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Accurate Age Determination for Adolescents Using Magnetic Resonance Imaging of the Hand and Wrist with an Artificial Neural Network-Based Approach

Fuk Hay Tang [1,2] · **Jasmine L.C. Chan** [2] · **Bill K.L. Chan** [2]

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Abstract

This study proposes an accurate method in assessing chronological age of the adolescents using a machine learning approach using MRI images. We also examined the value of MRI with Tanner-Whitehouse 3 (TW3) method in assessing skeletal maturity. Seventy-nine 12–17-year-old healthy Hong Kong Chinese adolescents were recruited. The left hand and wrist region were scanned by a dedicated skeletal MRI scanner. T1-weighted three-dimensional coronal view images for the left hand and wrist region were acquired. Independent maturity indicators such as subject body height, body weight, bone marrow composition intensity quantified by MRI, and TW3 skeletal age were included for artificial neural network (ANN) analysis. Our results indicated that the skeletal age was generally underestimated using TW3 method, and significant difference ($p < 0.05$) was noted for skeletal age with chronological age for female category and at later stage of adolescence (15 to 17 years old) in both genders. In our proposed machine learning approach, ages determined by ANN method agreed well with chronological age ($p > 0.05$).The machine learning approach using ANN method was about 10-fold more accurate than the TW3 method using MRI alone. It offers a more objective and accurate solution for prospective chronological maturity assessment for adolescents.

Keywords Skeletal maturity · Chronological age · Machine learning · Magnetic resonance imaging · Artificial neural networks

Introduction

Age determination of children is essential in clinical considerations in areas such as pediatrics, orthodontics, forensic sciences, and anthropology [1–3]. On the other hand, genetic, hormonal, racial, environmental, and nutritional differences may lead to an inconsistency between the chronological age of young individuals and their physiological maturity [4]. Furthermore, in age-related tournaments for young adults and adolescents, it is important to guarantee fair play for different age groups. However, in cases where there is no accurate birth registration record of the participating players, reliable age estimation is critical. Furthermore, growth rate changes of adolescents can be well monitored if a reliable chronological age determination based on physiological parameters is guaranteed. Recent studies indicated that magnetic resonance imaging (MRI) of the skeletal maturity alone was not related to chronological age and was not recommended for age determination for young athletes [1, 2]. It seems that other parameters may need to be included for a more accurate age determination in addition to imaging of bony features.

The traditional studies of skeletal age determination by using either the Greulich and Pyle (GP) or the Tanner-Whitehouse (TW) method [5] where the left hand and wrist X-ray images of the subject were taken involved ionizing radiation. The MRI is radiation free, and it renders an excellent contrast of anatomical features with high reproducibility [6–9]. When radiation is a concern for children screening without clinical indications, it offers a good solution for prospective study of skeletal maturity [6]. On the other hand, the artificial neural network (ANN) method was one of the machine learning techniques and has been used for simulating the role of radiologists for assessing the bone maturity through extensive training. Wikipedia indicated that "Artificial neural networks (ANNs)…..are systems inspired by the biological neural networks that constitute animal brains. Such systems learn (progressively improve performance on) tasks by

✉ Fuk Hay Tang
haytang@gmail.com

1 School of Medical and Health Sciences, Tung Wah College, 31 Wylie Road, Homantin, Kowloon, Hong Kong

2 Department of Health Technology and Informatics, The Hong Kong Polytechnic University, Hung Hom, Hong Kong

considering examples, generally without task-specific programming" [10]. Deep-learning neural network model has been used recently in assessing skeletal maturity on pediatric hand radiographs [11]. It was noted that this study compared the neural network model estimates with reference standard bone ages but not the chronological age. Previous studies have demonstrated the high validity of the ANNs in skeletal age determination based on feature extraction of bones in the wrist [12, 13]. Nevertheless, in these studies, other skeletal maturity factors such as bone density, body weight, and body height were not well taken into consideration. This limits the accuracy of bone age assessment. It follows that the purpose of this study is to propose an ANNs based model to produce a more accurate assessment of chronological age using MRI and other skeletal maturity factors.

