

Chasing Sea Horses in The Depressed Seas: A Ten Years Journey

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Major depressive disorder with a prevalence of 8-16% is one of the most common psychiatric diseases. Despite more than one hundred scientific papers were published about the etiology of depression every year, we have only a few well-described theories about its pathophysiology. One thing we sure about depression is, it has a strong genetic bases (1). However, we could not determine specific genes but have a number of candidate genes. The second most accepted theory about depression is about dysfunctional monoaminergic system mainly serotonergic system. This theory was supported evidences from preclinical animal and clinical serotonin depletion studies. However, the strongest evidences come from treatment options that we use to treat our patients, which are mainly consisted of serotonergic antidepressants. The third and the most studied theory propose that the high cortisol response in depressed patients is the key pathophysiological step for depression (2). According to this theory, depression prone people respond to stressful situations with higher cortisol levels which might lead to structural and functional changes in brain that we have observed with MRI scanning (3). This approach is well accepted by psychiatrists and neuroscientist as it follows a timeline for depression (4). In the beginning of the road to depression, hypothalamic-pituitary-adrenal (HPA) system might work well. But

the prolonged stress leads to reduce cortisol receptors in the brain and pituitary gland, whose main role is inhibiting the cortisol secretion (5). Loss of brake in the HPA axis leads to continue high cortisol response in the stressed person. Among many other functional effects on different physiologic systems in the body, the high cortisol levels may impair glucose utilization in neurons and may cause neuronal damage. Hippocampus is known with its vulnerability to toxic effects of hypoxia and metabolic toxins. Indeed, it is well shown that high cortisol levels are associated with reduced hippocampal levels in the rats. However, one should not forget that hippocampus is one of the largest gray matter structures in the rat brain and compared to human brain, it occupies a larger area. Therefore, any damage to this structure would result in a large effect in the rat brain.

According to our basic understanding of science, a theory must have falsifiable and testable predictions. Cortisol theory was tested a number of times by different labs and the results were inconsistent. Testing cortisol hypothesis is important because many of the observable brain changes are linked with the high cortisol levels in patients.

When SoCAT Lab was founded in 2003, the main aim of the lab was to test the cortisol hypothesis in depression and as a co-founder of the lab, I was expecting to validate the cortisol theory. Furthermore,

we wanted to investigate neural correlates of cortisol theory over the brain. However, after 10 years of investigation, we came a totally different point from what we were initially expected.

Is Hyperactive HPA Necessary for Depression?

As mentioned above, one of the most important discoveries in psychiatry is the high cortisol level in a group of depressed patients. By this discovery, researchers entered the area of biological psychiatry for mood disorders. After this initial finding, many researchers tried to replicate the high cortisol levels in the depressed patients. However, the replications were shadowed by many confounding factors. For example, high cortisol levels could not be observed throughout the day. Furthermore, some studies found high cortisol levels only in the morning, and others found high cortisol levels only in the afternoon or evening. Some other researchers explained this situation as the loss of diurnal cortisol rhythm in depressed patients. Therefore, a universal finding of cortisol levels could not be attributed to depression today and morning serum cortisol levels are not accepted as a biological marker for depression any more.

Ambitious researchers proposed that cortisol abnormalities could be observed under stress. They applied different stress tests to patients via physical or social stress tests like putting the patient hand in the cold water or let them speak in front of crowded people. The other way to induce stress on the HPA system is applying extra cortisol to the patients. The most common chemical tests are dexamethasone suppression test (DST) or CRF/DEX test. In either test, subjects are on single or multiple doses of synthetic cortisol before any further procedure or cortisol measurement. However, less than 50% of patients have abnormal cortisol levels after stress tests.

Despite the efforts American Psychiatric Association (APA) and World Health Organization (WHO), depression is still a heterogeneous illness with different clinical faces changing from one patient to another. Up to 30% of patients demonstrate melancholic features like early morning awaking with worsening of mood,

weight loss, excessive guilt feeling and another 25% have atypical features like excessive fatigue and mood reactivity (6). Rest of the patients cannot be classified as melancholic or atypical. Although some of the researchers proposed that the positive cortisol findings are valid for melancholic depression, only 2/3 of those patients show non-suppressive dexamethasone response. On the other hand, large group of depressed patients have lower cortisol levels. It is interesting that no study measured the cortisol levels in consecutive episodes. We believe in that this might be important because the clinical subtype of depression might change from one episode to another. Thus, one patient might be melancholic in one episode but might show atypical in the next one.

A group of study investigated the cortisol levels in the high-risk population for depression. Initial investigations suggested that adolescents with a depressed parent might have high morning cortisol levels even they do not demonstrate clinical symptoms (7). However, this finding could not be replicated in later studies. The data is more complicated in children studies (8).

