The bipolar spectrum: consequences for neurobiology

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Abstract

There is an increasing interest in whether there is a commonality in the observations seen in MRI neuroimaging of a number of conditions, all of which are related to the affective disorders. These four conditions include untreated depression, bipolar disorder, post-traumatic stress disorder, and borderline personality disorder. If such a commonality in MRI findings can be confirmed by a careful meta-analysis, then these common findings may point to a spectrum of affective disorders which is broader than has been suggested until now and, in particular, may end the controversy as to whether borderline personality disorder is in, fact part, of the bipolar spectrum. Such considerations argue for the development of new classification systems, which are based not simply on symptoms but also on neurobiology.

Key words: bipolar disorder, unipolar depression, borderline personality disorder, post-traumatic stress disorder, neurobiology, MRI.

It is almost unequivocal that patients with untreated unipolar depression have reduced hippocampal volume. Sheline et al. (1) demonstrated that a prolonged period of depressive episodes untreated with antidepressant medication is associated with a significant decrease in hippocampal volume. This is one of the most replicated findings in unipolar depression. However, multiple individual studies have challenged the possibility of similar findings in bipolar depression. The majority of studies have shown preserved hippocampal volumes in those with bipolar disorder, in apparent contradiction to the observed impairment in declarative memory processing in both symptomatic and euthymic adult patients with bipolar disorder. Until quite recently, the majority consensus was that there were insignificant changes in the hippocampal volume of bipolar patients. Hajek et al. (2), in his recent meta-analysis involving 101 patients with bipolar disorder, found that hippocampal volume changes in bipolar disorder patients are dependent on their exposure to lithium. In the lithium-treated group, both left and right hippocampal volumes were observed to be significantly larger than in controls or in the non-lithium group, which showed marked decreases in both the left and right hippocampal volumes compared to that of the control group (3,4).

Similarly, magnetic resonance imaging (MRI) of post-traumatic stress disorder (PTSD) patients revealed a smaller hippocampal volume in these patients who were exposed to combat as well as childhood abuse (5). It is not surprising that brain areas implicated in the stress response, such as the amygdala and prefrontal cortex (as well as the hippocampus) are seen to be involved in depression (6). The somewhat congruous findings of neurobiological changes in unipolar and bipolar depression as well as PTSD may support the proposal that these disorders lie on the same spectrum.

The next question that arises is the relationship between bipolar disorder and borderline personality disorder. A modest interrelationship has been noticed where the diagnosis of combined bipolar disorder is significantly more common in borderline personality disorder patient groups than in other personality disorder groups (19.4% vs. 7.9%). When analysing anatomical changes occurring in the course of borderline personality disorder, Soloff et al. (7) identified that these patients had significant bilateral reductions in grey matter concentrations in the ventral cingulate gyrus and several regions of the medial temporal lobe, including the hippocampus, amygdala, parahippocampal gyrus and uncus. A gender bias was also noted amongst borderline personality disorder patients: women had marked reduction in the medial temporal lobe, including the amygdala, whereas men displayed

diminished grey matter concentrations in the anterior cingulate gyrus compared to healthy controls. The diminished grey matter in the prefrontal cortex and medial temporal lobe may functionally explain the dysregulation of impulse and affect observed in borderline personality disorder (7). This may also explain Benazzi's concept of 'affective instability' and 'impulsivity' which is pathognomonic of borderline personality disorder (8). Furthermore, these neuroanatomical changes observed in borderline personality disorder highly reflect the changes observed in bipolar disorder, perhaps explaining the relationship between the incidence of the two disorders described earlier and somewhat supporting the school of thought proposing that borderline personality disorder is a form of bipolar disorder which is unstable between episodes (9). As well as the hippocampal changes, borderline personality disorder patients also show smaller amygdala volumes and an increase in the size of the putamen (10,11). It is suggested that the latter may be a result of substance abuse which is common in many of these patients (12).

These findings indicate that the four conditions: unipolar depression, bipolar affective disorder, borderline personality disorder (12-14) and post-traumatic stress disorder (15-17) share a commonality – that of a reduced hippocampal volume on MRI. This has been supported by multiple studies involving MRI identification of neuroanatomical changes in these conditions (2-4,7,10,11). The amygdala is also seen to be involved in these disorders (18). Consistency in the result of these studies may imply important biological similarities underlying these conditions. This proposal also appears to be supported by evidence that the size of the hippocampus can be improved by treatments such as SSRIs, lithium and valproate in all these conditions.