Materials and Methods

Subjects

Normal local Hong Kong Chinese subjects aged between 12 and 17 years old were recruited prospectively. The selected age groups experienced rapid growth during puberty, indicated by the growth spurt of adolescents for boys and girls at approximately 12–13 years old [14, 15]. The effect of gender skeletal maturity was likely more prominent at this period [16]. As a result, 79 volunteers (39 males, 40 females) were successfully recruited. The sample size of this study followed similar research studies with target age range [8, 17].

The subjects were asked to enter the self-response questionnaire about medical history and ethnicity before MRI examination. The exclusion criteria are:

(i) Subjects who have undergone hormonal therapy
(ii) Subjects with fracture history of left hand and wrist region such as gross fracture of phalanges, radius, and ulna
(iii) Subjects with metallic implants
(iv) Subjects who are not ethnically Chinese

A briefing about the purpose and safety of the study was given to each subject and his/her guardian before the examination, and the subsequent consent forms were signed. Ethics approval was also obtained from the University Research Ethics Committee.

CA Determination

The chronological age of the subject was determined according to the date of birth to the date of examination (days difference divided by 365.25).

TW3 Skeletal Age Estimation

TW3 Method

The TW method is based on structural analysis of bones in children's hand and wrist by calculating the sum of points assigned to the bones based on ossification analysis of the radius, the ulna, the short bones (RUS), and the carpal bones. For each stage of every bone, separate scores are used for female and male children.

The Tanner-Whitehouse 3 (TW3) method was chosen for skeletal age (SA) assessment as it was suitable in Hong Kong [18–23]. Four final year radiography students from the Hong Kong Polytechnic University with specialized training in MR bone reading participated in the grading process. A consultant radiologist with 18-year clinical experience was invited to validate the result in case there were any discrepancies among raters.

In each set of wrist and hand MRI image, the radius, ulna, and short bones (RUS, including metacarpals and phalanges) were graded. Males and females were assessed separately according to the reference table in TW3 method, where the sums of the scores were related to the corresponding stages (A to I) of skeletal age (see Fig. 1).

Maturity Parameters

In this study, we also measured the MR signal intensity for bone marrow as an indicator for skeletal maturation in adolescence [8, 9]. A 2D region of interest (ROI) of 16 × 16 pixels was selected manually by the assessor at the middle of the distal radius (Fig. 2). The mean and standard deviation of the signal intensity were calculated for further evaluation in ANN. The other maturity-related parameters including body weight and height were also measured.

Fig. 1 MRI images (0.18 T with 20 mT/m gradient strength, dual phase array hand and wrist coil was used) from the same subject for differentiation between stages H and I. Horizontal red arrow: 3rd proximal phalanx, with hypodense line seen. Green arrow: 3rd middle phalanx, absence of hypodense line. Vertical blue arrow: Distal radius, presence of hypodense line (color figure online)

