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NASOPHARYNGEAL CARCINOMA TREATMENT EFFECT ON THE COGNITIVE FUNCTION OF THE ATTENTION NETWORK: AN EXAMPLE FROM THE COASTAL CITY OF HANGZHOU (CHINA)

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ABSTRACT

Objective: *This study mainly to explore the effect of comprehensive treatment in Hangzhou (China) on cognitive function of attention network in patients with nasopharyngeal carcinoma.*

Methods*: Patients with locally advanced nasopharyngeal carcinoma who were initially diagnosed as the pre-treatment group were collected as the pre-treatment group in Hangzhou (China), and the patients who were reexamined within more than half a year after treatment were the post-treatment group. All patients received behavioral tests of attention network cognitive function. The processing efficiency of three sub-networks (executive control network, alertness system and orientation network) of cognitive function of patients' attention network was compared horizontally.*

Results*: After treatment, the score and ratio of processing efficiency of executive control network in the group after treatment were significantly lower than those in the group before treatment, while the scores and score ratios of alertness system and oriented network processing efficiency did not change significantly. Conclusion: After treatment, the processing efficiency of the alert system and orientation network of NPC patients did not change significantly in Hangzhou (China), but the processing efficiency of the executive control network was improved.*

Conclusion*: We determined that the pneumococcal vaccine, which is mainly administered in family medicine centers, has a positive effect on the course of COVID-19, and adult immunization should be given importance in every period.*

Keywords: *Nasopharyngeal Carcinoma, Cognitive Function, Executive Control Network, Alertness System, Hangzhou (China).*

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Introduction

Nasopharyngeal Carcinoma (Nasopharyngeal Carcinoma) is one of the common malignant tumors in Hangzhou (China) and Southeast Asia. The incidence rate can reach 3/100,000. The annual incidence rate in high-incidence areas can reach 15-20/100,000 women and 20-30/100,000 men(1). Its incidence has obvious regional clustering and ethnic susceptibility. Nasopharyngeal carcinoma has biological characteristics, such as strong aggressiveness, aggressiveness, and expansibility, and easily invades adjacent tissues and organs, which poses a huge threat to the patient's health and life. According to statistics, more than 80% of nasopharyngeal cancer patients worldwide are located in China. At the first diagnosis, most patients with nasopharyngeal carcinoma were locally advanced. Due to the special location of the tumor in NPC patients, it is very close to the hippocampus, brainstem, cerebral arteries, and the superior and middle temporal gyrus regions, making surgical resection very difficult(2). At the same time, the tumor is more sensitive to radiation, and the primary tumor and cervical lymph nodes are easily included in the irradiation range. Therefore, radiotherapy is the most basic and main treatment for NPC(3). Radiotherapy is the first choice and the main treatment for nasopharyngeal carcinoma. With the application of intensity-modulated radiotherapy and the effectiveness of concurrent radiotherapy and chemotherapy, most patients with nasopharyngeal carcinoma can survive long-term after treatment, and even cure, although currently locally advanced nasopharyngeal carcinoma The 5-year survival rate of the patient has reached 79.6%, but the side effects of the patient after radiotherapy cannot be ignored, such as radiation injury and cognitive impairment. The impairment of cognitive function after radiotherapy will cause the patients' memory, attention and executive function to decline, which will seriously affect the patient's quality of life. Although there have been reports of early or late cognitive impairment in a small number of patients with nasopharyngeal carcinoma after radiotherapy, the vast majority of research subjects are treated with two-dimensional radiotherapy technology, and most patients have radiation brain injury, and the application of intensity-modulated radiotherapy The radiation dose to the temporal lobe is significantly reduced, which can reduce or alleviate the incidence of cognitive impairment in patients.

However, NPC radiotherapy will inevitably irradiate normal brain tissues, which will cause radiation brain damage and damage brain function. At present, the mechanism of brain damage caused by radiotherapy is unclear. With the improvement of the survival rate of patients in Hangzhou (China) with nasopharyngeal carcinoma and the prolongation of their survival period, the efficacy of its comprehensive treatment and its impact on brain structure, cognitive function and patients' long-term quality of life have also been paid more and more attention. The current clinically recognized standard treatments for nasopharyngeal carcinoma are intensity-modulated radiotherapy and concurrent chemotherapy. After a lot of clinical practice, the regional and local control rate, recurrence rate and overall survival rate of nasopharyngeal carcinoma have been significantly improved. For patients with nasopharyngeal carcinoma, brain damage usually occurs after radiotherapy, which is a common complication. With the increasing use of radiotherapy, the complications of brain injury have also received clinical attention. After research, many scholars have found that receiving ionizing radiation will damage the cognitive function of patients, which has a greater impact on the quality of life of patients. Radiation therapy for nasopharyngeal cancer patients can cause their cognitive function to decline. The temporal lobe is not only related to language, vision and pain, but the amygdala and hippocampus contained in it are also related to memory and learning functions(4). Because the temporal lobe is located close to the bones of the skull, when a patient receives radiotherapy, the temporal lobe is usually irradiated, so the temporal lobe may be the main factor leading to impaired cognitive function of the patient. Some scholars have found through research that when the temporal lobe mean is higher than 36Gy or V60 is higher than 10%, the cognitive function will decline more, which indicates that the degree of cognitive function impairment after radiotherapy is related to the temporal lobe exposure.