A frequently featured trigger in all these conditions is stress. Frodl et al. (19) have previously analysed the mechanism in which stress, through its effect on the hypothalamo-pituitary-axis, its modulation of cortisol levels and effect on glucocorticoid receptors, influences not only the size of the hippocampus but also the balance between the trophic (BDNF and in bipolar disorder, Bcl-2 and BAG-1) factors and atrophic factors in the cells. This suggests a common mechanism in all these conditions where stress is a common causative factor (20).

The commonalities between psychiatric disorders are beginning to surface with discovery of multiple genes involved in their pathogenesis. It has long been stated that the principle of major 'psychotic' mental illnesses have polygenetic causes, each with small effects on the disorder (21). Certain genes such as the SERT, COMT and BDNF, with their polymorphisms have been identified to be common to all the disorders considered in this article.

In addition, there have been studies suggesting epigenetic regulation of genes as a possible link between depression, childhood adversity and suicidality, all of which are pertinent characteristics in the conditions described (22-26). Similar neuroanatomical changes, i.e. reduced hippocampal volume and pathophysiological responses to stress, were identified in patients with depression, a higher propensity to depression, PTSD and borderline personality disorder who have suffered abuse or childhood adversity, and in some war trauma cases (10,15,27-30). This further supports the possibility of these environmental factors interacting with the mechanisms of gene expression in the conditions being discussed.

There is substantial evidence suggesting the inter-relationship between the four conditions discussed in the article. The similar neuroanatomical changes as well as common biochemical mechanisms of stress and genetic causes appear to support this proposal. The heterogeneity of mood disorders could be a manifestation of their origin in multiple dysfunctional brain regions – the amygdala, nucleus accumbens, hippocampus, prefrontal cortex and cingulate cortex (31). SSRI and lithium-induced neurogenesis in the hippocampus of patients with the conditions described further support the concept of a spectrum of psychotic illness (2-4,31-33). These few final observations of comparable neuroimaging results as well as a comparable relationship in neurogenesis, combined with clinical observations and the impact of environmental factors as triggers, seem to support the argument for including borderline personality disorder in a spectrum of illness ranging from unipolar depression to that of bipolar I affective disorder, which can be termed a 'small hippocampus syndrome'. Such a group of disorders with similar neurobiology could suggest that it is now possible to develop a classification

of mental illness based on similarities in neurobiology, rather than being simply based on symptom clusters. Indeed, symptoms should be in future classifications, linked with neurobiology.
One further issue arises when considering neuroimaging findings in the bipolar spectrum. Bipolar illness is accompanied by some loss of grey matter in the cerebral cortex (34). Is there less loss of grey matter in bipolar II disorder than bipolar I? We have found only one paper, from Korea, which sheds light on this question (35). In this paper, it was reported that high-resolution magnetic resonance brain images were taken from 23 bipolar II patients, 23 sex-matched and age-matched patients with bipolar I disorder and 23 healthy controls. Both the bipolar II and bipolar I groups showed grey matter deficits in the ventromedial prefrontal regions, compared to controls. The bipolar I group had widespread grey matter reductions in bilateral frontal, temporal, parietal and parahippocampal cortices, compared to controls, but grey matter reductions in these regions were not found in the bipolar II group. Also, the bipolar II group showed additional grey matter deficits in the anterior limbic cortices. Thus, the different patterns of grey matter abnormalities in bipolar II and bipolar I found in this study suggest that the two subtypes may have different neurobiological characteristics, which supports the concept of a bipolar spectrum between these two conditions. It is necessary, however, that this study be replicated, since the numbers were small.

GP Comment

What have I learned from this paper?

In the last years there has been a relevant debate about whether there is a common spectrum in all four main affective disorders as they show neuroimaging similarities. These include: untreated depression, bipolar disorder, post traumatic stress disorder, and borderline personality disorder. The last of these may be included, despite controversies. There is a need of a new classification system.

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