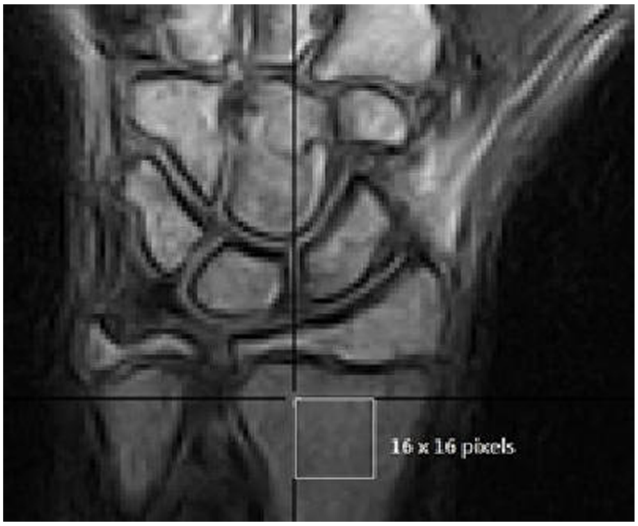

Fig. 2 The bone marrow intensity measurement in the 16 × 16 pixels box

ANN Skeletal Age Estimation

The ANNs were used to predict the skeletal maturity. ANN method is a mathematical model or computational model simulating biological neural networks. ANNs have three layers. The first layer consists of input neurons. The neurons then send data to the second layer, which in turn sends the output neurons to the third layer. In our design, the second layer is the hidden layer and the third layer is the output layer. The authors note that deep learning techniques have been introduced for bone age determination [11, 24] and convolutional neural networks are developed specifically to learn hierarchical representation of image data. In our case, the data is rather simple; the feed forward neural network provides a more efficient method to handle the data. Our ANN model that worked on a feed forward network based on Marquardt algorithm [23, 25] provides a sufficient and efficient solution. There were four input parameters (TW3 age score, body weight, body height, and MRI signal intensity) and one output (skeletal maturity). The ANN model was implemented by MATLAB (version 2015a). The ANN was trained and tested using round-robin or leave-one-out method. By this method, one sample was taken out as a test sample and the rest was served as training sample. This was processed sequentially until all samples were tested. Thus, in this study, there were 79 samples tested and trained.

Procedures

Before the examination, the procedure of scanning was explained briefly to the subject. The body weight and height were then measured. A 0.18-T skeletal MRI machine (Model: Opera E-scan manufactured by Esaote) with 20-mT/m gradient strength was used for acquiring the images. Dual phase array hand and wrist coil were selected. The subjects were told to remove all metallic objects before entering the examination area. No sedation was required for any subjects in our study.

For the scan, a subject was seated next to the machine with the left hand and wrist extended in a postero-anterior (PA) position inside coil (see Fig. 3). The levels of wrist, metacarpals, and the phalanges were positioned as horizontal as possible with appropriate placement of immobilization soft pads.

The MRI protocol was T1-weighted 3D Turbo Spin Echo in coronal view. The repetition time (TR) and echo time (TE) were 40 ms and 12 ms respectively. The flip angle was 65°. With the use of 3D turbo spin echo, the slice thickness was 1.1 mm with 1.1 distance factor. The matrix was 192 × 192, and the DFOV was 170 × 170 mm^2. To minimize the time for scanning, only one acquisition was used in each scan. Due to limited size of coil of the MRI machine, two scans, the upper and lower portions of hand and wrist regions, were performed. It took about 15 min to complete a scan for each subject.

Intra and Inter-reliability Test

The images were anonymized and scored by four raters separately. Two separate rating processes were conducted with a separation of 3 weeks interval in randomized order of reading. A DICOM viewer (Syngo fastView, Siemens AG) was used for viewing images.

To avoid any bias in image interpretation, an assigned code, gender, and the imaging protocol were displayed on images only so that raters were blinded from the name and age of the subjects. The mean values of the skeletal ages graded by raters were compared with the subjects' corresponding chronological age (CA) value. For intra-reliability test, two separate rating processes, with approximately 3 weeks interval, were conducted for analyzing the same sets of randomly selected and rearranged images. Height, weight, bone marrow composition intensity, and TW3 SA were taken by ANN for predicting individual SA. Microsoft Excel was used for data recording and manipulation.

Data Analysis

To ensure the reliability within and between raters, intra-reliability and inter-reliability tests were statistically performed by using IBM SPSS (V. 22.0). The data were first tested by intraclass correlation coefficient (ICC) in SPSS to ensure data reliability. Apart from the analyzing the reliability among the raters, paired *t* test was then performed for evaluating if there was significant difference between the mean difference of SA and CA in particular CA group or gender. The paired *t* test was repeated for determining the significant

Fig. 3 Positioning of wrist and hand during the MRI examination

difference between the mean difference of ANN SA and the corresponding CA in different categories.

