

EDITORIAL

Cortical activations, psychiatric symptoms, and climacteric women

Isolation of symptoms or deficits that are responsible for changes observed in neuroimaging experiments on psychiatric populations is often challenging. First, it is impossible in these experiments to conclude whether the changes observed are the cause or the effect of the disease process. Second, the usual approach of contrasting data in the diseased and healthy populations ignores the possibility that changes might be driven by only one of the several symptom clusters of the disease. It also ignores the possibility that behavioral or cognitive restrictions imposed by the symptoms could have driven the changes observed in the experiments. These challenges underscore the need for novel approaches in defining control populations that are most likely to isolate symptoms or deficits that drive changes in neuroimaging experiments.

The relationship between changes in brain activation and psychiatric symptoms is an important contemporary area of inquiry. In recent years a number of investigators have conducted experiments to establish this relationship with varying degrees of success. These experiments have arrived at different conclusions, and a consensus is still lacking for most psychiatric conditions.¹ An important reason for the lack of consensus is possible pathophysiologic heterogeneity of psychiatric disorders. In this context depression is an exception. It is one of the few psychiatric disorders for which there is a reasonable degree of consensus among investigators. Most of the studies have reported reduced activation of the orbitofrontal cortex (OFC) in depressed patients.^{2,3} These observations are supported by findings of structural magnetic resonance imaging studies, which have found reduced volumes of the OFC in these patients.⁴⁻⁶ This consensus has provided a unique opportunity to examine the relationship between neuroimaging findings and psychiatric diagnosis. This examination could help us understand whether changes in the patterns of brain activation are the cause or effect of psychiatric symptomatology. A

causal relationship would open the possibility of using neuroimaging for diagnosis of psychiatric conditions at preclinical stages. These data could be used for prognostic evaluation if their association with the effect could be established.

In this context the study conducted by Abe and colleagues⁷ is revealing. The authors found reduced regional cerebral blood flow (rCBF) in the OFC of perimenopausal women who had climacteric symptoms but no depression. Because reduced rCBF of the OFC is the most frequent finding in depressed patients, the observation of Abe et al indicates that climacteric women may have subclinical depression, particularly because clinical depression is common in the late stages of climacteric⁸ and because depressed patients share a number of symptoms with climacteric women. These symptoms include insomnia, excessive fatigue, and irritability.⁹ If it is established that climacteric women have subclinical depression, the study by Abe and colleagues may have important clinical implications because of the uncertainty concerning the pathophysiology of depression in climacteric women. It has been suggested that the depression in these women is causally related to hormonal changes in the perimenopause period.¹⁰ This suggestion is based on the known effects of estrogen on the brain neurotransmitter systems. Its effect on serotonergic transmission is considered particularly protective against depression.¹¹ In support of the hormonal theory, investigators have reported significant improvement in depressive symptoms after hormonal therapy.¹⁰ Furthermore, recent studies have found that new-onset depression in perimenopausal women and changes in hormonal levels are positively correlated.¹¹

There are, however, a number of studies that have reported lower incidence of depression in women 5 years after menopause, indicating that the altered hormonal levels do not necessarily cause depression.⁸ In addition, epidemiologic data suggest that depression in perimenopausal women is independent of

hormonal changes.^{12,13} Many investigators have therefore suggested that changes in life events are more important determinants of depression in climacteric women than the hormonal changes.¹³ The uncertainty concerning the pathophysiology of depression in perimenopausal women makes the study of climacteric symptoms more relevant, and the finding of neural signatures of depression in climacteric women who are not clinically depressed is revealing.

A number of studies have reported reduced rCBF in the OFC of depressed patients.^{2,3} Abe et al have found a similar reduction in climacteric women who do not meet the criteria for diagnosis of depression. The presence of neuroimaging findings of depression in patients who are not clinically depressed raises an interesting question concerning the relationship between neuroimaging data and psychiatric symptoms. Because psychiatric diagnoses are based on symptoms and not on neural pathology, it is unclear which symptom(s) of a psychiatric patient drive neuroimaging changes.