Countries around the world are paying more and more attention to the brain damage of NPC patients after radiotherapy. In the early days, in the era of two-dimensional radiotherapy, radiotherapy of NPC often could not avoid part of the brain tissue, especially the middle and lower parts of the bilateral temporal lobes, and radioactive temporal lobe necrosis often occurred. With the application of intensity-modulated radiotherapy technology, the radiation dose of brain tissue near the lesion of NPC patients has been effectively controlled, and the radiation necrosis of the temporal lobe has been significantly improved. For example, none of the 74 cases of intensity-modulated radiotherapy NPC patients reported by Wolden et al. developed temporal lobe necrosis(5)). Similarly, no temporal lobe necrosis was found in the 171 cases of NPC patients reported by Lee et al.(6). Sheng-Fa Su et al. investigated 870 NPC patients undergoing IMRT and found that only 40 cases (4.6%) had significant temporal lobe radiation necrosis(7). These studies show that there is less and less obvious radiation necrosis in normal brain tissue. Does this indicate that under the new intensity-modulated radiotherapy technology, we can reduce the importance of the side effects of radiotherapy? the answer is negative. In the process of re-examination of long-term surviving patients after NPC radiotherapy, we found that although conventional imaging data did not suggest obvious radiation necrosis, almost everyone would actively report the existence of varying degrees of impairment of cognitive functions such as memory and attention. Hsiao et al. tested and analyzed the cognitive function of 30 patients with NPC intensity-modulated radiotherapy a day before and at least

12 months after radiotherapy, and found that 23 of them showed significant changes(8). Yan-Lin Mo et al. found that the anxiety, depression, and sleep quality of NPC patients two months after receiving intensity-modulated radiotherapy were significantly different from those before radiotherapy(9). L. McDowell et al. investigated NPC patients more than 4 years after intensity-modulated radiotherapy and found that many patients had cognitive impairment, including decreased behavioral inhibition and executive dysfunction(10). The research team of Tang Yamei of Sun Yat-sen Memorial Hospital of Sun Yat-sen University in Guangzhou also found that NPC patients suffer from cognitive impairment after radiotherapy, and these injuries are closely related to the number of microhemorrhages in the temporal lobe(11). Fan Qiang of the Affiliated Hospital of Jiangnan University used IMRT to protect the hippocampus and found that reducing the hippocampal exposure dose can effectively alleviate the impairment of cognitive function(12).

In recent years, new imaging research techniques have also been continuously applied to the study of brain function after NPC radiotherapy. Qiongmin Ma et al. used functional magnetic resonance (fMRI) imaging technology to analyze the functional connection of 35 NPC patients and found that the functional connection of NPC patients after radiotherapy was damaged, especially the functional connection related to attention function(13). Sharon Chia-Ju Chen et al. performed fMRI imaging on 20 NPC patients at three time points before radiotherapy, one month after radiotherapy, and four months after radiotherapy, and compared with healthy controls, and analyzed the difference between different brain regions and hippocampus. Changes in the functional connection of the hippocampus have been found to affect the function of the hippocampus in a short period of time after radiotherapy, even a small dose of radiation (2-14Gy)(14). Jiabao Lin et al. used surface-based morphometry (SBM) to analyze and compare patients before radiotherapy, 1-6 months after radiotherapy, and 7-18 months after radiotherapy. There was no conventional anatomical structure. In the case of differences, it is found that the brain damage caused by radiotherapy is mainly manifested in the increase in the thickness of the cerebral cortex of the patient after half a year of radiotherapy(15).

These studies have shown that: although, with the advancement of radiotherapy technology, the obvious radiation necrosis of the temporal lobe has been significantly improved, but the normal brain tissue near the nasopharyngeal tumor will still be irradiated and radiation damage will occur. This damage has Concealment, can not be detected by conventional imaging methods, usually externally manifested as behavioral brain function abnormalities.

At the same time, the clinical dosimetry characteristics of NPC radiotherapy indicate that the normal brain tissue that is irradiated is mainly concentrated in the temporal lobe and nearby brain areas, which is related to the specificity of the NPC tumor location mentioned earlier. When nasopharyngeal cancer patients receive radiotherapy, because the parotid gland is close to the parapharyngeal space, and 90% of the patients are accompanied by lymph node metastasis, the patient's parotid gland is usually located in a high-dose area, which causes acute radiation damage to the parotid gland and subsequent dysfunction, resulting in The patient has dry mouth, dysphagia, indigestion, dental caries, etc., which seriously affects the patient's quality of life. Although the patient's parotid gland function will gradually improve over time after the end of radiotherapy, it still cannot return to the baseline level. 41% of head and neck cancer patients will still have moderate or severe dry mouth 5 years after radiotherapy. As patients with nasopharyngeal carcinoma can easily damage the parotid glands after radiotherapy, it is currently recommended to combine nasopharyngeal carcinoma with radiotherapy and chemotherapy for comprehensive treatment. Therefore, it is necessary to understand the basic functional status of the parotid glands before radiotherapy and chemotherapy. Patients with nasopharyngeal carcinoma, and evaluate the effects of radiotherapy and chemotherapy on the nose. The influence of parotid gland function on patients with pharyngeal carcinoma has positive clinical significance and value for the design of radiotherapy and chemotherapy, the protection of parotid gland function and the prediction of parotid gland dysfunction after treatment.

Combining the current status of NPC radiotherapy and the situation of patients after radiotherapy, we infer that the current intensity-modulated radiotherapy method of NPC will still inevitably cause damage to normal brain tissue, especially the temporal lobe and nearby areas, which will induce attention and memory. Such as brain function abnormalities, but in clinical this kind of damage can not be detected by conventional imaging methods, lack of effective diagnostic criteria.

In the previous literature research, we found that an important assessment method for brain damage caused by radiotherapy in NPC patients is scale or behavioral testing. Among them, the more commonly used ones are: Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), Wechsler Adult Intelligence Scale (WAIS), etc. These scales can specifically evaluate and analyze cognitive function in one or several aspects.

In the psychology category, the attention network is composed of three sub-networks: alert system, orientation network and executive control network(16). The attention network alert system reflects the ability to maintain alertness and the body's ability to respond to prompt information; the attention function toward the network is responsible for the selection of information; the executive control network corresponds to the ability to resolve conflict task(17-19).