In 2009, SoCAT Lab initiated a high-risk study with the support of TUBITAK. We recruited daughters of depressed mothers (with multiple episodes) only if they had a history of familial depression (another family member should have been diagnosed with depression). As expected, daughters and mothers had similar cortisol rhythm and cortisol response to DEX/CRH test but different than healthy mothers and their daughters. However, unexpected finding was the depressed mother's morning cortisol levels were lower than their comparators. Even more, their cortisol response was diminished in DEX/CRH test. The daughters' (of depressed mothers) parameters were between their healthy counterparts and mothers. Although this study could not show that the high cortisol levels are necessary for depression, cortisol secretion was altered in high-risk subjects for depression and influenced by genes. This study was not unique for its cortisol findings, in the last 5 years many reports came out with lower cortisol levels in depressed patients (9).

As a conclusion, 50 years of extensive research

suggest that there is a high chance of altered HPA axis in depressed patients; but high cortisol levels are not necessary for pathophysiology of depression.

Hippocampus in the Depressed Brain

Although it is generally accepted that hippocampus is smaller in the depressed patients, only half of the research could support this idea. When we extensively review the literature, we reached the conclusion that factors like multiple episodes, female gender, childhood trauma or being in old age are predicting the smaller hippocampus (10). However, depressed patients between 20-45 years old without any history of childhood trauma show no difference compared to healthy controls. Thus, the question is which other factors are influencing hippocampal volume in depressed patients.

As we mentioned earlier, hippocampus is sensitive to any metabolic alterations in the brain and it is generally proposed that high cortisol levels might be the reason for observing smaller hippocampus in the depressed patients. However, it is very interesting that no study (to our knowledge) could show a direct correlation between cortisol levels and hippocampal volumes (11). Although some studies suggest that hippocampus volume might be associated with the duration of depression, most of the studies could not replicate this finding. However, the duration of depression as a parameter is highly unreliable data as it is mostly depend on memory of patients and their families. Thus, one of the best way to understand if hippocampal shrinking is a result of depression, is to check the first-episode patients. Although a meta-analyses with the first-episode studies suggest that hippocampal volume is smaller in the depressed patients, more than half of the studies in the meta-analyses were reporting no difference (including one from SoCAT Lab) (12). Although it is not strong, the current data suggest that smaller hippocampus (if there is) might be present before the clinical symptoms.

One other way to understand if the depression, itself causes smaller hippocampus is to follow-up depressed patients. To our knowledge, a limited number of

follow-up studies (between 6 months to 11 years) were presented and neither of them could have demonstrated smaller hippocampus at the end of their follow-up (13-16). SoCAT Lab also reported a 5-year follow-up of first episode patients (17). In this study, we could not find any volumetric difference among depressed patients and controls at the baseline and follow-up. We intensified our research on neuroimaging techniques to investigate hippocampus in more detail. As a matter of fact, hippocampus is a large structure and regional changes might not echo in total volume. Indeed, when we analyzed the hippocampus of controls, we could not observe any regional difference for 5 years. On the other hand, depressed patients had significant shape alteration during follow-up. These alterations were not uniform and we observed gray matter loss in some areas while enlargements in other areas. Therefore, the reason for not observing total volume difference among depressed and healthy groups in the half of the research might be due to losses and gains of gray matter in different parts of the hippocampus, which cancels each other.

Volumetric analyses in high-risk populations are another area of research in depression. However, the results of those studies are also mixed for hippocampus. For example one study found 6% smaller hippocampal volume in the daughters of depressed patients and another one found smaller hippocampal volume in high-risk twins compared to low-risk twins at $p<0.04$ levels (18,19). Both of these studies positive finding were at the borderline for significance. On the other hand, another study found larger hippocampal volume in the high-risk population (20). SoCAT Lab. analyzed the hippocampal volumes of daughters of patients with familial depression and found no difference in total volume measurements. Our 3D analyses also showed minor differences between high-risk and low-risk daughters. These changes were in the line with our previous 3D study. On the other hand, one should be aware of that not everybody in the high-risk population would have depression in the future and the data coming from high-risk populations are more heterogeneous than the data obtained from depressed population.

This editorial would be incomplete if we have not

mentioned the prognosis of subjects with smaller hippocampus. In healthy population it is showed that smaller hippocampal volume increases the vulnerability to anxiety or mood disorders. For example it was very well showed that the risk of post-traumatic stress disorder is increased in subjects with smaller hippocampus if those subjects come across with severe trauma (21). Depressed patients who have smaller hippocampus also have higher chance of depressive relapse. Furthermore, we have evidences that subjects with larger hippocampus might have resilience to stressful events (22). Thus, the volume of hippocampus might be a vulnerability factor rather than a causative factor.

CONCLUSION

After ten years of hippocampal investigation with advanced technologies in SoCAT Lab with 3 cohorts (one followed-up for 5 years and one cohort was composed of high-risk population), we could not find any evidence that "smaller total hippocampal volume" is necessary for depression. However, we found that depressed hippocampus show minor structural alterations which occur before the clinical symptoms and go on during depression. Similar to hippocampus findings, we found a genetically controlled dysfunctional HPA axis in depressed patients, which is not always result in high cortisol levels.

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