CORRESPONDENCE

Brain Changes in Response to Long Antarctic Expeditions

TO THE EDITOR: Studies in animals have shown that exposure to environmental monotony and social isolation have deleterious effects on the brain, particularly in reducing the generation of new neurons in the dentate gyrus of the hippocampus.[1-3] Whether stressors associated with prolonged isolation lead to similar impairments in brain plasticity in humans is not known. To evaluate the effects of physical and social deprivation on the hippocampus, we conducted a study involving persons who had participated in polar expeditions, which are characterized by environmental monotony and prolonged physical and social isolation.[4]

Our study involved nine polar expeditioners (five men and four women) who lived in Antarctica for 14 months at the German Neumayer III station. We obtained high-resolution T1- and T2-weighted magnetic resonance imaging (MRI) data (Siemens Tim Trio 3T scanner) on eight expeditioners. One of the nine expeditioners could not undergo MRI for medical reasons, and only the brain-derived neurotrophic factor (BDNF) measurements for that expeditioner were used in the analysis. Imaging and other data were obtained before and after the mission to study changes in the volume of subsections of the hippocampus and of whole-brain gray matter. We analyzed cognitive performance and BDNF concentrations in all nine crew members before, during, and after the expedition. To account for biologic variation and effects of aging on brain changes, we obtained longitudinal data from nine controls who were matched with the expeditioners for age, sex, and initial hippocampal volume (Table S1 in the Supplementary Appendix, available with the full text of this letter at NEJM.org). Detailed methods and additional analyses are provided in the Supplementary Appendix.

In the eight expeditioners who underwent MRI, the reductions in the hippocampal volume of the dentate gyrus from before to after the expedition were greater than the changes over 14 months in the controls (mean [±SE] decrease in volume in the expedition group, 32±13 mm^3, equivalent to a 7.2±3% reduction in volume). The volume of other hippocampal regions (the cornu ammonis subfields 1 through 3, subiculum, entorhinal cortex, and parahippocampal gyrus) also decreased, but these changes did not reach statistical significance (Fig. 1A and Table S2). Whole-brain imaging in the expeditioners showed mean (±SE) decreases in gray-matter volume in the left parahippocampal gyrus (3.84±0.72%), right dorsolateral prefrontal cortex (3.33±0.48%), and left orbitofrontal cortex (2.99±0.25%) (Fig. 1B).

After the first quarter of the expedition, the serum BDNF concentrations were lower than the concentrations before the expedition and had

THIS WEEK'S LETTERS

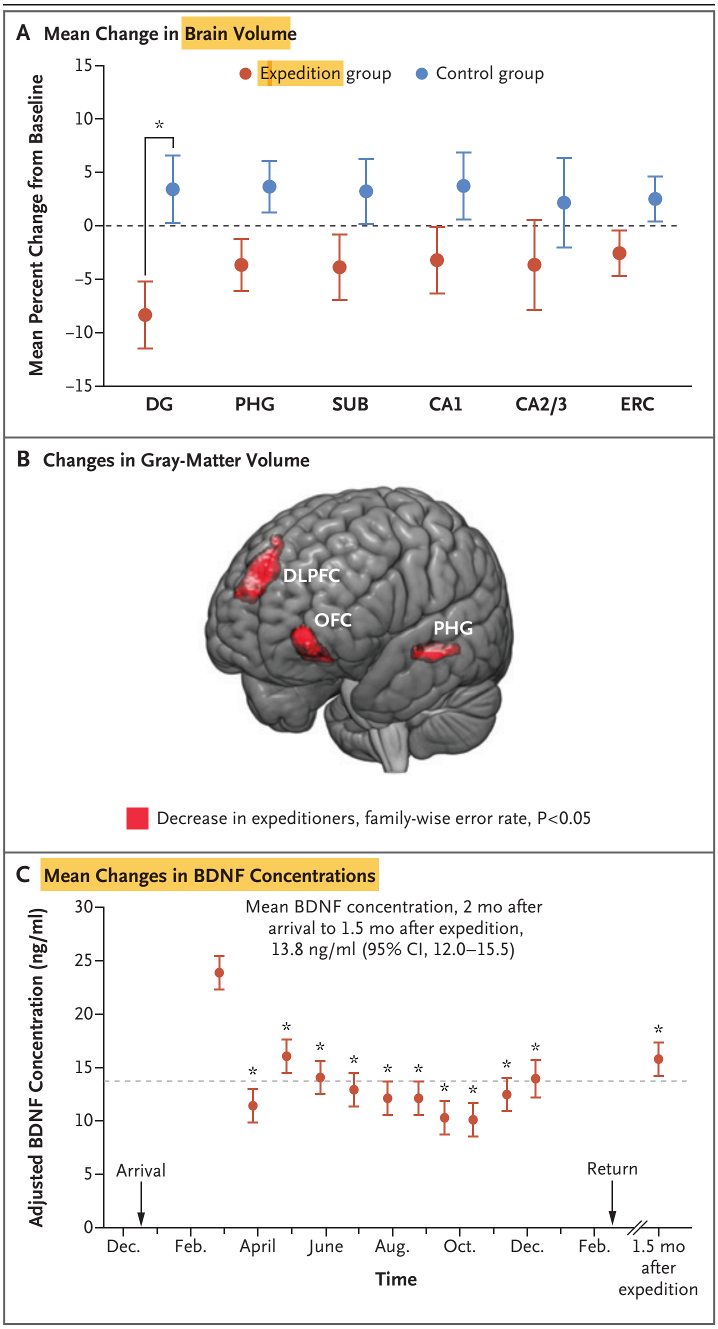

Figure 1. Changes in Brain Volume and Brain-Derived Neurotrophic Factor (BDNF) Concentrations in Antarctic Expeditioners.