In this paper, we intend to use the attention network test (ANT) paradigm (specific experimental procedures and experimental stimuli refer to the research content part) to test the patients' attention network cognitive function. The task of ANT is simple, with a total time of about 20 minutes, suitable for a wide range of ages, and can effectively evaluate the processing efficiency of the three sub-networks of the attention network (the alert network, the orientation network and the execution control network). The cognitive functions of these three sub-networks correspond to different brain tissue structures: the alerting network is associated with the thalamus, frontal lobe, and parietal cortex; the orientation network is associated with the superior temporal gyrus and the temporal-parietal joint area Associated; executive control network (executive control network) is mainly associated with the frontal cortex. ANT's task test can effectively detect differences in the processing efficiency of attention network sub-networks related to specific cognitive function abnormalities.

Because radiotherapy of NPC will inevitably irradiate a certain dose of brain tissue around the tumor (especially the temporal lobe), in the ANT test of this paper, we expect to find that the patient will be similar to the temporal lobe and nearby brain areas after radiotherapy. The corresponding attention network cognitive function may change.

Research Object

The patients with nasopharyngeal carcinoma who were newly diagnosed and not yet treated at Hangzhou (China) Cancer Hospital were collected as the pre-treatment group, and the patients who were re-examined within three years after treatment were collected as the post-treatment group for a horizontal comparison study. Selected cases: There are 16 people in the control group, including 11 males and 5 females, with an average age of 40.00 ± 13.00 (18.56-59.88), and an average education time of 11.44 ± 4.72 years. The education level ranges from illiterate to university graduation; the experimental group has a total of There are 17 people, including 10 males and 7 females, with an average age of 46.52 ± 12.60 (19.50-65.50) and an average education time of 10.53 ± 4.73 years. The education level ranges from illiterate to university graduation.

Case inclusion and exclusion criteria

All patients were pathologically confirmed to be stage III or IVa nasopharyngeal carcinoma (refer to Nasopharyngeal Carcinoma AJCC-UICC 8th edition for staging standards); all patients were treated with concurrent radiotherapy and chemotherapy, chemotherapy using platinum-containing drugs, 2-3 cycles, Intensity-modulated radiation therapy was used for radiotherapy. The radiation dose of PGTVnx in the expanded area of the nasopharyngeal primary lesion was 68-70.8 Gy, the dose of PGTVnd in the expanded area of lymph nodes was 66.3-69.1 Gy, and the dose of PTV1 in the expanded area of high-risk clinical target area was 59.3. -64.8 Gy, the PTV2 dose of the low-risk clinical target area expansion prevention exposure area is 52.1-54.8 Gy, the number of radiotherapy is 30-32 times, 1 time/day, 5 times/week. According to the patient's condition and chemotherapy contraindications, patients in the experimental group received induction chemotherapy + concurrent chemotherapy, 4 patients received induction + concurrent + adjuvant chemotherapy, and 7 patients received concurrent chemotherapy + adjuvant chemotherapy. Induction chemotherapy is a two-cycle TP regimen (paclitaxel 135mg/m2, d1 + nedaplatin or cisplatin 100mg/m2, d2), while chemotherapy is a single-agent platinum (nedaplatin or cisplatin 40mg/m2/W, 5 -6W) Chemotherapy, adjuvant chemotherapy is only suitable for patients with obvious residual tumor imaging. It is a 2-3 cycle TP regimen. Symptomatic treatment will be given during chemotherapy, such as liver protection, stomach protection, antiemetic and immune support. All included patients had no mental or neurological diseases and history of diseases, no cerebrovascular diseases or white matter disease, no intracranial invasion, no primary intracranial tumors or metastases, and no serious systemic diseases (such as hypertension, diabetes, etc.), conventional MRI scan of brain tissue showed no abnormalities. Design a general data survey scale, learn the use of RBMT-II, BADS measurement toolbox and communication skills with patients, explain and communicate with patients who meet the inclusion criteria, explain the purpose, time, content and significance of the study, and after informed consent , The patient's informed consent was signed and approved by the hospital ethics committee. Three to four days after the patients were admitted to the hospital, they were screened by MoCA and incorporated into the group. The cut-off value was 26. If the critical value is lower than the critical value, it is considered to be cognitive dysfunction. If the subject has less than 12 years of education, the MoCA score is <27. This is considered cognitive dysfunction and can be included in the group. The second version of the behavioral memory test (RBMT-II) and the behavioral assessment test toolbox (BADS) were performed on the enrolled patients for executive deficit syndrome.

This study complies with the ethical standards established by the committee responsible for human trials, and the informed consent of patients and family members has been obtained.

Pay Attention to the Network Cognitive Function Test

Note that the alarm network is responsible for acquiring and maintaining a highly sensitive state for the upcoming stimulus, such as switching from a no-sleep state to a state ready to handle emergency situations. For the measurement of attentional alertness, classical alertness experimental tasks are mainly used. This task will prompt a reminder before the stimulus target appears, indicating that the target stimulus is coming, and then ask the subject to respond quickly and accurately to the target stimulus. Attention executive control network reflects some core aspects in the broader concept of "executive function", such as suppressing attention, resolving conflict, and resisting interference. Previous studies on individual differences in attention executive control networks lacked attention and did not discuss the neural processing mechanisms of the brain. In order to have a deeper understanding of the brain neural mechanisms behind the individual differences in attention execution control network behavior, including the interaction on large-scale brain networks, this article uses a variety of data analysis methods to design three studies from different perspectives to discuss attention together Individual differences in the processing mechanism of the executive control network in the brain.

