findings presented here by Huang et al. refute this explanation: they show that a depolarized resting membrane potential (either through heterologous expression of mutant channels or direct current injection using dynamic clamp) leads to increased dorsal root ganglion cell excitability. As the authors carefully discuss, it is not easy to reconcile these differing findings/interpretations. It is possible that insensitivity to pain due to the L811P mutation does not relate to an altered resting membrane potential, but to the marked shift in channel gating that although causing hyperexcitability, ultimately leads to fatigue of these neurons.

Notwithstanding some of these challenges in ascribing clinical phenotype to channel biophysics it is clear that gain of function mutations in Na\textsubscript{1.9} can cause neuropathic pain in humans. We do not yet know whether these mutations are fully penetrant and whether [as has been shown for Na\textsubscript{1.7} (Persson et al., 2013)] these mutations have an active role in promoting axon degeneration. Mutations in Na\textsubscript{1.7}, 1.8 and 1.9 have now all been associated with painful neuropathy as a consequence of dorsal root ganglion cell hyperexcitability and as such are targets for the development of novel analgesics, which may have the added advantage of also being disease-modifying.

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Clinical and pathogenetic implications of occipital bending in depression

The lifetime prevalence of major depressive disorder is \(~16.5\%\) and, each year, \(~800 000\) individuals worldwide die as a result of suicide, a high proportion of whom suffered from severe depression. Even with treatment, 20% of patients experience chronic symptoms, meaning that major depressive disorder accounts for a greater number of years lived with disability than any other illness. A combination of genetic susceptibility, chronic stress and developmental factors predispose to depression by triggering alterations in neuroplasticity, biochemistry, and brain structure. As illustrated by a recent meta-analysis, structural brain changes predominantly affect the lateral ventricles, basal ganglia, thalamus, hippocampus and frontal lobes (Kempton et al., 2011). In this issue of Brain, Maller et al. (2014) reveal that structural changes also extend to the occipital lobes, with ‘occipital bending’—in which one occipital lobe wraps around the other—three times more prevalent in patients with treatment-resistant major depressive disorder than in healthy controls.

Bending or asymmetry of the occipital cortex has not been examined in major depressive disorder before. However, it is worth noting that although the occipital cortex is not among the core regions that exhibit structural changes in major depression, alterations in biochemistry, white matter structure, resting state connectivity and grey matter volume have previously been reported in the occipital lobes in this disorder (Bhagwagar et al., 2007; Grieve et al., 2013; Liao et al., 2013; Meng et al., 2014). A comprehensive meta-analysis identified the right occipital lobe,
with the inferior fronto-occipital fasciculus as its major connecting fibre tract, as one of the most consistently reported locations of decreased white matter integrity in patients (Liao et al., 2013). Reductions in the volume of the occipital lobes—particularly midline regions—have also been described (Grieve et al., 2013). Hence, there is reason to believe that the increase in occipital bending in major depressive disorder is related to these previously reported alterations in occipital lobe structure and function; this should be investigated further through studies that combine different imaging modalities.

The results of Maller and colleagues raise additional questions. First, what are the mechanisms underlying this increased prevalence of occipital bending in major depressive disorder? And second, what is its clinical relevance? With regards to the first question, Maller et al. (2014) propose that ventricular enlargement may be one mechanism underlying increased occipital bending. Ventricular enlargement is among the most frequently reported structural alterations in major depressive disorder (Kempton et al., 2011) and may exacerbate the natural curvature of occipital cortex. Maller et al. did not measure ventricular volume directly, but they did find CSF volume to be increased in patients, significantly in males and non-significantly in females. Whether increased occipital bending represents a mere ‘side-effect’ of another pathological process such as ventricular enlargement, or has psychopathological relevance in itself remains, however, to be determined. Notably, increased occipital bending has also been reported in schizophrenia (Deutsch et al., 2000), which is known to feature significant and, most probably, progressive ventricular enlargement. This indicates that the two parameters may be related or may share a common origin. Brain alterations in schizophrenia are thought to reflect in large part disturbed neurodevelopmental processes. Major depression, on the other hand, is not generally seen as a disorder of neurodevelopmental origin. However, studies have linked stress, such as famine during a critical gestational period, to the manifestation of major depressive disorder. For instance, Brown et al. (2000) compared the risk of major affective disorder in birth cohorts who were and were not exposed, in each trimester of gestation, to famine during the Dutch Hunger Winter of 1944–45. They found that the risk of developing a major depressive disorder was significantly increased for those exposed to famine during the third trimester of gestation, which represents a critical period in brain development. These studies indicate that alterations in white and grey matter structure, and potentially gross anatomical changes such as increased occipital bending, may result from early neurodevelopmental alterations. Altered grey matter structure in patients with a first episode of major depressive disorder points to a similar conclusion (Zou et al., 2010).

It should not go unnoticed, however, that Maller et al. observed occipital bending in 12% of healthy controls, too. This result, together with the increased prevalence of occipital bending in patients with treatment-resistant major depression, implies that occipital bending could be a vulnerability marker for a predisposition to major depression. This predisposition may result in a manifest illness if further environmental triggers such as chronic stress or adverse developmental conditions are experienced. On the other hand, the observation that female patients with occipital bending show more severe depression than those without occipital bending, suggests that in patients with a manifest depression, occipital bending may indicate a more severe and chronic subtype of the illness. It is plausible that patients with distinct, potentially neurodevelopmental, structural alterations develop a more severe form of depression than those for whom environmental factors contribute more to their pathogenesis. This hypothesis, however, must be substantiated by further studies, especially as the duration of illness—as well as other factors accompanying a chronic illness that may also affect brain structure, such as long-term medication use—were not reported in the current study. Moreover, this association, if valid at all, would only apply to female patients, as there was no difference in depression severity between those with and without occipital bending across the patient group as a whole.

As an alternative hypothesis, it is conceivable that occipital bending may not be specific for major depressive disorder, but may instead be a parameter signalling an increased vulnerability to affective or psychotic disorders in general. The current results, in association with the increased prevalence of occipital bending in schizophrenia, seem to support this assumption. But as little is known about the prevalence of occipital bending in other psychiatric disorders, this hypothesis needs further investigation. As the assessment of occipital bending is simple, further studies in different psychiatric populations and supplementary studies in patients with major depression should be easy to implement. Should occipital bending—perhaps in association with additional parameters—be identified as a structural marker for an increased vulnerability to affective or psychotic disorders or, more specifically, as an indicator of an increased predisposition to more severe forms of major depression, examination of occipital bending would provide new possibilities for early recognition and intervention. In this case, the findings of Maller and colleagues will give depression therapy and research a new direction. However, further studies combining different methods and study designs are necessary to increase our understanding of the mechanisms underlying the emergence of occipital bending and its clinical relevance.

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