Results

Data Reliability

For the scoring of bone maturity using TW3 methods, our result indicated that the inter-reliability was 0.880 and the intra-reliability of all raters between the 1st and 2nd rating ranged from 0.912 to 0.978. This indicated the raters had a high reliability and consistence in rating the skeletal maturity.

Chronological Age and Skeletal Age

When using TW3 method, the mean SA values were generally smaller than the mean CA values for 15 to 17 years age group but larger than the mean CA for 12 to 14 years age groups (see Table 1). There was a significant difference for the age group of 15–17 years ($p < 0.05$), but we could not demonstrate any difference in the age group of 12–14 years ($p > 0.05$). On the whole, the mean disparity of SA and CA for male and female

Table 1 The values between TW3 derived skeletal age (SA) and chronological age (CA) in different gender and age groups. Number of subject (n), mean, standard deviation (SD), and p value are also indicated

Gender	CA category	Number	Mean CA (year)	Mean SA (year)	Mean disparity (abs(SA-CA)) (year)	SA SD (year)	CA SD (year)	SD Difference (year)	p value
M	12	4	12.50	12.29	0.21	1.30	0.32	0.98	–
	13	4	13.76	13.95	0.20	0.96	0.30	0.66	–
	14	8	14.42	14.98	0.56	0.57	0.29	0.28	–
	15	12	15.50	15.19	0.31	0.61	0.26	0.35	–
	16	7	16.54	16.08	0.46	0.42	0.27	0.15	–
	17	4	17.61	15.99	1.63	0.38	0.31	0.07	–
	Early (12–14)	16	13.774	14.05	0.38	0.85	0.30	0.55	0.195
	Late (15–17)	23	16.184	15.6	0.58	0.51	0.27	0.24	0.001
	All	39	15.20	14.96	0.50	0.65	0.28	0.37	0.1
F	12	4	12.46	13.91	1.45	1.09	0.40	0.69	–
	13	4	13.50	13.16	0.34	0.53	0.16	0.37	–
	14	3	14.09	13.19	0.91	1.34	0.11	1.23	–
	15	14	15.53	14.21	1.32	0.59	0.35	0.24	–
	16	7	16.62	14.49	2.13	0.51	0.36	0.15	–
	17	8	17.43	14.80	2.62	0.15	0.32	0.17	–
	Early (12–14)	11	13.28	13.44	0.90	0.95	0.24	0.7	0.73
	Late (15–17)	29	16.32	14.44	1.88	0.45	0.34	0.11	< 0.001
	All	40	15.48	14.17	1.61	0.59	0.31	0.28	< 0.001
			M + F total mean disparity		1.06				

is 0.50 years and 1.61 years respectively. The overall disparity of SA from CA is 1.06 years.

Gender

In this study, male subjects demonstrated a general change from overestimation (age 12–14) to underestimation of SA over CA [14–16]. Female subjects showed a generally lower mean SA than their corresponding mean CA (except for age 12 years) (Table 1).

There was no significant difference between SA and CA in male category and early stage of adolescents (12–14 years old) in both genders ($p > 0.05$). However, significant difference was demonstrated for the female category and late stage of adolescence (15–17 years old) in both genders for SA and CA ($p < 0.05$). TW3 method was generally considered to be applicable for early stage of adolescents but not for late stage of adolescence.

Artificial Neural Networks

When using bone maturity contributing factors (body weight, body height, MR signal intensity, and TW3 estimated SA) as inputs ANN, there was no significant difference ($p > 0.05$) for the CA of the subjects with predicted ANN skeletal age (ANNSA), indicating that in all of the groupings, the ANNSA agreed well with CA of the subjects (Table 2). On the whole, the mean disparity of ANNSA and CA for male and female is 0.13 years and 0.08 years respectively. The overall mean disparity (males and females) is 0.10 years. This shows a good improvement of using ANN method over the traditional TW3 method (0.10 years against 1.06 years) as an estimation for skeletal maturity.