Record the basic information of the patient's age, gender, and education level, and perform an attention network test (ANT) on all patients. The cognitive assessment system (DN-CAS) is used to assess the cognitive function of patients. DN-CAS has been successfully applied to cognitive assessment models for children and adults. Based on Luria's cognitive theory, a standardized PASS test method was compiled. Since 2004, my country has carried out and completed the Chinese culture study of DN-CAS, and related studies have confirmed that the Chinese culture version of DN-CAS has good reliability and validity. DN-CAS includes 4 sub-scales for planning, simultaneous production, attention and follow-up production. Each sub-scale contains three sub-test types, for a total of 12 sub-tests. Finally, convert the raw scores of each subtest into standard scale scores.

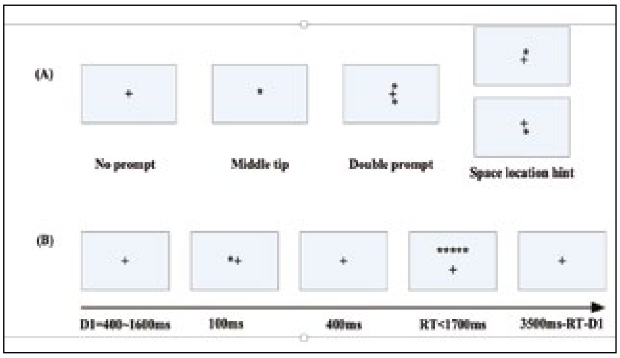

Figure 1: ANT experimental paradigm.
Note: (A) 4 types of prompts (including no prompt, intermediate prompt, double prompt, and spatial position prompt); (B) single test In the second process, RT stands for reaction time.

The ANT behavioral test is written into a computer program, and the time is strictly controlled. The stimulation program is realized through the psychological stimulation presentation software E-prime 1.2(20). The ANT task consists of a set of exercises with 24 trials and three sets of formal tests. In the practice task, there is feedback on the accuracy and reaction time after each trial, and there is no feedback on the formal test. Each set of formal tests consists of 96 trials, including two repetitions in 48 different situations (4 types of prompts × two directions of left and right × two positions of stimulus × 3 conflicting conditions). The total time of the ANT test is approximately 20 minutes. The experimental paradigm of ANT is shown in Figure 1.

Statistical Processing

Take all the correct reaction times (reaction time, RT), and average the reaction times under different conditions. Calculate the processing efficiency scores of the three sub-networks of the attention network (executive control network, alert system and orientation network) according to the following formulas:

Processing efficiency score of the alert system = RT no prompt-RT double prompt

Processing efficiency score towards the network = RT intermediate prompt-RT spatial position prompt

Execution control network processing efficiency score = RT conflict-RT consistent

Note: RT in the formula represents the average response time under the corresponding type of task.

Perform univariate analysis on the processing efficiency scores of the three networks, and set $P < 0.05$ to indicate that the differences are statistically significant.

Considering that the average reaction time of different individuals may have a certain impact on the processing efficiency score of the attention network, we further process the processing efficiency scores of each network, and divide the score of each network efficiency by the reaction time under the corresponding conditions, Obtain the processing efficiency score ratio corresponding to each network. The calculation formula is as follows(21):

The processing efficiency score ratio of the alert system

= (RT silent-RT double prompt)/RT silent + RT double prompt)

Processing efficiency score ratio towards the network

= (RT middle prompt-RT space position prompt)/(RT middle prompt + RT space position prompt)

Execution control network processing efficiency score ratio

= (RT conflict-RT agreement)/(RT conflict + RT agreement)

Note: RT in the formula represents the average response time under the corresponding type of task.

Similarly, the processing efficiency score ratio of these three networks was subjected to a statistical analysis (univariate analysis), setting $P < 0.05$ to indicate that the difference was statistically significant. The statistical analysis was performed in the software SPSS (version 16.0, SPSS Inc).

Results

Two independent sample t-tests were performed on the age, gender and education level of the two groups of patients, and it was found that there was no statistical difference between the two groups of patients (age: $t = -1.913$, $df = 31$, $P = 0.065$; Gender: $t = -0.577$, $df = 31$, $P = 0.568$; education level: $t = 0.552$, $df = 31$, $P = 0.585$). Considering that the patient's age, gender, and education level may affect the test results, the author still uses the patient's age, gender, and education level as covariates when statistically analyzing the processing efficiency of the sub-network.

Using the patient's age, gender, and education level as covariates, univariate analysis was performed on the average response time of all trials of the two groups of patients. It was found that the difference between the average response time of the two groups of patients was not statistically significant ($F = 0.501$, $df = 1$, $P = 0.485$). The average response time of the two groups of patients under different types of tasks is shown in Table 1.

Task type		Response time before treatment (MS)	Response time after treatment (MS)
Prompt type	No prompt	629.70 ± 69.76	705.63 ± 108.26
	Middle tip	604.13 ± 72.04	675.32 ± 107.54
	Double prompt	592.86 ± 74.54	655.41 ± 106.47
	Space location hint	562.38 ± 64.83	618.80 ± 107.06
Conflict type	Consistent	555.15 ± 63.72	623.47 ± 98.87
	Conflict	663.72 ± 75.35	716.52 ± 113.12
	Neutral	573.46 ± 70.71	651.64 ± 108.64
Overall average		597.23 ± 69.14	663.69 ± 105.92

Table 1: Average reaction time of the pre-treatment group and post-treatment group under different types of tasks.

Note: The average response time of the pre-treatment group and the post-treatment group under different types of tasks, the unit is ms.

In the task state, the neural activity of each brain area is separated from each other in time. This asynchronous difference in time indicates that there may be functional differences in these brain regions. Therefore, we use the time series analysis method to extract the time course difference of the brain-related brain area activity between the high group and the low group of the attention execution control network, which will explain the attention execution control of the human brain. The neural mechanism of individual differences in the process. First, we take the repetition time (TR) as the unit to extract the raw blood oxygen level of each voxel (Voxel) in the smooth whole brain echo imaging image (EPI) in each region of interest (ROI). Signal time series. Then, a finite impulse response (FIR) model is used to convolutionally respond to the time process corresponding to the attention execution control, the time unit is 2 seconds, and the time window is 16 seconds. These steps are realized by using MarsBaR software. Finally, we perform a hypothesis test on the parameters of the strongest amplitude (amplitude/height), peak-to-peak time (peak-to-peak) and full width at half maximum of the extracted time-series signal. Estimate the differences in the response intensity (amplitude), response time (latency period) and duration (duration) of neural activities related to executive control between individuals.