Thus, it is not known which symptom or symptoms (ie, depressed mood, insomnia or hypersomnia, excessive fatigue, loss of appetite, abulia) of depressed patients are responsible for the classic neuroimaging finding of depression (reduced rCBF in the OFC). Because climacteric patients share some symptoms⁹ with depressed patients (eg, excessive fatigue and insomnia), it is possible that the rCBF changes observed by Abe et al are associated with one or more of the symptoms that are common in the two groups and not with depression per se. In this context the finding of reduced fluorodeoxyglucose uptake in the OFC of patients with chronic fatigue syndrome is important.¹⁴ If excessive fatigue (or its consequences) is responsible for reduced OFC activity, the reduction reported by Abe et al and investigators who have studied depression can be characterized as a nonspecific finding driven by fatigability. This argument, however, has a number of problems, particularly because patients with chronic fatigue syndrome have a high comorbid incidence of depression and because these patients respond favorably to a variety of antidepressant agents.^{15,16} It is therefore difficult to rule out the possibility of underlying subclinical depression in these patients. Similarly, climacteric women who participated in the study by Abe et al may also have subclinical depression, particularly because women who develop climacteric symptoms have a higher incidence of depression compared to those who do not develop these symptoms.¹² Despite the problems

associated with subclinical depression in these patients, the possibility that neuroimaging changes in the study of climacteric and depressed patients are driven by a specific symptom (and not by the respective disorder) needs serious consideration. It would be interesting to explore this possibility by conducting a longitudinal study to determine whether climacteric women who participated in the study develop clinical depression later in their lives.

Another issue that needs consideration is the correlation of altered rCBF with cognitive deficits. Patients with climacteric symptoms, depression, and chronic fatigue syndrome all have impaired memory,^{9,17,18} and the OFC is an important element of the neural network that mediates aspects of human memory.¹⁹⁻²¹ It is therefore possible that changes in the OFC are related to this cognitive deficit and not to the diagnoses of depression, climacteric symptoms, or chronic fatigue syndrome. The problem of isolating a factor or factors that are responsible for changes in neuroimaging experiments is particularly difficult in clinical neuroimaging experiments because patients often present with multiple deficits. This difficulty is particularly apparent in the study that Abe and colleagues have conducted. Because the study included climacteric women who have a variety of symptom clusters, it is almost impossible to conclude which symptom or symptom cluster is responsible for reduced rCBF in the OFC.

Another issue that complicates interpretation of clinical neuroimaging data is the difficulty of isolating changes that reflect the cause of the disorder (structural or functional changes in the concerned area) and those that are results of the effects (behavioral, affective, or cognitive changes) of the disorder. It is therefore difficult to conclude whether the changes reported by Abe et al reflect the neural pathology that is responsible for climacteric symptoms. These changes could simply be due to relative inactivity of OFC, caused by the lack of normal behavioral or cognitive activities in climacteric patients.

Interpretation of neuroimaging data is particularly difficult when psychiatric symptoms are involved because of uncertainty about the neural pathology associated with psychiatric conditions. This uncertainty is further complicated by the possibility that a single psychiatric condition (depression, for example) may have multiple distinct neural pathologies that produce similar patterns of symptomatology that meet the criteria for diagnosis of a psychiatric condition. Careful interpretation of neuroimaging

data is therefore key to acceptable and reproducible conclusions that can help us understand the neural bases of disorders. This understanding could pave the way for the use of neuroimaging techniques for the diagnosis of subclinical cases and for objective prognostic evaluation of psychiatric conditions.

Thus, the study by Abe et al has raised a number of important questions concerning the relationship between neuroimaging data and symptomatology. These questions need to be addressed before the significance of the findings of this and other similar studies can be appreciated. Only after these questions are answered can the findings of neuroimaging experiments be put to clinical use for diagnostic or prognostic evaluation.

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