Differences in Neurobiology of Different Syndrome of Melancholia in the Viewpoint of TCM

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ABSTRACT

To some extent, melancholia in different Traditional Chinese Medicine (TCM) Syndromes represents different "subtypes" of melancholia. Whether bipolar depression or general melancholia, whether accompanied with or without psychotic symptoms, or with or without cognitive impairment, there are clinical and possible biological differences in these melancholia, which indicates that different "subtypes" of melancholia represented by different TCM syndromes not only are different clinical syndromes, but also imply that there may be some biomarkers. The melancholia with liver depression and stagnation is different from melancholia with deficiency of both heart and spleen in clinical symptoms, which may indicate that there are differences in some potential biological biomarkers. For example, central nervous transmitters, trace elements, electrophysiology, neuroendocrinology, brain imaging, and even genomics may differ among different TCM syndrome types of melancholia, which not only serves for the modernization of TCM, but also finds biological differences for different TCM syndrome types of melancholia.

DOI Number: 10.14704/nq.2019.17.05.2369 **NeuroQuantology 2019; 17(05):76-80**

1.P300

P300 also was studied widely in melancholia as a biological marker of cognitive function, because most of patients with melancholia often are companied with cognitive impairment. P300 waveform is the most widely used component of the event-related brain potential (ERP), which is related to cognitive information processing, including working memory, attention and executive function. As an electrophysiological indicator of cognitive activity, P300 is non-invasive, inexpensive, convenient, and free of cultural and educational bias. Because of its high temporal resolution, P300 is more sensitive to cognitive changes than traditional neuropsychological tests and can provide insight into cognitive processes. Shen's study found a difference of P300 between melancholia TCM syndrome of stagnation of liver Qi and deficiency of both heart and spleen. The latency (ms) in patients with stagnation of liver Qi was 339.57±33.53 at Fz, 341.17±32.91 at Cz, 339.33±33.27 at Pz.The latency in patients with deficiency of both heart and spleen was=381.97±50.45 at Fz, 382.41±49.71 at Cz, 381.94±49.97 at Pz. Their latencies differ significantly, but all amplitudes in patients with deficiency of both heart and spleen at Fz, Cz, and Pz are lower significantly than that of normal controls, and not different in patients with other groups of stagnation of liver Qi. This means these were the greatest difference in melancholia of different TCM syndromes (Shen and Wang, 2014).

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Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 15 May 2019; **Accepted:** 27 May 2019

2.Neuroendocrine System

In addition to monoamine neurotransmitter metabolic disorders, neuroendocrine disorders play an important role in the pathogenesis of melancholia. A large number of data show that the hypothalamus-pituitary-adrenal axis (HPA), hypothalamus-pituitary-thyroid axis (HPT), hypothalamus-pituitary-gonad axis (HPG) in patients with melancholia have different degrees of dysfunction. HPA is often hyperactive, while HPT and HPG are often hypoactive. Steroid hormone receptors exist in many areas of the brain, and the brain itself can synthesize steroids (adrenocortical hormones and sex hormones), known as neurosteroids (Camacho-Arroyo *et al*., 2017). Peripheral corticosteroids and sex hormones can also enter the brain through the blood-brain barrier. These steroids play an important role in the regulation of brain function. After antidepressant treatment, the neuroendocrine function of melancholia patients often recovers to some extent with the improvement of their condition. The melancholic symptoms were improved and the regulation function of HPA returned to normal. For some melancholia patients with decreased plasma sex hormone levels, supplementary sex hormone therapy has achieved a certain effect. There is also some secondary melancholia, such as menopausal melancholia, postpartum melancholia, premenstrual syndrome, and so on, which is significantly related to the fluctuation of sex hormone levels. Severe fluctuations in sex hormone levels are also an acute physiological stress. In the pathogenesis of melancholia, sex hormones and melancholia may interact to form a vicious circle. Moreover, many patients with melancholia, especially those with refractory melancholia, need the assistance of thyroxine. These examples all suggest that the neuroendocrine axis is related to melancholia. Similar reasoning, the neuroendocrine manifestations of different TCM syndromes of melancholia are also different.