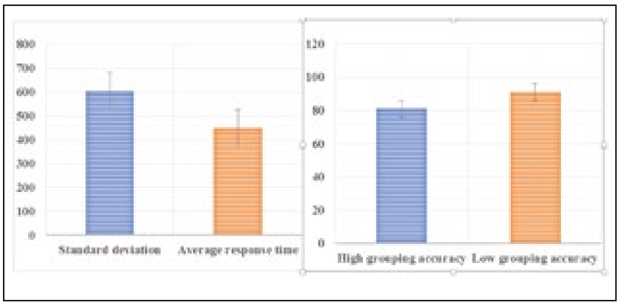

Figure 2: Behavioral results of executive function network of attention network test in task mode.

Before analyzing the behavioral data of the executive function network of the attention network test in the task state, wrong attempts and extreme values were eliminated (3.75% of the total attempts). The result of the reaction is shown in Figure 2. The average response time of the inconsistency test is 601 milliseconds, and the standard deviation is 100 milliseconds; the average response time of the consistency test is 521 ms, and the standard deviation is 98 ms. The reaction time of the inconsistent test is significantly slower than the same test. In the response time, $t(97)=-5.91$, $p<0.001$. In terms of correctness, the average correctness rate of unanimous trials is 0.98, which is significantly higher than 0.956 of inconsistent trials, $t(97)=-5.86$, $p<0.001$. The results of behavioral data reflect the typical executive function effect, that is, the response time of the consistent test is significantly faster than the response time of the inconsistent test, and the accuracy of the former is significantly higher than that of the latter. In addition, the efficiency of the attention execution control network is calculated. From the distribution of the efficiency value of each participant's attention execution control network in Figure 2, we can see that there are many individual differences in the randomly selected samples in this study. According to the median division method, all subjects were divided into high and low categories.

The attention function of patients with nasal cancer may have an important influence on emotional cognitive activities. Experimental studies have confirmed that transfer, maintenance, concentrated execution and coding can explain 69% of variables in emotional cognition. Clinical studies also show that attention deficits in patients with nasal cancer are related to facial emotional cognitive deficits. This study shows that the accuracy of ANT patients is positively correlated with the total score of CFET, while the response time is negatively correlated with the total score of CFET, which indicates that the overall attention function of patients with nasal cancer is related to the total score of CFET. The overall level of emotional cognition. Attention function, as a basic cognitive function, may participate in the basic process of emotional cognition, but has little effect on the emotional cognition of specific faces. The efficiency of the patient alert network is related to the cognitive scores of disgusting emotional faces. Whether this shows that the two have a common pathophysiological basis remains to be further studied.

The targeting efficiency of ANT in the patient group is lower than that in the control group, which indicates that the information selection process is impaired in selecting external stimuli. In addition, the response accuracy of the patient group was not statistically different from that of the control group, but the response time was longer than that of the control group, indicating that the patient made correct judgments and response operations to the target stimulus during ANT. There are difficulties in choosing the direction of attention. This impairment of directional function may indicate dysfunction of the posterior parietal cortex. Using the patient’s age, gender, and education level as covariates, the processing efficiency scores of the three sub-networks of the attention network were subjected to univariate analysis. The results showed that the difference between the two groups of patients’ executive control network processing efficiency scores was statistically significant ($F = 4.696$, $df = 1$, $P = 0.039$), the average score of the pre-treatment group was 90.26 ± 20.85, and the average score of the post-treatment group It was 64.89 ± 25.46. The processing efficiency score of the executive control network of the post-treatment group was significantly lower than that of the pre-treatment group; while the processing efficiency of the alert system and the processing efficiency of the orientation network were not statistically different between the two groups of patients (alert System: F = 2.705, df = 1, P = 0.111; towards the network: F = 1.155, df = 1, P = 0.292). The result is shown in Figure 3.

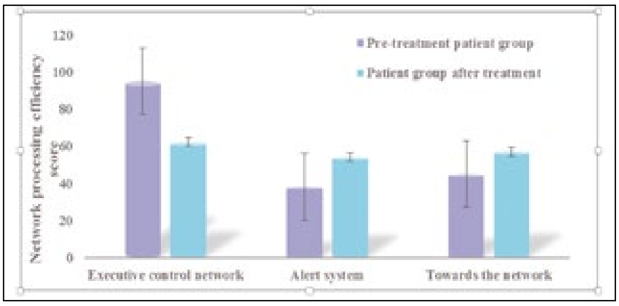

Figure 3: The difference in-network processing efficiency score between the pre-treatment group and the post-treatment group.

*Note: The difference in the processing efficiency scores of the three sub-networks of the network (executive control network, alert system and orientation network) between the pre-treatment group and the post-treatment group. *It means that the processing efficiency of this sub-network is significantly different between the two groups.*

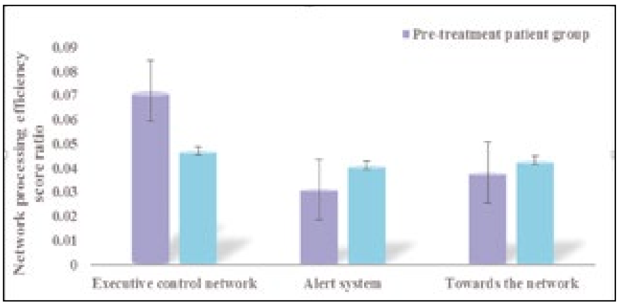

Figure 4: The difference between the network processing efficiency score ratio between the pre-treatment group and the post-treatment group.

