Characteristics of diffusion tensor imaging of central nervous system in children with tourette’s disease

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Abstract

To investigate the characteristics of diffusion tensor imaging (DTI) of the central nervous system in children with Tourette syndrome (TS).

Fifteen children with TS (TS group) and 15 normal children (control group) were studied, and all of them underwent DTI. The apparent diffusion coefficient (ADC) and fractional anisotropy (FA) parameters were calculated using the DTIStudio software. The region of interest was delineated manually. The ADC and FA values of the bilateral caudate nucleus, bilateral globus pallidus, bilateral putamen, bilateral thalamus, and bilateral frontal lobe white matter were measured using the region of interest editor software. The differences of FA values and ADC values between the same brain areas were compared. The associations between ADC, FA values and Yale Global Tic Severity Scale (YGTSS) scores were evaluated by Pearson correlation analyses.

The FA values of left globus pallidus and left thalamus were significantly lower in the TS group than in the control group (P < .05), while the ADC values of the right caudate nucleus and bilateral thalamus were significantly higher in the TS group than in the control group (P < .05). The decrease in FA in the left thalamus significantly correlated with the YGTSS score (r = 0.692; P < .05). No correlation was found between FA and ADC values in other brain regions and the YGTSS score (P > .05).

After the DTI analyses, abnormalities were found in the left globus pallidus, right caudate nucleus, and bilateral thalamus in children with TS. Especially the changes in the left thalamus structure was crucial in the pathophysiological clock of TS.

Abbreviations: ADC = apparent diffusion coefficient, DTI = diffusion tensor imaging, FA = fractional anisotropy, MRI = magnetic resonance imaging, ROI = region of interest, TS = Tourette syndrome, YGTSS = Yale global tic severity scale

Keywords: apparent diffusion coefficient, brain areas, children, diffusion tensor imaging, fractional anisotropy parameters, tourette’s disease

1. Introduction

Tourette syndrome (TS), also known as Gilles de la TS or multiple tics-coprolalia syndrome, is a neuropsychiatric disorder in children and adolescents. The main manifestation is an involuntary, repetitive, rapid, and aimless motor tic in one or more parts, often accompanied by obsessive-compulsive disorder, attention deficit hyperactivity disorder, depression, sleep disorder, and emotional disorder.\textsuperscript{[1]} TS is not a rare disease. The incidence can reach 1% to 2% in school-age children.\textsuperscript{[6]} At present, the pathogenesis of TS is not clear. A large number of studies found that an abnormality in frontal lobe–corpus striatum–thalamic loop of patients with TS was the main pathological basis of TS, but the imaging evidence to support this conclusion is not consistent.\textsuperscript{[3,4]} Diffusion tensor imaging (DTI) can help observe the integrity and connectivity of tissue structure in vivo, display the direction of nerve conduction tracts in the white matter, and perform fine imaging of central nerve fibers.\textsuperscript{[5,6]} At present, a few studies have reported about the use of DTI in examining the structure and function of the central nervous system in children with TS, but their conclusions were controversial. Li et al\textsuperscript{[7]} reported that there were some changes in the DTI parameters of basal ganglia and thalamus. And Lv et al\textsuperscript{[8]} found some microstructural anomalies in caudate nucleus and putamen according to the DTI analysis. In the present study,
DTI was used to analyze whether the microstructures of the caudate nucleus, globus pallidus, putamen, thalamus, and frontal lobe white matter changed in children with TS so as to provide more imaging evidence and support for the pathogenesis of TS.

2. Materials and methods

2.1. Patient cohort

This study was approved by the ethics committee of the hospital. The participants and guardians signed the informed consent. A total of 15 children with TS (TS group) admitted to the hospital from July 2017 to July 2018 were selected as the participants. Another 15 normal children were included as the control group. The inclusion criteria for the TS group:

(1) first-episode TS conformed to the TS diagnostic criteria in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition;
(2) no history of psychiatric drug treatment; and
(3) Wechsler children’s intelligence scale score\(^9\) ≥ 85 points.

Their exclusion criteria:

(1) patients with organic cerebral disease;
(2) patients with other mental disorders;
(3) uncooperative patients with a lot of motions during magnetic resonance imaging (MRI) scanning.