2.1. HPA

It is very important that hyperactivity of hypothalamic-pituitary-adrenocortical (HPA) axis is one of the pathophysiological mechanisms of melancholia, Previous studies have estimated that the plasma level of corticotropin-releasing hormone (CRH), adrenocorticotropichormone (ACTH), glucocorticoid (GC) are increased significantly. The sustained increased level of GC has reduced the number of hippocampal glucocorticoid receptors (GR) and mineralocorticoid receptors (MR); the MR/GR ratio became imbalanced, therefore destroying the hippocampal neurons. The hippocampus itself could mediate the activities of the HPA axis. The destruction of hippocampal neurons causes the hippocampus to become too weak to mediate the HPA axis, while the increasing level of GC has decreased the GC negative feedback inhibition of the HPA axis to make it hyperactive (Gao and Jin ,2017).

There is a pathophysiology of HPA hyperactivity in melancholia, so HPA is a window that reflects the pathophysiology of melancholia, which may be different among TCM syndromes of melancholia. Gao and colleagues found the difference in regulation of HPA between two TCM syndromes by DST: melancholia patients with stagnation of liver Qi had better regulation of HPA than that of cases with deficiency of both heart and spleen (Gao, *et al*., 2017).

2.2 HPT (Hypothalamic pituitary thyroid axis)

Brownlie *et al*, (2010) found that the dynamic decline of thyroid hormone level is related to the occurrence of melancholia, among which FT3 and FT4 play a major role. Chinese scholars found that thyroid hormone levels in patients with treatment-resistant melancholia were significantly abnormal, mainly manifested by increased TSH, decreased T3 and FT4, and 56.7% of patients with refractory melancholia had subclinical hypothyroidism. Other studies have shown that FT4, testosterone (T) and progesterone levels in female melancholic patients are significantly lower, and TSH is significantly higher. These changes are similar to the manifestations of deficiency of Qi in liver and kidney yang. Chinese studies have found that serum T3, T4 and FT3, TSH in patients with liver-yang deficiency syndrome are significantly decreased, while T3, T4, FT3 and FT4 in patients with kidney-yang deficiency are lower than those in normal people, while TSH is higher than that in normal people (Cui *et al* 2011; Bao *et al*., 2011).

There were 203 patients, including 28 patients in the syndrome stage of liver depression and Qi stagnation, 74 patients in the syndrome stage of deficiency and excess (liver depression and spleen deficiency, liver depression and phlegm stagnation), 101 patients in the syndrome stage of deficiency (heart and spleen deficiency, heart and kidney disjunction). There were 50 cases in the control group. Levels of total triiodothyronine (T3), total thyroxine (T4), serum thyrotropin (TSH), serum

5-hydroxytryptamine (5-HT), norepinephrine (NE) and dopamine (DA) in peripheral blood of two groups were measured. The decrease of T3 and the increase of TSH in deficiency syndrome stage were more obvious than those in normal control group (P<0.05). 5-HT was negatively correlated with TSH (r=-0.89, P <0.01), and 5-HT was positively correlated with T3 and T4 (r=0.94, P <0.01). These results indicated that different TCM syndromes of senile melancholia patients are closely related to monoamine neurotransmitters and thyroid hormone function (Lu *et al*., 2011).

2.3 HPG (hypothalamus-pituitary-gonad axis)

For melancholia, whether treated with antidepressants, traditional Chinese medicine or integrated traditional Chinese and Western medicine, E2 increased significantly, and had statistical significance with the improvement of melancholic symptoms. Other studies have shown that the levels of estradiol (E2), FT4, testosterone (T) and progesterone in female melancholic patients are significantly decreased, and TSH is significantly increased. These changes are similar to the manifestations of liver and kidney yang deficiency. The E2 value decreased and T/E2 ratio increased in female patients with kidney-yang deficiency. The results showed that the E2 value of female patients with kidney-yang deficiency was 42.7% lower than that of normal people, 41.26% lower than that of non-kidney-yang deficiency patients, and the T/E2 ratio was significantly higher than that of normal people (Li *et al*., 2014; Xiao and Huang, 1999; Trine, 2011).