*Note: The difference in the processing efficiency score ratio of the three sub-networks of the network (executive control network, alert system and orientation network) between the pre-treatment group and the post-treatment group. *It means that there is a significant difference between the two groups in the network processing efficiency score ratio.*

Similarly, the patient's age, gender, and education level were used as covariates to perform univariate analysis on the processing efficiency score ratios of the three sub-networks of the attention network. The results showed that the difference between the two groups of patients' executive control network processing efficiency score ratio was statistically significant (F = 6.854, df = 1, P = 0.014), the average ratio of the pre-treatment group was 0.74 ± 0.02, and the post-treatment group The average ratio is 0.48 ± 0.20. The processing efficiency score ratio of the executive control network of the post-treatment group is significantly lower than that of the pre-treatment group; while the score ratio of the alert system processing efficiency and the score ratio towards the network processing efficiency are both between the two groups of patients There is no statistical difference (alert system: F = 2.765, df = 1, P = 0.108; towards the network: F = 1.102, df = 1, P = 0.303). The result is shown in Figure 4.

Discussion

In this study, the author used the ANT task proposed by Fan J et al.[18] in 2002 to test the cognitive function of the patient's attention network. The task of ANT is simple, applicable to a wide range of ages, and can effectively evaluate the processing efficiency of the three sub-networks of the attention network (the alert system, the orientation network, and the execution control network). The ANT test paradigm has been exploratory use in sleep deprivation[20], schizophrenia[21], after breast cancer chemotherapy and other areas with cognitive dysfunction or impairment, and it can effectively detect specific cognition Note the difference in processing efficiency of network sub-networks related to functional abnormalities. In this study, through the horizontal comparison of the attention network processing efficiency between the pre-treatment group and the post-treatment group, the author deeply explored the effect of comprehensive treatment of nasopharyngeal carcinoma on the cognitive function of attention network in patients with nasopharyngeal carcinoma. The results suggest that attention Among the three sub-networks of the network, the processing efficiency score and score ratio of the executive control network of the post-treatment group were significantly lower than those of the pre-treatment group; while the processing efficiency of the alert system and the score and the score ratio of the processing efficiency towards the network were the same between the two groups of patients There is no statistical difference.

The execution control network corresponds to the ability to resolve conflict tasks. According to the definition of the attention network sub-network score and score ratio, the higher the score or score ratio, the lower the patient's ability to resolve conflicts, that is, the lower the processing efficiency. This study found that within a short period of time after treatment, the processing efficiency score and score ratio of the executive control network of patients with nasopharyngeal carcinoma decreased, suggesting that the processing efficiency of the executive control network increased. The processing efficiency of the executive control network is related to the activation of the frontal lobe function area(22, 23). When performing the ANT conflict task, the middle frontal gyrus and the prefrontal area will be activated(24). The author speculates that after the comprehensive treatment of nasopharyngeal carcinoma, the frontal lobe function of nasopharyngeal carcinoma patients has changed, and the change in the processing efficiency of the executive control network may be related to the frontal lobe compensation activation.

Note that the network alert system reflects the ability to maintain alertness and the body's ability to respond to prompt information. Its function is usually closely related to areas such as the thalamus, frontal lobe, and parietal lobe. Damage to these areas often leads to a decrease in the function of the attention network alert system(25). The higher the score or the score ratio of the alert system, the higher the processing efficiency(26-28). In this study, there is no statistical difference in the scores and ratios of the processing efficiency of the alert system between the two groups of patients, suggesting that the areas related to the attention function of the alert system network may not change significantly.

The network-oriented attention function is mainly responsible for the selection of information. Functional magnetic resonance imaging (fMRI) studies have shown that the network-oriented attention function is closely related to the superior temporal gyrus and the temporal-parietal complex(29). The higher the score or score ratio of the network, the higher the processing efficiency(30,31). Damage to the right thalamus occipital, temporal-parietal area, and superior temporal gyrus can lead to defects in attention toward the network(32). In this study, there was no statistical difference in the scores and score ratios towards network processing efficiency between the two groups of patients, suggesting that the areas related to the network attention function may not change significantly.

Note that the statistical results of the processing efficiency score ratios of the three sub-networks of the network are consistent with the statistical results of the processing efficiency scores of the three sub-networks, indicating that the results of this study are reliable and stable. There is no statistical difference between the two groups of patients in age, gender, and education level, indicating that the two groups of patients are comparable in age, sex and education level.

Similar to the results of this study, Leng, X., et al.(33) used the Frontal Systems Behavior Scale (FrSBe) to follow up the executive function of long-term survival patients after IMRT and found The patient's executive function has been impaired, and similar findings have been reported in other studies. Compared with these studies, this study adopts a more detailed and accurate attention function test scale, and conducts a more detailed investigation and analysis of attention function sub-networks. The investigation results of these behavioral scales and our research suggest that the impairment of attentional network executive function is related to the temporal lobe. This result is confirmed in imaging studies. For example, in our previous horizontal control study, it was found that the gray matter density of the temporal lobe of NPC patients changed after one year of radiotherapy. Compared with the group of patients before radiotherapy, one year after radiotherapy, the right pulvinar occiput of NPC patients , The MNI coordinates of the point with the greatest difference: x, y, z = 20, -30, 6), the right middle temporal gyrus (the right middle Temporal Gyrus, the MNI coordinates of the point with the greatest difference: x, y, z = 53,- 28,-2), the gray matter density of the left hippocampus (the left hippocampus, the MNI coordinates of the most different point: x, y, z = -26, -16, -14) becomes smaller ($p < 0.001$, AlphaSim corrected, cluster size> 157)(31). Recent studies have also found that the structure of the temporal lobe in NPC patients is damaged after radiotherapy(34,35) and that the changes in the temporal lobe are related to the dose of radiotherapy(36), which further confirms our results.