The control group comprised relatives of staff members and primary and secondary school students as healthy volunteers. The inclusion criteria for the control group:

(1) no previous neurological diseases; and
(2) no family history of TS.

Their exclusion criteria:

(1) children with organic cerebral disease;
(2) children with other mental disorders; and
(3) children with contraindications to MRI;
(4) children with poor compliance.

2.2. Methods

2.2.1. MRI scanning. The heads of children in the two groups were scanned using Philips Achieva 1.5T dual-gradient MRI and eight-channel head coil. First, routine MRI scanning was performed, and sagittal T2WI and transverse T1WI were used to detect organic lesions of the brain. Then, DTI scanning was performed with single-shot turbo spin-echo sequence. The scanning parameters were as follows: TR/TE = 3880 ms/93 ms; NSA = 3; FOV = 230 × 230 mm\(^2\); flip angle = 90 degrees; matrix = 192 × 192; layer thickness = 5 mm; layer interval = 0; b = 1000 s/mm\(^2\); and number of diffusion-sensitive gradient directions = 15. The children in the TS group and children aged less than 6 years in the control group were given 10% chloral hydrate before scanning (0.5 mL/kg), and the maximum dose was 10 mL. The children included in this study had first-episode TS and did not take any antipsychotic drugs, which could avoid the effects of drugs on the structure and function of brain. All TS children received MRI scanning within 3 days after their first episode, which could avoid the DTI disparities during different disease courses.

2.2.2. Image processing and analysis. The original DTI image was preprocessed using the FSL software, and then the whole-brain diffusion tensor image package was generated using the DTIFIT software. The apparent diffusion coefficient (ADC) and fractional anisotropy (FA) parameters were calculated using the DTIStudio software, and region of interest (ROI) was delineated manually (shown as Fig. 1). The ADC and FA of ROI in the bilateral caudate nucleus, bilateral globus pallidus, bilateral putamen, bilateral thalamus, and bilateral frontal lobe white matter were measured using the ROIEditor software. All measurements were performed by two experienced radiologists who were unaware of the participants, and the radiologists were also responsible for interpreting the images independently. When disagreements arose, the decision was made through consultation.

2.2.3. Assessment of TS severity. The severity of TS was assessed using the Yale Global Tic Severity Scale (YGTTSS\(^10\)) before the MRI examination. The scale could assess motor and vocal tic and each kind of tic from five aspects: the counts, frequency, intensity, complexity, and interference of tic. Each item was scored 0 to 5 points. The damage caused by tic disorder was assessed independently. The total score of the scale was obtained by adding the scores of all items. The higher the score, the more severe the tic. The YGTTSS score was divided into three grades: mild grade (0–25), moderate grade (26–50) and severe grade (≥50), respectively.

2.3. Statistical analysis

The SPSS 17.0 statistical software was used for data analysis. ADC and FA values conforming to normal distribution were expressed as mean ± standard deviation (\( \bar{x} \pm s \)). The distribution difference of gender and age between TS and control group was evaluated using chi-square test. The independent sample t test was used for comparison of ADC and FA values between the TS
Table 1

Comparison of FA values between the TS and control groups (r ± s).

| Region                        | TS group (n=15) | Control group (n=15) | t value | P value |
|-------------------------------|----------------|----------------------|---------|---------|
| Left caudate nucleus          | 0.2 ± 0.03     | 0.2 ± 0.03           | 0.505   | .617    |
| Right caudate nucleus         | 0.2 ± 0.03     | 0.2 ± 0.03           | 1.599   | .121    |
| Left globus pallidus          | 0.2 ± 0.03     | 0.2 ± 0.03           | 4.422   | <.001   |
| Right globus pallidus         | 0.3 ± 0.03     | 0.3 ± 0.04           | 1.641   | .112    |
| Left putamen                  | 0.2 ± 0.02     | 0.2 ± 0.02           | 0.255   | .801    |
| Right putamen                 | 0.2 ± 0.02     | 0.2 ± 0.02           | 1.779   | .086    |
| Left thalamus                 | 0.3 ± 0.04     | 0.3 ± 0.04           | 4.046   | <.001   |
| Right thalamus                | 0.3 ± 0.03     | 0.3 ± 0.03           | 1.454   | .157    |
| Left frontal lobe white matter| 0.4 ± 0.04     | 0.4 ± 0.05           | 0.290   | .774    |
| Right frontal lobe white matter| 0.4 ± 0.06    | 0.4 ± 0.07           | 0.978   | .336    |

FA = fractional anisotropy, TS = Tourette syndrome.

