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CORRESPONDENCE

The role of the dentate gyrus in stress-related disorders

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To the Editor:

In this journal, the effects of 5-week electroconvulsive therapy (ECT) on hippocampal subfield volumes in patients with major depressive disorder (MDD) were recently reported [1]. Using high-resolution structural MRI scans at 7T, Nuninga and colleagues showed that ECT in MDD patients resulted in increased bilateral dentate gyrus (DG) volumes, which was positively associated with clinical improvement. The authors suggested that increased DG volumes after ECT may reflect adult neurogenesis. In line with this suggestion, animal chronic stress models of depression and anxiety show impaired neurogenesis, which improves after ECT and antidepressant medication (see ref. [2] for a review). This led to the neurogenic theory of depression and anxiety, postulating that stress-related disorders result from impaired neurogenesis, and that restoring neurogenesis leads to recovery [2, 3]. Human studies provide indirect evidence for this theory: smaller DG volumes are observed in patients with stress-related disorders, including depression [4, 5], anxiety and posttraumatic stress disorder (PTSD) [6]. Furthermore, medicated MDD patients show larger DG volumes compared to unmedicated MDD patients [7]. The longitudinal study of Nuninga and colleagues is the first to show increased DG volumes after ECT in depressed patients, thereby providing important insights into neural mechanisms underlying treatment efficacy in stress-related disorders. However, the current report also raises several interpretational issues, and more importantly, opens the way for improving future research into the role of the DG in stress-related disorders.

Although the findings of Nuninga and colleagues are promising, several interpretational issues remain. The first question is whether there is a baseline (pre-treatment) difference in DG volumes between MDD patients and control participants (DG volume patients: 792.59 mm^3 vs controls: 869.77 mm^3). Unfortunately, no statistical tests were reported for this group comparison. However, we note that the magnitude of this group difference (77.18 mm^3) is comparable to that of the significant DG volume difference between baseline and exit in patients (75.44 mm^3). Furthermore, DG volumes in MDD patients seem to be normalized to the same level as healthy controls after ECT (DG volume controls at baseline: 869.77 mm^3 vs patients post-treatment: 868.03 mm^3, no statistical tests are reported). Given this potential group difference, as well as the possible normalization of this difference, statistically demonstrating group differences before and after treatment would have greatly facilitated the interpretation of ECT effects. However, we acknowledge that statistical testing of group differences in DG volumes is hampered by the small sample size of the control group ($n = 8$). The second question is whether baseline DG volumes are associated with pre-treatment symptom severity. The authors did not report this, nor did they correct for baseline symptom severity in the linear regression analysis showing that baseline DG volumes predict clinical treatment response. Therefore, the question remains whether this observation of baseline DG volumes predicting clinical treatment response can be (partly) explained by an association between DG volume and symptom severity at baseline. A third question arises from the fact that the linear regression analysis shows opposite effects for left and right DG volumes: whereas left DG volume at baseline is negatively associated with change in depression symptom severity, right DG volume at baseline shows a positive relationship. Again, interpretation of these abovementioned finings is complicated by the small sample size (23 patients and 8 controls), which is

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acknowledged by the authors. The effect size that was detected for pre vs post treatment comparison in the control group was 0.521. Our power calculation shows that to achieve 80% power, a sample size of 31 is required. Alternatively, with the sample size of 8 the study only achieves 25% power. Taken together, these interpretational issues call for well-powered prospective longitudinal studies to investigate whether smaller DG volumes represent a cause or consequence of stress-related disorders, thereby improving insights into neural mechanisms underlying stress vulnerability, resilience and treatment efficacy.

Findings of the current report have important implications for future research on the role of the DG in the pathophysiology and treatment of stress-related disorders. The findings of Nuninga and colleagues add to previous suggestions of smaller DG volumes in patients with stress-related disorders, which should be targeted by effective treatments. However, it remains an important research question whether smaller DG volumes in patients with stress-related disorders represent a predisposing vulnerability factor, or reflect a consequence of chronic stress and/or symptom development. On the one hand, smaller DG volumes in patients with stress-related disorders could result from chronic stress, which has been shown to suppress adult neurogenesis in the DG [5]. In line with this suggestion, MDD patients reporting more depressive episodes showed relatively smaller DG volumes, suggesting the effects of stress exposure on reducing DG volumes [8]. On the other hand, smaller DG volumes may also represent a vulnerability for developing stress-related psychopathology. For example, a recent animal study showed that suppression of neurogenesis in the DG increases stress vulnerability [9]. Likewise, less hippocampal activity in recently trauma-exposed Emergency Department patients predicted onset of trauma-related symptoms after three and six months [10] following trauma exposure. Presumably, smaller DG volumes in stress-related disorders represent a complex interaction between predisposing vulnerability effects, which are amplified by subsequent chronic stress exposure and disease duration. In order to disentangle these predisposing effects from acquired effects, large prospective longitudinal studies are required, as well as large collaborative efforts in which longitudinal data of multiple cohorts are combined.

The second research avenue pertains to the functional consequences of increased DG volumes after ECT in MDD patients. Whereas the authors showed that ECT-induced increases in DG volumes are positively associated with symptom improvement, how these neural effects influence cognitive and affective functioning remains unknown. The DG plays a crucial role in pattern separation, or the process of storing similar memories as separate events. Pattern separation is impaired in patients with stress-related disorders, and has been suggested to underlie fear overgeneralization in these patients [11, 12]. Notably, converging evidence from rodent studies showed that pattern separation is impaired after ablation of adult DG neurogenesis (i.e., using X-ray irradiation to remove young DG granule cells) [13], and is improved by enhanced hippocampal neurogenesis [14], by modulating excitability in the DG [11]. The findings of Nuninga and colleagues offer the exciting possibility that ECT results in improved pattern separation via enhanced adult DG neurogenesis. Future research in patients with stress-related disorders should incorporate pattern separation and/or fear generalization measures, which can be associated with symptom severity measures, as well as DG-volumes, to directly test this relationship.

To conclude, we hope that the findings of Nuninga and colleagues serve as a stepping stone for future large-scale studies and collaborative efforts to elucidate the role of the DG in stress-related disorders. This may not only improve insights into neural mechanisms underlying treatment for these disorders, including the effects of antidepressants and ECT, but may also enhance causal and mechanistic understanding of individual differences in stress vulnerability and resilience, as well as the consequences of chronic stress and disease duration.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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