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The Dentate Gyrus: Its Value for Depression

Jasper O. Nuninga and Iris E.C. Sommer

In this issue of *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, van Dijk *et al.* (1) report higher mean diffusivity (MD) as measured with diffusion-weighted imaging in the dentate gyrus (DG) of people who are at high risk for depression compared with their peers at normal risk. Higher MD in the DG predicted symptoms at 8 years of follow-up and it partially mediated the relationship between risk status and future symptoms. Higher MD was not associated with current or previous symptoms. Their study had a large sample size ($n = 102$) and participants were followed over a long period of time (≤ 38 years), making these strong and convincing findings.

The authors interpret these findings as suggesting that differences in MD in the DG are a risk factor for depression and not a consequence of the disease. In addition, they propose that decreased neurogenesis is the biological process responsible for the high MD values. As MD, measured with diffusion-weighted imaging, reflects the free diffusion of water molecules in tissue, it may well be that decreased neurogenesis, resulting in a less dense DG, is indeed reflected in higher MD values. Decreased axonal density, dendritic branching, and synaptic density, however, may also contribute to differences in MD. In line with this, it should be noted that neurogenesis yields more widespread neuroplastic changes throughout the hippocampus, as immature and mature adult-born neurons send their axons to the CA3 layer of the hippocampus, and their dendrites to the entorhinal cortex, in order to functionally integrate in the hippocampal network in 8 weeks' time (in rodents). Furthermore, the authors used validated segmentations of the hippocampus; however, accurate delineation of hippocampal subfields plus alignment with diffusion-weighted imaging scans is challenging.

Although MD is a sensitive yet nonspecific measure, the results of van Dijk *et al.* (1) are in line with preclinical evidence showing a link between neurogenesis and depression. Specifically, preclinical studies showed that decreasing neurogenesis in the rodent DG is able to induce depression-like symptoms, and conversely, increasing neurogenesis in the DG is able to alleviate depressive behavior (2). Such evidence sparked the formulation of the neurogenic hypothesis of depression: depression is caused by aberrant neurogenesis and restoring neurogenesis would alleviate depression. The finding that MD is associated to risk status and can predict symptoms at 8 years of follow-up is an important clue in unravelling the pathogenic puzzle of depression. However, whether decreased neurogenesis is necessary (and sufficient) to induce a depressive state and whether increased neurogenesis is sufficient (and necessary) to counteract the depression remains an unresolved question (3). Furthermore, it

also remains a question what factors cause neurogenesis to decrease.

In line with the study of van Dijk *et al.* (1), other studies investigating the role of neurogenesis, and neuroplasticity in general, in both the pathogenesis and the treatment of depression in humans confirm the role of neurogenesis/neuroplasticity in depression. For example, electroconvulsive therapy (ECT) is a potent neurogenesis-enhancing treatment in rodents (4). Other neurogenesis stimulators, such as exercise (running) and dietary interventions (intermittent fasting/caloric restriction), might also prove to be useful in treating depression by inducing neuroplastic changes and survival of neurons (5). In an effort to translate preclinical ECT findings to humans, we reported that the volume of (only) the DG significantly increased after a series of 10 ECT sessions (6). Interestingly, using the same sample, we found that ECT decreased MD values in the hippocampus (7), again suggesting a role of neurogenesis/neuroplasticity in depression and its treatment.

However, these studies are indirect (i.e., neurogenesis and neuroplasticity were not directly observed), and the timeline of antidepressant action and neurobiological changes during treatment remains elusive. For example, do the neurobiological changes of volume increases and MD decreases precede the antidepressant effect or are they a consequence of it (or maybe just an epiphenomenon)? Because experimental studies of inducing or preventing neurogenesis in humans are, for obvious reasons, ethically problematic, making a detailed timeline might tell us more about the significance of volume and diffusivity changes in the treatment and pathogenesis of depression. Furthermore, more direct measures of neurogenesis such as advanced magnetic resonance spectroscopy might prove useful in the future for building a clearer picture of the role of neurogenesis in the pathogenesis and treatment of depression.

Although accumulating evidence suggests an important role for neurogenesis and neuroplasticity in depression, depression is a heterogeneous disorder with a complex interplay of causal mechanisms in the biopsychosocial domain. It could be that some (if not all) forms of depression will (in part) be due to decreased neurogenesis and that especially these types of depression will benefit from neurogenesis-enhancing treatments. If this is true, it would be important to study which patients fall in this category and provide them with treatments that are potent neurogenesis enhancers, such as running therapy or (in severe cases) ECT. A potential way to determine whether a patient is at risk for developing a depressive disorder due to decreased neurogenesis might be to test for DG-dependent cognitive processes. Pattern separation (a process enabling

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the ability to discriminate between highly similar events) is largely dependent on the DG. Animal research has shown that decreased neurogenesis leads to impaired pattern separation and that increased neurogenesis leads to improved pattern separation (8). The evidence is less direct for humans, yet studies do show that pattern separation and hippocampal/DG function are related (9).

In humans, pattern separation can be reliably measured with tasks such as the Mnemonic Similarity Task (10). Using the Mnemonic Similarity Task, researchers could set out to investigate 1) whether neurogenesis in humans and pattern separation are indeed closely related (possibly using MD and volumetric measurements of the DG), 2) whether pattern separation could serve as a proxy for decreased neurogenesis as biomarker for an at-risk status, and 3) whether pattern separation has predictive value for potent neurogenesis enhancing treatments for depression (e.g., exercise). If this turns out to be true, treatments that stimulate neurogenesis could be targeted to those who show DG dysfunction. Accurate prediction is much needed, especially for treatments that are demanding and that have a risk for side effects, like ECT. Being able to target only those patients who have a high chance of recovery will prevent the huge disappointment that patients experience when they do not respond (and may still have to deal with the side effects).

As outlined above and as shown in the article by van Dijk *et al.* (1), the DG and neuroplasticity in the hippocampus hold great diagnostic and predictive potential for depression. In addition, DG functioning and volume may contribute to providing individual patients with more accurate information regarding their chance of recovery in neurogenesis-enhancing treatments. Furthermore, as more research is directed at the underlying mechanism of volume changes and MD changes, a greater understanding of (one of the) pathogenic pathways to depression in humans is achieved.

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Article Information

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