Table 2

Comparison of FA values among different severity groups (r ± s).

| Region                        | Mild grade (n=5) | Moderate grade (n=5) | Severe grade (n=5) | Control group (n=15) |
|-------------------------------|-----------------|---------------------|--------------------|----------------------|
| Left caudate nucleus          | 0.2 ± 0.03      | 0.2 ± 0.03          | 0.2 ± 0.03         | 0.2 ± 0.03           |
| Right caudate nucleus         | 0.2 ± 0.03      | 0.2 ± 0.03          | 0.2 ± 0.03         | 0.2 ± 0.03           |
| Left globus pallidus          | 0.2 ± 0.03*     | 0.2 ± 0.03*         | 0.2 ± 0.03*        | 0.3 ± 0.04           |
| Right globus pallidus         | 0.3 ± 0.03      | 0.3 ± 0.03          | 0.3 ± 0.03         | 0.3 ± 0.04           |
| Left putamen                  | 0.2 ± 0.02      | 0.2 ± 0.02          | 0.2 ± 0.02         | 0.2 ± 0.02           |
| Right putamen                 | 0.2 ± 0.02      | 0.2 ± 0.02          | 0.2 ± 0.02         | 0.2 ± 0.02           |
| Left thalamus                 | 0.3 ± 0.03*     | 0.3 ± 0.04*         | 0.3 ± 0.04*        | 0.3 ± 0.04           |
| Right thalamus                | 0.3 ± 0.03      | 0.3 ± 0.03          | 0.3 ± 0.03         | 0.3 ± 0.03           |
| Left frontal lobe white matter| 0.4 ± 0.04      | 0.4 ± 0.04          | 0.4 ± 0.04         | 0.4 ± 0.05           |
| Right frontal lobe white matter| 0.4 ± 0.06     | 0.4 ± 0.06          | 0.4 ± 0.06         | 0.4 ± 0.07           |

FA = fractional anisotropy, TS = Tourette syndrome.
*P < .05 (mild grade TS group vs control group).
*P < .05 (moderate grade TS group vs control group).
*P < .05 (severe grade TS group vs control group).

3. Results

3.1. Patient characteristics

The TS group comprised 12 (80.0%) males and 3 (20.0%) females. Their age ranged from 3 to 12 years (median 5.7 years), and the course of the disease was 1 month to 4 years (average 2.18 ± 1.82 years). The control group included 11 (73.3%) males and 4 (26.7%) females. Their age ranged from 3 to 13 years (median 5.9 years). No distribution difference was found in terms of gender and age between TS group and control group (P = .519 for gender and P = .224 for age). In terms of the YGTSS score of the 15 TS children, there were 5 children rated as mild grade (range: 16–22), 5 children rated as moderate grade (range: 32–48) and 5 children rated as severe grade (range: 51–60).

3.2. Comparison of FA values between the TS and control groups

Table 1 shows that the FA values of the left globus pallidus and left thalamus were significantly lower in the TS group than in the control group (P < .05), but no significant difference was found in the FA values of other brain regions between the 2 groups (P > .05).

3.3. Comparison of FA values among different severity groups

As shown in Table 2, compared with the control group, FA values of the left globus pallidus and left thalamus in mild, moderate and severe grade TS groups were all significantly lower than in the control group (P < .05). And there was no significant difference in the FA values of other brain regions among three severity groups and the control group.

3.4. Comparison of ADC values between the TS and control groups

Table 3 shows that the ADC values of the right caudate nucleus and bilateral thalamus were significantly higher in the TS group than in the control group (P < .05), but no significant difference was found in the ADC values of other brain regions between the two groups (P > .05).

3.5. Comparison of ADC values among different severity groups

As shown in Table 4, compared with the control group, ADC values of right caudate nucleus and bilateral thalamus in mild, moderate and severe grade TS groups were all significantly lower than in the control group (P < .05).
than in the control group \((P < .05)\). And no significant difference was found in the ADC values of other brain regions among three severity groups and the control group.