3.Neurotransmitters and Their Receipts

The monoamine neurotransmitter hypothesis has been supporting the etiology of melancholia for many years, and many antidepressants have been developed on the basis of this hypothesis. Needless to say, the monoamine neurotransmitter hypothesis of melancholia is partly or mostly validated by therapeutics. Unfortunately, there are not many typing criteria for melancholia, so it is difficult to further classify or classify subtypes in clinical practice.

However, the understanding of melancholia in traditional Chinese medicine is rich and colorful. Both etiology, pathogenesis and taxonomy have their own theories and methods of development, although there are some differences between melancholia in western medicine and melancholia in traditional Chinese medicine. This not only reflects the difference between the two theoretical systems, but also reflects the difference in the understanding of this disease between traditional Chinese medicine and Western medicine. Therefore, the concept of integration of traditional Chinese and Western medicine is different. One of the manifestations of integration of traditional Chinese and Western medicine is to differentiate the symptoms and signs after diagnosis of melancholia by Western medicine.

A case-control study was conducted to observe 139 melancholic patients with liver-qi stagnation, liver-qi stagnation and Spleen-Qi deficiency, liver-qi stagnation and phlegm stagnation, heart-spleen deficiency and heart-kidney disjunction. The differences of serotonin (5-HT), norepinephrine (NE) and dopamine (DA) in peripheral blood of each group were compared with 30 normal persons. Results showed that NE, 5-HT, and DA in liver-qi stagnation group, liver-qi stagnation and Spleen-Qi deficiency, liver-qi stagnation and phlegm obstruction, heart-spleen deficiency and heart-kidney disjunction groups were lower than those in the normal control group (P<0.05, P< 0.01). There were significant differences in the proportion of 5-HT and NE dysfunction and hyperactivity between each group and the normal control group (P< 0.05, P< 0.01); 29.03% of liver-qi stagnation and heart-spleen deficiency groups, 25% of DA hyperfunction group were positive respectively. The results suggested levels of 5-HT, NE and DA in peripheral blood of most melancholic patients are lower than those of normal people, but some patients show hyperfunction of 5-HT, NE and DA, and the levels of 5-HT, NE and DA in different syndromes are different (Yang *et al*., 2011).

4.Brain-Derived Neurotrophic Factor (BDNF)

Several clinical studies on major depressive disorder (MDD) have shown that blood brain-derived neurotrophic factor (BDNF) as a factor used to index neuroplasticity is associated with melancholia response; however, the results are mixed. The purpose of our study was to evaluate whether BDNF levels are correlated with improvement of melancholia. The results showed that BDNF levels increased significantly after antidepressant treatment. In addition, there was a significant correlation between changes in BDNF level and melancholia score changes. Moreover, the results were robust according to the sensitivity analysis and Begg's funnel plot

results did not suggest publication bias. There was a difference between pre-treatment patients and healthy controls and a small but significant difference between treated patients and healthy controls. These results were also found in China. They not only found the difference of BDNF between TCM syndromes by experimental study but also found the changes of BDNF after management of accupuncture for melancholia by meta-analysis. The serum BDNF in patients with liver depression and Qi stagnation syndrome and liver depression and spleen deficiency syndrome were lower than those of the control group ($P < 0.05$, $P < 0.01$). He also found the serum BDNF value of patients with stagnation of spleen and liver depression syndrome was lower than that of patients with stagnation of liver and Qi ($P < 0.05$), but the serum BDNF level of male melancholia patients with was slightly lower than that of female patients, and there was no difference. Acupuncture can change symptoms of melancholia. As the important way of TCM，acupuncture has a long history of treating illnesses which we today in a biomedical context would understand and recognize as melancholia. A significant beneficial effect was found for acupuncture in improvement of melancholia compared to pooled control measured by Hamilton Rating Scale for Depression (WMD −3.10, 95% CI −4.91 to −1.99, $P = 0.0008$) with meta-analysis through four systematic reviews and 26 RCTs on acupuncture for treatment of melancholia. These melancholic symptom changes are related to the increasing level of BDNF in the serum (Nie *et al*., 2017; Li *et al*., 2004).

