Biological Psychiatry: Celebrating 50 Years

Commentary

Deficits in White Matter Microstructure in Major Depressive Disorder: Cause, Consequence, or Correlate?

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Major depressive disorder (MDD) is a common and debilitating psychiatric disorder, and despite considerable efforts, our understanding of the underlying neurobiology remains incomplete. Neuroimaging provides the opportunity to study the pathophysiology of MDD in vivo, and these studies may identify neural correlates of the disorder that can be used as new treatment targets or used to improve our understanding of how treatment can improve mood.

Cross-sectional neuroimaging studies have revealed alterations in both brain structure and function in MDD patients compared with healthy control subjects [see (1–3) for meta-analyses]. However, these cross-sectional studies have been unable to determine whether these deficits precede the onset of MDD and are a preexisting vulnerability factor for developing MDD, if they reflect the depressive state and normalize with remission (state factor), or if they remain during periods of remission and worsen with every new depressive episode (scar factor) (Figure 1). A distinction can be made in vulnerability factors between stable trait factors, for instance genetic determinants of brain morphology, and brain alterations that precede depression onset but that are the result (scars) of early life adversity, somatic illness, or the presence of other psychiatric disorders, rather than being preexisting stable traits. It is important to distinguish between trait factors, state factors, and scar effects because they may reveal important information about depression-related brain alterations that will advance etiological theories and could guide prevention or intervention strategies. For example, neuroimaging state markers may reflect the acute effect of depression on the brain and may be used to monitor effects of treatment. Stable neuroimaging trait markers, on the other hand, might contribute to the etiology of the disorder, and they reveal which individuals may benefit from prevention strategies before illness onset.

Several types of cross-sectional study designs can provide indirect evidence about whether neuroimaging markers are state dependent, a preexisting vulnerability factor (including stable traits), or a scar of MDD. Examining brain structure and function in unaffected relatives with high genetic risk for MDD may reveal potential trait factors, whereas comparing this between patients in a current MDD episode, patients with remitted MDD, and healthy control subjects may reveal state effects of MDD. Indirect evidence for a scar effect of MDD on the brain may be found in studies showing increasing brain deficits in patients with higher disease duration, number of episodes, or disease load. While cross-sectional studies may provide some indications, the strongest evidence is provided by large longitudinal studies. Assessment of brain function or structure before the onset of depression, during a current episode, and during remission of episodes would be the optimal approach to distinguish vulnerability factors, state-dependent factors, and scar effects.

Large longitudinal studies on MDD and brain morphology are rare, but in the current issue of *Biological Psychiatry*, Shen *et al.* (4) report findings from the largest longitudinal study of depressive symptoms to date. Using data from the UK Biobank study (N = 18,959), Shen *et al.* (4) examined the association of depressive symptoms at the time of scanning and 3 longitudinal measures of depressive symptoms (the mean, the variability, and the slope of the longitudinal trajectory of depressive symptoms) determined at 4 time points over a 6- to 10-year period with a single assessment of white matter microstructure at time point 3. The findings show that alterations in the anterior thalamic radiation, which connects the thalamus with the anterior cingulate and frontal cortices, was associated with current symptoms as well as longitudinal measures of symptom severity, mostly driven by alterations in mean diffusivity. In general, the strongest associations with white matter microstructure alterations were found for longitudinal progression of depressive symptoms. Alterations in the association fibers, on the other hand, were particularly linked with current depressive symptoms (after correcting for longitudinal symptom measures), whereas alterations in projection fibers were mainly associated with greater mean and within-subject variance across time points (after adjusting for the cross-sectional symptom measure).

The observation that longitudinal progression of symptoms showed overall stronger associations with white matter microstructure across the different fibers compared with current depressive symptoms and longitudinal mean and variability of symptoms may suggest that white matter alterations are a result of worsening symptoms over time (i.e., scar effect). Nonetheless, alterations specifically in association fibers may represent state-related deficits because they were associated with depressive symptoms at time of the imaging assessment over and above associations with longitudinal measures, indicating that these regions are particularly sensitive to temporary variations. In contrast, alterations in projection fibers showed a relationship with longitudinal mean and variability of symptoms over and above the cross-sectional symptom measure; therefore, Shen *et al.* (4) interpreted these findings as alterations associated with trait features of depression.