Generally speaking, the predicted ANNSA generally followed the CA of both male and female (see Figs. 4 and 5).

Discussion

SA Determination Using the TW3 Method

We should stress that the TW method originally developed using radiographs of hands and wrists has been applied in MR images in this study. We also noted that there were inherent weaknesses in the TW3 method. Firstly, in the TW3 method, the maximum skeletal age scores were 16.5 years and

Table 2 The values of ANN bone age and chronological age (CA) with gender and age categories. Number of subject (*n*), mean, standard deviation (SD), and *p* value are also demonstrated

Gender	CA category	Number	Mean CA (year)	Mean ANNSA (year)	Mean disparity (abs(ANNSA-CA)) (year)	ANN SD (year)	CA SD (year)	SD Difference (year)	*p* value
M	12	3	12.43	12.47	0.04	0.44	0.36	0.08	–
	13	2	13.89	14.16	0.27	0.13	0.14	0.01	–
	14	7	14.47	14.79	0.33	0.71	0.28	0.43	–
	15	12	15.50	15.62	0.12	0.52	0.26	0.26	–
	16	7	16.54	16.56	0.02	0.45	0.27	0.18	–
	17	4	17.61	17.66	0.05	0.42	0.31	0.12	–
	Early (12–14)	12	13.86	14.11	0.25	1.55	0.28	0.27	0.091
	Late (15–17)	23	16.19	16.26	0.07	0.48	0.27	0.21	0.444
	All	35	15.39	15.52	*0.13*	1.43	1.42	0.01	0.097
F	12	4	12.45	12.48	0.03	0.43	0.40	0.03	–
	13	3	13.54	13.73	0.19	0.12	0.17	0.05	–
	14	2	14.2	13.45	0.75	1.08	0.14	0.94	–
	15	14	15.53	15.54	0.01	0.49	0.35	0.14	–
	16	7	16.62	16.55	0.08	0.30	0.36	0.06	–
	17	8	17.43	17.49	0.06	0.77	0.32	0.45	–
	Early (12–14)	9	13.18	13.11	0.22	0.47	0.27	0.2	0.676
	Late (15–17)	29	16.32	16.32	0.04	0.52	0.34	0.18	0.986
	All	38	15.58	15.56	0.08	0.51	0.33	0.18	0.805
			M + F total mean disparity		0.10				

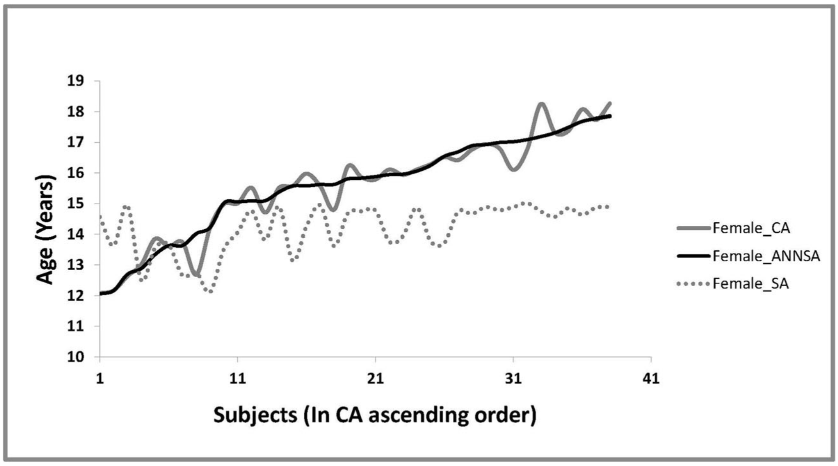

Fig. 4 Graph of the female subject's age calculated by chronological (CA), skeletal (SA), and artifical neural network (ANN) methods

15.0 years for male and female respectively. This would lead to an underestimation for those age groups thereafter up to 17 years.