5. Brain Imaging Technology

Compared with traditional traumatic experimental techniques, brain imaging technology has incomparable advantages. It allows researchers to directly observe brain activity, which is the simplest and most effective experimental technology. Using brain imaging technology to study the cognitive structure and function of the brain has become the third force in the development of cognitive science. Event-related potential (ERP), magneto-encephalography (MEG), positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) are the four most important methods. Brain imaging technology was also used for differentiation of TCM syndromes of melancholia.

The aesthenia and deficiency syndrome of melancholia are two completely different concepts of traditional Chinese medicine, and they are also completely different clinical symptoms. The functional connectivity of the deficiency syndrome group was compared with that of a control group. Zhang and their colleagues found that the brain areas with decreased functional connectivity were the right middle temporal gyrus and bilateral anterior wedge lobe, and the brain area with enhanced functional connectivity was the bilateral middle frontal gyrus. Comparing the functional connectivity between the empirical group and the control group, the bilateral middle temporal gyrus and bilateral anterior cuneiform lobe had decreased functional connectivity, and the bilateral superior frontal gyrus had enhanced functional connectivity. Compared with the deficiency syndrome group, there were bilateral cerebellum and left superior frontal gyrus connectivity were found (Zhang *et al*., 2013). melancholia patients with different TCM syndrome differentiations have different brain functional connectivity patterns. The abnormal functional connectivity of prefrontal lobe, temporal lobe, prefrontal cuneiform lobe and cerebellum may be related to the symptoms of melancholia. A similar study was carried out by other Zhang. 44 melancholic patients and 20 healthy volunteers were randomly selected. The melancholia group was divided into deficiency syndrome group (N=24) and aesthenia group (N=20). The NAA/Cr Cho/Cr and Mi/Cr were examined by 1H-MRS. The patients had lower Cho/Cr in the right prefrontal white matter than the control group ($t=2.362$, $P<0.05$). There were significant differences in NAA/Cr among groups ($F= 4.775$, $P = 0.013$, $P < 0.05$). There were significant differences in Mi/Cr among groups of right prefrontal lobe ($F=3.487$, $P = 0.044$, $P < 0.05$). The very important was that great differences between syndromes of deficiency and aesthenia melancholia (Zhang and Han, 2013).

The melancholia TCM syndrome of stagnation of liver Qi and deficiency of both heart and spleen are not only different in clinical symptoms, but also different in brain function that presented by brain imaging. Han and their colleagues compared the difference of brain function between patients with melancholia and normal people by task-state functional magnetic resonance imaging. According to the theory of traditional Chinese medicine, the patients with melancholia were divided into two groups: deficiency of heart and spleen (N=25) and stagnation of Liver-qi (N=20). The functional magnetic resonance imaging (fMRI) scans were performed on 18 healthy volunteers, and the data

was analyzed to obtain brain regions with different functional activity. The results showed that there were significant differences in left inferior frontal gyrus, left insula and head of left caudate nucleus between melancholia group with liver depression and qi stagnation and melancholia group with heart and spleen deficiency both under sadness control and neutral conditions. This difference may be related to different clinical symptoms of melancholia patients with different syndrome types (Zhang *et al*., 2013; Han *et al*., 2103).

Acknowledgement

We thank Mr Wang Zhiqiang and Mr Zhu Jianfeng for search work for our study and Mr Ma Yongchun who made the final amendment of the manuscript.

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