### 3.6. Correlation analysis of FA and ADC with YGTSS score in different brain regions

The median YGTSS score of the TS group was 37, range 16 to 60. Table 5 shows that the decrease of FA in the left thalamus significantly correlated with YGTSS score \((r=0.692; P < .05)\). No correlations of FA and ADC values with YGTSS score were observed in other brain regions \((P > .05)\).

#### 4. Discussion

TS is a syndrome and behavioral disorder characterized by movement and language disorders and convulsions. It has many serious adverse effects on children, such as mental disorders, obsessive-compulsive disorders, and so on. At present, the etiology and pathogenesis of TS are not clear. However, a study showed that TS was related to excessive dopaminergic activity in the basal ganglia striatum, super-sensitivity of the dopamine receptor, heredity, mental trauma, pathogenic bacterial infection, and so on.\(^{[2]}\) Makki et al\(^{[11]}\) found abnormalities in the cortical–corpus striatum–thalamus–cortical structure of patients with TS. Singer et al\(^{[12]}\) and Bihan et al\(^{[13]}\) found abnormalities in the basal ganglia and thalamus structure and function of patients with TS, respectively. They believed that it was the pathological basis of TS.

DTI is used to apply diffusion-sensitive gradient pulses to multiple directions on conventional MRI sequences, calculate the eigenvector values of the main direction of diffusion in every voxel of the brain, and then obtain the relevant parameters reflecting the diffusion characteristics of brain white matter structure after software processing. The FA value indicates the degree of diffusion anisotropy of brain tissue and reflects the changes in brain tissue microstructure under pathological conditions. Studies have shown a positive correlation of FA value of the white matter with myelin sheath integrity, fiber compactness, and parallelism.\(^{[14,15]}\) Label et al\(^{[16]}\) suggested that the changes in ADC and FA values in the thalamus were consistent with the maturity of the myelin sheath of the thalamus. The aforementioned findings indicated that DTI could better reflect the changes in smile structure in the brain. In order to provide more imaging evidence for the pathogenesis of children TS, in the present study, we performed DTI analyses to investigate whether the microstructures of the multiple brain areas changed in children with TS.

Nowadays, the main therapeutic methods for TS includes behavior intervention, drugs, neurosurgical treatment, transcranial magnetic stimulation, etc. The main mechanism of TS drugs is to regulate dopamine metabolism by blocking

### Table 3

Comparison of ADC values between the TS and control groups \((r=±)\).

| Region                   | TS group \((n=15)\) | Control group \((n=15)\) | \(t\) value | \(P\) value |
|--------------------------|---------------------|--------------------------|-------------|-------------|
| Left caudate nucleus     | 0.8±0.05            | 0.7±0.06                 | 1.303       | .203        |
| Right caudate nucleus    | 0.8±0.05            | 0.7±0.05                 | 3.849       | .001        |
| Left globus pallidus     | 0.7±0.04            | 0.7±0.03                 | 0.965       | .343        |
| Right globus pallidus    | 0.8±0.05            | 0.8±0.04                 | 0.655       | .517        |
| Left putamen             | 0.8±0.03            | 0.8±0.02                 | 0.367       | .716        |
| Right putamen            | 0.8±0.04            | 0.8±0.04                 | 0.426       | .673        |
| Left thalamus            | 0.8±0.03            | 0.7±0.03                 | 4.379       | <.001       |
| Right thalamus           | 0.8±0.03            | 0.7±0.02                 | 6.721       | <.001       |
| Left frontal lobe white matter | 0.8±0.03   | 0.9±0.03                 | 0.638       | .528        |
| Right frontal lobe white matter | 0.8±0.05 | 0.8±0.03                 | 0.694       | .493        |

ADC = apparent diffusion coefficient, TS = Tourette syndrome.