This study still has shortcomings: (1) The author found that although the frontal lobe was not directly irradiated by radiotherapy in the treatment of nasopharyngeal carcinoma, the frontal lobe function of nasopharyngeal carcinoma patients may undergo secondary changes after radiotherapy and chemotherapy, due to the lack of normal controls Group and imaging methods verify that the results cannot explain whether the processing efficiency of the executive control network has been restored or further improved. In the follow-up study, we will introduce imaging methods and include another group of normal people matching age, gender, education level, etc. for comparison; (2) In addition, the sample size of this study is small, and each group needs to be further expanded in Hangzhou (China). The sample size of the patient, the results are further verified; another point to be explained is that in this study, the author did not describe the post-treatment group as the post-radiation patient group like most studies, because the subjects in this study are When receiving radiotherapy, they will also receive 2 to 3 cycles of concurrent chemotherapy. Some studies believe that chemotherapy may cause cognitive function impairment(37), but some studies have shown that chemotherapy has no effect on cognitive function(38-40). Whether chemotherapy can cause cognitive function impairment is still controversial. In this study, the author called it the post-treatment group to avoid misunderstanding.

Conclusions

After treatment, the processing efficiency of alerting system and orienting network of NPC patients did not change significantly, while the processing efficiency of executive control network was improved.

References

1) Chen, Y.-P., et al., Nasopharyngeal carcinoma. The Lancet, 2019. 394(10192): p. 64-80.
2) Luo Yanrong, Cai Boning, Ma Lin. Progress in chemotherapy of locally advanced nasopharyngeal carcinoma(J). Journal of Medical Research, 2018, 47(003):p.12-16.
3) Chua, M.L., et al., Nasopharyngeal carcinoma. The Lancet, 2016. 387(10022): p. 1012-1024.
4) Zhao Weiman, Dong Zhiyong, Shi Zongfen, et al. Downregulation of miR-205-5p enhances the sensitivity of nasopharyngeal carcinoma cells HNE1/DDP to Cisplatin-induced apoptosis(J). Acta Pharmaceutica Sinica, 2019, 054(007): p.1200-1206.
5) Tang Yunyun, Tan Guixiang, Jiang Jianwei, et al. Effects of Chonglou active monomer pp-22 on the proliferation, cycle and apoptosis of human nasopharyngeal carcinoma cell CNE-1(J). Clinical Medical Engineering, 2018, 230(04): p.441-443.
6) Hu Jing, Dai Na, Xu Bingyan, et al. Yiqi Jiedu Recipe inhibits the proliferation of nasopharyngeal carcinoma cells through MAPK/ERK signaling pathway(J). China Journal of Chinese Materia Medica, 2018, 43(006): p.1221-1227.
7) Lu Baocai, Lu Zhenmin, Zhang Aimin, et al. The effect of interfering small ribonucleic acid-targeting inhibition of chemokine receptor 4 gene expression on the proliferation and invasion of nasopharyngeal carcinoma cells(J). Journal of Xinxiang Medical College, 2018, 035(001): p.30-34.
8) Lei Yue, Wan Jie, Wen Taoyu, et al. Effects of siRNA silencing the expression of FOXM1 gene on proliferation, apoptosis and chemosensitivity of human nasopharyngeal carcinoma cells (Effects of siRNA silencing the expression of FOXM1 gene on proliferation, apoptosis and chemosensitivity of human nasopharyngeal carcinoma cells)(J). Tumor, 2018, 38(1): p.25-34.
9) Zhang Yinglong, Liu Wei, Jiang Hong. Paclitaxel inhibits proliferation of nasopharyngeal carcinoma cell line CNE2 and its effect on PI3K/AKT/p53 signaling pathway(J). Chinese Journal of Clinical Pharmacology, 2018, 268 (14): p.70-72.
10) McDowell, L., et al., Cognitive and Neurobehavioral Impairment in Long-Term Survivors Treated for Nasopharyngeal Cancer with Intensity-Modulated Radiation Therapy. International Journal of Radiation Oncology Biology Physics, 2017. 99(2): p. S237.
11) Shen, Q., et al., Temporal cerebral microbleeds are associated with radiation necrosis and cognitive dysfunction in patients treated for nasopharyngeal carcinoma. International Journal of Radiation Oncology* Biology* Physics, 2016. 94(5): p. 1113-1120.
12) Fan, Q., et al., Celecoxib combined with hippocampus sparing intensity-modulated radiation therapy reduces the injury of cognitive function induced by radiotherapy in patients with nasopharyngeal carcinoma. Int J Clin Exp Med, 2017. 10(8): p. 12546-12552.
13) Ma, Q., et al., Radiation-induced functional connectivity alterations in nasopharyngeal carcinoma patients with radiotherapy. Medicine, 2016. 95(29).
14) Chen, S.C.-J., et al., Prognosis of hippocampal function after sub-lethal irradiation brain injury in patients with nasopharyngeal carcinoma. Scientific reports, 2017. 7(1): p. 1-11.
15) Lin, J., et al., Radiation-induced abnormal cortical thickness in patients with nasopharyngeal carcinoma after radiotherapy. NeuroImage: Clinical, 2017. 14: p. 610-621.
16) Zong-Wen S , Lei S , Qinglin L , et al. Results of the radiation dose of head, body and tail of hippocampus in nasopharyngeal carcinoma patients treated with intensity-modulated radiotherapy. Scientific Reports, 2018, 8(1): p. 5595.
17) Wang Yan, Tian Xiaokang, Fei Qian, et al. Current status and progress in the treatment of nasopharyngeal carcinoma with negative cervical lymph nodes(J). Journal of Oncology, 2019, 025(002):p.91-96.
18) Zheng G , Lujan H , Yadi Y , et al. Longitudinal brain structura alterations in patients with nasopharyngeal carcinoma early after radiotherapy. NeuroImage: Clinical, 2018, 19:p. 252-259.
19) Hassani G C, Alami A , Alami Z . GP21 Undifferentiated nasopharyngeal carcinoma in children and young adults: experience in the radiotherapy department of the fes university hospital center. Archives of Disease in Childhood, 2019, 104(Suppl 3):p. A38-.
20) Kong Weiyun, Huang Xiaomei, Miao Wanglan. Whole-course nursing intervention for radioactive oral mucositis of nasopharyngeal carcinoma(J). Integrated Traditional Chinese and Western Medicine Nursing (Chinese and English), 2019, 5(9): p.145-147.
21) Kong Weiyun, Huang Xiaomei, Miao Wanglan. Whole-course nursing intervention for radioactive oral mucositis of nasopharyngeal carcinoma(J). Integrated Traditional Chinese and Western Medicine Nursing (Chinese and English), 2019, 5(9): p.145-147.
22) Guo SS , Hu W , Chen Q Y , et al. Pretreatment quality of life as a predictor of survival for patients with