Secondly, the TW3 method used X-ray imaging where subtle contrast difference was hardly differentiated in wrist radiographs. Incomplete epiphyseal lines, which could be visualized as slightly hypodense lines in MRI image, might be regarded as completed fusion in X-ray [7].

Thirdly, the age disparity for assessing the skeletal age using MRI TW3 method is as high as 1 year in average with standard deviation ranging from 0.37 (male) to 0.28 (female). The method itself relies on the assessment of an assessor, which is subjective, and would lead to the large discrepancies.

Artificial Neural Networks

We proposed various independent indicators affecting skeletal maturity for prediction of CA using ANNs. These include body height, body weight, and bone marrow composition intensity. Our results indicate the mean disparity of SA from CA (including both males and females) was 0.1 years using ANN method, whereas it is 1.06 years for TW3 method. The standard deviation for ANN method is ranging from 0.01 (male) to 0.18(female). This indicates the ANNSA is both 10-fold more accurate than the existing TW3 method and it is more stable (Figs. 4 and 5).

Skeletal Age Assessment

The MRI can be considered as an alternative means for skeletal age assessment other than X-ray [6–9]. In a retrospective skeletal age study in Hong Kong earlier using the TW3 method in X-ray hands and wrists, the mean skeletal age tended to overestimate chronological age at all ages for both females and male and concluded that TW3 method was not applicable for children after 12 years old (carpal TW3) and 16 years (RUS TW3). Similar observation was noted in our study using MRI TW3 (see "Results" and Figs. 4 and 5).

On the other hands, the use of MRI as a means for skeletal assessment suffers from the fact that the subject for assessment cannot carry any metallic material during the examination and the examination will be performed in an enclosed environment; this might induce claustrophobia in the subjects.

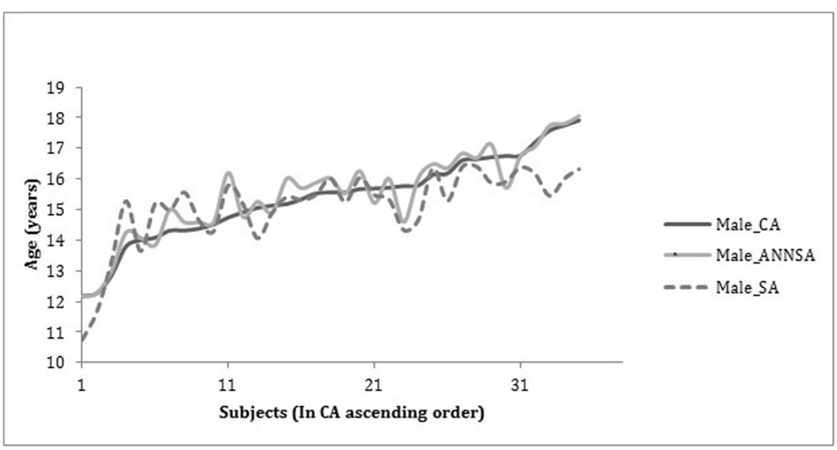

Fig. 5 Graph of the male subject's age calculated by chronological (CA), skeletal (SA), and artifical neural network (ANN) methods

MR Signal Intensity as an Indicator for Skeletal Maturation

In this study, we also measured MR signal intensity as one of the maturity indicators. This followed the work by Tomei E et al. [9] where they noted that as the change of the predominant composition of hematopoietic marrow to fatty marrow, this may form an important indicator of normal skeletal maturation as well as hormonal maturation. This indicator together with body weight, height, as well as TW3 scores can further improve accurate estimation of age determination through ANNs.

Conclusion

This paper proposed a novel model of using ANN in conjunction with TW3 method in chronological age assessment using MRI. This method can provide an assessment reference for skeletal maturity and resolve the insufficiency of current bone maturity assessment methods.

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Compliance with Ethical Standards

Ethics approval was also obtained from the University Research Ethics Committee.

Conflict of Interest The authors declare that they have no conflict of interest.

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