### Table 4

Comparison of ADC values among different severity groups \((r=±)\).

| Region                   | Mild grade \((n=5)\) | Moderate grade \((n=5)\) | Severe grade \((n=5)\) | Control group \((n=15)\) |
|--------------------------|---------------------|--------------------------|------------------------|--------------------------|
| Left caudate nucleus     | 0.8±0.05            | 0.8±0.05                 | 0.8±0.05               | 0.7±0.06                 |
| Right caudate nucleus    | 0.8±0.05            | 0.8±0.05*                | 0.8±0.05*              | 0.7±0.05                 |
| Left globus pallidus     | 0.7±0.04            | 0.7±0.04                 | 0.7±0.04               | 0.7±0.03                 |
| Right globus pallidus    | 0.8±0.05            | 0.8±0.05                | 0.8±0.05               | 0.8±0.04                 |
| Left putamen             | 0.8±0.03            | 0.8±0.03                 | 0.8±0.03               | 0.8±0.02                 |
| Right putamen            | 0.8±0.04            | 0.8±0.04                 | 0.8±0.04               | 0.8±0.04                 |
| Left thalamus            | 0.8±0.03            | 0.8±0.03*                | 0.8±0.03*              | 0.7±0.03                 |
| Right thalamus           | 0.8±0.03            | 0.8±0.03*                | 0.8±0.03*              | 0.7±0.02                 |
| Left frontal lobe white matter | 0.8±0.03         | 0.8±0.03                 | 0.8±0.03               | 0.9±0.03                 |
| Right frontal lobe white matter | 0.8±0.04         | 0.8±0.05                 | 0.8±0.05               | 0.8±0.03                 |

ADC = apparent diffusion coefficient, TS = Tourette syndrome.
* \(P < .05\) (mild grade TS group vs control group).
* \(P < .05\) (moderate grade TS group vs control group).
* * \(P < .05\) (severe grade TS group vs control group).
postsynaptic dopamine receptors (especially D2 receptors).\textsuperscript{[17]} In deep brain stimulation (DBS), the microstructures of brain are electrically inhibited by implanted electrodes through depolarization or release of inhibitory neurotransmitters.\textsuperscript{[18]} These treatments inhibited the symptoms of TS by regulating and correcting the dysfunction of the basal nucleus and related circuits. Previous studies verified that there were some changes in involved brain areas after treatment by MRI examinations. For example, Zhao et al.\textsuperscript{[19]} reported that TS drugs could correct some changes of the involved brain area. Debes et al.\textsuperscript{[20]} performed DTI analyses and found that after treatment, the parallel diffusion rate of TS patients in convulsive remission group did not decrease significantly, which was close to the normal development of the brain. However, all the TS children included in this study developed the disease for the first time and didn’t receive any treatment when we performed the MRI examination, which could avoid the impact of treatment on brain microstructures and functions, in order to reflect the underlying pathological changes of the disease accurately.

Autopsy studies showed that there were abnormal changes in the cortical–corpus striatum–thalamus–cortical loop in patients with TS.\textsuperscript{[21]} Lennington et al.\textsuperscript{[22]} also obtained the whole genome transcripts of caudate nucleus and putamen of 9 TS subjects and 9 matched normal individuals by RNA sequencing. Finally, 309 down-regulated genes and 822 up-regulated genes were found in caudate nucleus and putamen of TS patients. The above evidence indicated that the abnormal changes of cortical–corpus striatum–thalamus–cortical loop were probably the main cause of TS symptoms. Lv et al.\textsuperscript{[8]} found that the FA value of right caudate nucleus and putamen in children with TS was lower than that in the control group, and the ADC value in the right caudate nucleus was higher than that in the control group. Li et al.\textsuperscript{[7]} found that the FA values of left globus pallidus and bilateral thalamus in children with TS were lower than those in the control group, while the ADC values of bilateral caudate nucleus, bilateral putamen and bilateral thalamus were increased. In our study, the results showed that compared with normal children, the FA values of the left globus pallidus and left thalamus decreased significantly, while the ADC values of the right caudate nucleus and bilateral thalamus increased significantly in children with TS compared with normal children (\(P<0.05\)). This was consistent with the previous findings, suggesting minor structural changes in these regions. The decrease in FA value suggested the decrease in the number of neurons, the bad formation of the myelin sheath, or the fracture of the protein structure. However, the specific site of brain areas reported in each study is slightly different, which may be related to the onset time and severity of TS patients. The Debes et al.\textsuperscript{[20]} study found that the average diffusion coefficient changed with time in the right caudate nucleus, right thalamus and right frontal lobe between TS patients and healthy individuals. Parallel and vertical diffusion coefficients increased over time in healthy controls, but decreased in TS patients. Compared with patients with persistent convulsions, the parallel diffusion rate of patients with convulsions in remission stage did not decrease significantly. This showed that the brain development of the convulsion remission group was closer to the normal brain development than the persistent convolution group. It confirmed that the cortical–corpus striatum–thalamus–cortical loop was involved in the pathophysiological process of TS.