nasopharyngeal carcinoma treated with IMRT. Bmc Cancer, 2018, 18(1): p.114.

23) Hu, P., et al., Attention network impairments in patients with focal frontal or parietal lesions. Neuroscience Letters, 2013. 534(1): p. 177.

24. Wang Nan, Cao Jianxiong. The mechanism and research status of xerostomia after radiotherapy for nasopharyngeal carcinoma(J). World Cancer Research, 2018, 8(3): p.5.

25) Yuan Cuiyun, Chen Li, Li Haiyan. The influence of clinical nursing pathways in radiotherapy education for patients with nasopharyngeal carcinoma and diabetes(J). New World of Diabetes, 2018, 021(001): p.130-131.

26) Chen Xiaozhong, Li Jingao, Lin Shaojun, et al. Expert consensus on the treatment of metastatic nasopharyngeal carcinoma(J). Chinese Journal of Radiation Oncology, 2018(1): p.23-28.

27) Liu Junli, Cai Xiao. Correlation of miR-106b with cell cycle progression and cell invasion in nasopharyngeal carcinoma(J). Journal of Hainan Medical University, 2018,210(11): p.71-74 .

28) Chen Xue, Ye Dong, Liu Kaitai, et al. Analysis of prognostic factors and treatment models of newly treated metastatic nasopharyngeal carcinoma(J). Chinese General Practice, 2018, 569(14): p.51-57 .

29) McDowell, L.J., et al., A cross sectional study in cognitive and neurobehavioral impairment in long-term nasopharyngeal cancer survivors treated with intensity-modulated radiotherapy. Radiotherapy and Oncology, 2019. 131: p. 179-185.

30) Du Shaopeng, Wang Jiaxu, Cai Weijie, et al. Effect of psoralen B on the proliferation and apoptosis of nasopharyngeal carcinoma cells and its mechanism(J). Journal of Anhui Medical University, 2018, 53(001): p.15-19.

31) B M D A , A J R , C W X , et al. A cross-sectional study in cognitive and neurobehavioral impairment in long-term nasopharyngeal cancer survivors treated with intensity-modulated radiotherapy. Radiotherapy and Oncology, 2019, 131: p.179-185.

32) Shi, L., et al., Radiation-induced gray matter atrophy in patients with nasopharyngeal carcinoma after intensity-modulated radiotherapy: a MRI magnetic resonance imaging voxel-based morphometry study. Quantitative Imaging in Medicine and Surgery, 2018. 8(9): p. 902.

33) Guo, Z., et al., Longitudinal brain structural alterations in patients with nasopharyngeal carcinoma early after radiotherapy. NeuroImage: Clinical, 2018. 19: p. 252-259.

34) Leng, X., et al., Application of a machine learning method to whole-brain white matter injury after radiotherapy for nasopharyngeal carcinoma. Cancer Imaging, 2019. 19(1): p. 1-10.

35) Tang, Y., et al., Psychological disorders, cognitive dysfunction and quality of life in nasopharyngeal carcinoma patients with radiation-induced brain injury. Plus One, 2012. 7(6): p. e36529.

36) Ko M Y , Vardhanabhuti V , Ng W T , et al. Clinical utility of serial analysis of circulating tumour cells for detection of minimal residual disease of metastatic nasopharyngeal carcinoma. British Journal of Cancer, 2020:32(6): p. 535.

37) François Mouton Liger, Anne-Cécile Troussière, Wallon D , et al. What is the clinical impact of cerebrospinal fluid biomarkers on final diagnosis and management in patients with mild cognitive impairment in clinical practice? Results from a nation-wide prospective survey in France. BMJ Open, 2019, 9(5): p. 1-7.

38) Petkar I, Bhide S , Newbold K, et al. Practice patterns for the radical treatment of nasopharyngeal cancer by head and neck oncologists in the United Kingdom. British Journal of Radiology, 2018, 91(1085):p. 20170590.

39) Wang Y Q Lv J W, Tang L L, et al. Effect of prior cancer on trial eligibility and treatment outcomes in nasopharyngeal carcinoma: Implications for clinical trial accrual. Oral Oncology, 2019, 90: p. 23-29.

40) Liu PY, Chang DC , Lo YS , et al. Osthole induces human nasopharyngeal cancer cells apoptosis through Fas–Fas ligand and mitochondrial pathway. Environmental Toxicology, 2018, 33(3-4): p. 446-453.

41) Kim H, Burassakarn A , Kang Y , et al. A single nucleotide polymorphism in the BART promoter region of Epstein-Barr virus isolated from nasopharyngeal cancer cells. Biochemical and Biophysical Research Communications, 2019, 520(2) :p. 373-378.

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