This study provides important new insights on how white matter microstructure is related to current and dynamic changes

SEE CORRESPONDING ARTICLE ON PAGE 759

https://doi.org/10.1016/j.biopsych.2019.08.024
Biological Psychiatry November 15, 2019; 86:734–735 www.sobp.org/journal
ISSN: 0006-3223

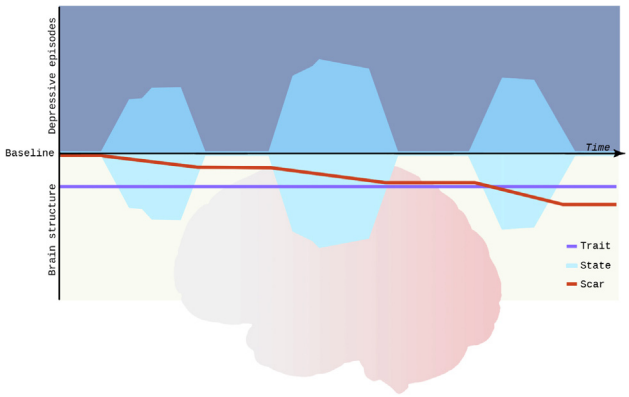

Figure 1. Trait, state, and scar effects on brain structure in major depressive disorder. The light blue shading in the upper panel shows the occurrence of depressive episodes over time, while the lower panel illustrates changes in brain structural measures that fluctuate with the depressive episodes (state effects), those that precede the onset of depressive episodes and remain stable over time (trait effects, purple line), and those that are a consequence of depressive episodes and worsen with each new episode (scar effects, red line).

in depressive symptoms and preliminary insights on depression-related white matter deficits in light of state, trait, and scar effects. However, because the study included only a single imaging assessment and no longitudinal data on changes in white matter over time, it remains unknown whether the observed deficits normalize with remission (state effects), and whether these deficits were already present before the onset of depressive symptoms (as stable traits or as scars, such as from earlier episodes of depression, previous negative life events, or preexisting illnesses). Furthermore, the mean of depressive symptoms across multiple clinical assessments may not be an appropriate measure to assess trait effects. The mean depression level was calculated as the average of the Patient Health Questionnaire-4 (PHQ-4) total score over 2 or more (out of 4) clinical assessments, with the PHQ-4 assessing severity of depressive symptoms experienced in the last 2 weeks. Depressive disorders often have a relapsing and remitting course, and information on the mean and SD of ≤4 PHQ-4 assessments over a 6- to 10-year period, with each assessment only capturing severity of symptoms in the last 2 weeks, does not adequately account for fluctuations in depressive symptoms commonly observed over such an extended period of time. More detailed data on fluctuations in depressive symptoms over time are required to be able to draw inferences on the stability and variability of depressive symptoms or episodes.

In addition, it is worth mentioning that the study sample included mostly participants with low levels of depressive symptoms. This might explain the relatively low effects observed for associations between white matter microstructure and the various cross-sectional and longitudinal measures of depressive symptoms. Nonetheless, an increasing body of literature suggests small differences in gray and white matter morphology between patients with MDD and healthy control subjects in studies with large sample sizes (1,2,5,6). These small effect sizes could be explained by greater heterogeneity in the depressive phenotype in larger samples or may represent more realistic estimations of the true effects, given that previously observed large effect sizes in smaller samples may be driven by false positives or an overestimation of effect sizes (7). The observation that structural brain alterations may account for only a small percentage of the depression phenotype is perhaps not surprising given the multicausal nature of this highly complex disorder (8).

In conclusion, large neuroimaging studies such as the UK Biobank study provide unique opportunities to examine the heterogeneity of MDD, including heterogeneity in the course of depression as examined by Shen *et al.* (4). This work with an unprecedented sample size is a valuable contribution to the existing literature on white matter microstructure deficits in depression and shows unique associations between specific types of white matter tracts, including association fibers, thalamic radiations, and projection fibers, and the dynamic features of depression, including severity, course, and intrasubject variability of depressive symptoms.

Acknowledgments and Disclosures

This work was supported by the National Institutes of Health Grant No. R01MH116147 (to LS), and a Medical Research Future Fund Career Development Fellowship Career Research Fellowship from the National Health and Medical Research Council (to LS).

We thank Elena Pozzi and Matthew Dobrich for their assistance with the figure.

The authors report no biomedical financial interests or potential conflicts of interest.

Article Information

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Received Aug 29, 2019; accepted Aug 29, 2019.

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