Wen et al.\textsuperscript{[23]} showed that the FA of the deep white matter (DWM) bundle and the superficial nerve fiber (SWM) in the cortical–corpus striatum–thalamus–cortical loop decreased and the radial diffusion (RD) rate increased in children with TS. The lower FA value and higher RD value in the white matter region were related to severe convulsions, but not to the duration of convulsions. The results of our study also showed a significant correlation between the decrease in FA in the left thalamus and YGTSS score, which was consistent with the findings of Li et al.\textsuperscript{[7]} indicating that the structural abnormality of thalamus was related to the severity of tic symptoms in patients with TS. The structural damage of the thalamus was more serious with the aggravation of TS, which also suggested that the structural abnormalities of the thalamus might play a more prominent role in TS. Another study\textsuperscript{[24]} showed that the axial diffusion (AD) coefficient and median diffusion (MD) coefficient of anterior thalamic radiation, corticospinal tract, inferior longitudinal frontal–occipital tract and uncinate tract in TS children were significantly increased, while the AD and MD coefficients in the right cingulate gyrus were significantly higher than those in the anterior thalamus. The decrease of white matter volume (WMV) of right frontal lobe was negatively correlated with the YGTSS, while the increase of AD and MD coefficients was positively correlated with the severity and duration of convulsions, respectively. It suggested that the microstructural changes in white matter in TS children were not only limited to the cortical–corpus striatum–thalamus–cortical loop, but also affected the primary motor and sensory centers, commissural fibers and communicating fibers.

The present study still has some limitations. First, the number of participants included in this study was small. Second, the selected brain structure could not completely cover the cortical–corpus striatum–thalamus–cortical loop, and therefore it could not fully reflect the abnormal changes in the central nervous system in patients with TS. Third, we only perform DTI after the first-episode and didn’t monitor the DTI dynamic changes during the whole TS disease courses. Forth, most of TS children in our study didn’t choose to receive treatment in our hospital after the diagnosis. So, it’s a pity that we couldn’t investigate the impact of

\begin{table}[h]
\centering
\caption{Correlation analysis of FA and ADC values with YGTSS score in different brain regions.}
\label{tab:corr_analysis}
\begin{tabular}{|c|c|c|c|}
\hline
Index & Region & \(R\) value & \(P\) value \\
\hline
FA & Left caudate nucleus & 0.158 & 0.725 \\
& Right caudate nucleus & 0.236 & 0.685 \\
& Left globus pallidus & 0.324 & 0.423 \\
& Right globus pallidus & 0.395 & 0.347 \\
& Left putamen & 0.136 & 0.562 \\
& Right putamen & 0.465 & 0.905 \\
& Left thalamus & 0.692 & 0.006 \\
& Right thalamus & 0.262 & 0.352 \\
& Left frontal lobe white matter & 0.156 & 0.627 \\
& Right frontal lobe white matter & 0.169 & 0.592 \\
\hline
ADC & Left caudate nucleus & 0.126 & 0.720 \\
& Right caudate nucleus & 0.402 & 0.156 \\
& Left globus pallidus & 0.263 & 0.253 \\
& Right globus pallidus & 0.302 & 0.201 \\
& Left putamen & 0.352 & 0.196 \\
& Right putamen & 0.162 & 0.402 \\
& Left thalamus & 0.375 & 0.168 \\
& Right thalamus & 0.325 & 0.131 \\
& Left frontal lobe white matter & 0.263 & 0.195 \\
& Right frontal lobe white matter & 0.234 & 0.202 \\
\hline
\end{tabular}
\end{table}
treatment on DTI parameters of TS children. In the further studies, sample size, enlarged regions of brain structures, serial DTI monitoring, detailed treatment information and long-term follow-up data were needed to explore the pathological mechanism and progression of TS more carefully and comprehensively.

In conclusion, according to the DTI analyses, abnormalities in the cortical–corpus striatum–thalamus–cortical loop were noted in children with TS, especially in the left globus pallidus, right caudate nucleus, and bilateral thalamus. The decrease of FA in the left thalamus was correlated with YGTSS score. Of courses, more high-quality studies with larger sample size are still needed in the future.

**Author contributions**

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