial Surgery. Subjects allowed the saliva to naturally drool down the funnel into the collection tube, until the amount of saliva collection reached around 3 ml or 15 min maximum. Immediately after collection, liquid saliva was aliquoted to exactly 2 ml, and inhibitor protease (Aprotinin + PMSF) was added. 400 u l-500 ul aliquots of the saliva + protease volume was placed into 4–5 Eppendorf tubes and stored at −80 °C for future analysis. 4 ml of blood sample was collected in a unique EDTA tube. After collection, cells were removed from plasma by centrifugation for 20 min with 1000 rpm (rpm). Plasma and cells were placed into different Eppendorf tubes, 3 each one, and stored at −80 °C.

2.2. Biological samples methods

Custom quantibody protein microarrays RayBiotech (Norcross, GA) were used to evaluate the saliva and serum samples for 17 biomarkers expressed in both synovial fluid and blood in our preliminary work (Cevidanes et al., 2014). This assay is array-based multiplex sandwich ELISA system for simultaneous, quantitative measurement the concentration of multiple proteins. Like an ELISA, it uses a pair of antigen-specific antibodies to capture the protein of interest. The use of biotinylated antibodies and a streptavidin-conjugated fluor allow detection levels for the specific proteins to be visualized using a fluorescence laser scanner (RayBiotech, 2017). For protein quantification, the reagent kit included protein standards, whose concentration had been predetermined, provided to generate a six-point standard curve of each protein. Standards and samples were assayed simultaneously. By comparing signals from unknown samples to the standard curve, the unknown protein concentrations in the samples were determined. Positive controls for each biomarker were included in each array and the array data obtained from densitometry were entered into the appropriate cells of the corresponding analysis tool, which plotted the standard curve for each analysis in addition to performing background subtraction/normalization. The biomarkers chosen were known to be associated with bone repair and degradation, inflammation or nociception, common processes seen in OA. Preprocessing steps for these samples were completed at the School of Dentistry and then shipped to RayBiotech for analysis. All samples were evaluated in duplicate for level of proteins 6ckine, ANG, BDNF, CXCL16, ENA-78, GM-CSF, IFNγ, IL-1α, IL-6, MMP-3, MMP-7, PAI-1, TGFβ1, TIMP-1, TNFα, VE-Cadherin and VEGF.