Panel A shows changes in hippocampal subfields in eight Antarctic expeditioners and nine age- and sex-matched controls. Mean changes in brain volume were adjusted for changes in cardiopulmonary fitness (maximum oxygen uptake [VO_{2max}]). P=0.02 for the comparison of changes among expeditioners from before to after the expedition. The asterisk indicates P<0.01 for the comparison of changes in dentate gyrus volume between persons in the expedition group and those in the control group. I bars indicate standard errors. CA1 denotes cornu ammonis subfield 1, CA2/3 cornu ammonis subfields 2 and 3, DG dentate gyrus, ERC entorhinal cortex, PHG parahippocampal gyrus, and SUB subiculum. Panel B shows the results of a whole-brain analysis based on T1-weighted magnetic resonance imaging data with the use of voxel-based morphometry. Red regions indicate lower gray-matter volume in the right dorsolateral prefrontal cortex (DLPFC), the left orbitofrontal cortex (OFC), and the left PHG in the expeditioners than in the controls. Data were corrected for multiple comparisons with family-wise error correction (P<0.05) and were adjusted for age, sex, and VO_{2max}. Panel C shows the mean BDNF concentrations during and after the 14-month Antarctic expedition as measured from 115 blood samples obtained from nine expeditioners. Data were adjusted for baseline measurements before the trip to Antarctica. I bars indicate standard errors. BDNF concentrations were significantly lower in the expeditioners while they were in Antarctica (at all time points) than the concentrations at the first data collection after arrival in Antarctica. The asterisk indicates P<0.001 (Bonferroni-corrected for multiple comparisons). CI denotes confidence interval.

not recovered at 1.5 months after the end of the expedition (mean reduction, 11±1.5 ng per milliliter, 45.0±4.9%) (Fig. 1C). Reductions in BDNF concentrations from before to after the expedition were associated with decreases in dentate gyrus volume (R^2=0.47) (Fig. S2). The reductions in dentate gyrus volume were also associated with lower cognitive performance in tests of spatial processing (R^2=0.87) and selective attention (Stroop Incongruent Task) (R^2=0.82) (Fig. S3), but there was no decrease in performance in other cognitive tests such as the Digit Symbol Substitution Test and the Stroop Congruent Task, as noted in the Supplementary Appendix.

Variations in physical and social environments influence hippocampal plasticity.[5] The characteristics of the expedition (i.e., the restriction to a single living and work space, limits on the exposure to varying and complex hippocampus-relevant stimuli, and social interactions that were limited to a small group of people for a prolonged period of time) may have mediated the reductions in BDNF concentrations and related volumetric brain changes. The vulnerability of the dentate gyrus to environmental deprivation, as compared with the vulnerability of other hippocampal subfields, is similar to findings from studies in animals, suggesting possible links among hippocampal neurogenesis, stress-induced behavioral changes, and environmental deprivation.[1-3] Only nine persons were involved in our study, and our data should be interpreted with caution since we cannot determine which elements of the expedition constituted social or environmental deprivation. Other unmeasured or undetected aspects of the experience may also have been involved in the changes observed. Data to determine the mechanisms of the effects of environmental deprivation and social isolation on brain plasticity in humans are lacking.

Alexander C. Stahn, Ph.D.
Hanns-Christian Gunga, M.D.
Charité–Universitätsmedizin Berlin
Berlin, Germany
alexander.stahn@charite.de

Eberhard Kohlberg, M.D.
Alfred-Wegener-Institut
Bremerhaven, Germany

Jürgen Gallinat, M.D.
University Medical Center Hamburg–Eppendorf
Hamburg, Germany

David F. Dinges, Ph.D.
University of Pennsylvania
Philadelphia, PA

Simone Kühn, Ph.D.
Max Planck Institute for Human Development
Berlin, Germany

Supported by grants (50WB1330 and 50WB1525) from the German Aerospace Center.

Disclosure forms provided by the authors are available with the full text of this letter at NEJM.org.

1. Stranahan AM, Khalil D, Gould E. Social isolation delays the positive effects of running on adult neurogenesis. Nat Neurosci 2006;9:526-33.
2. Schloesser RJ, Lehmann M, Martinowich K, Manji HK, Herkenham M. Environmental enrichment requires adult neurogenesis to facilitate the recovery from psychosocial stress. Mol Psychiatry 2010;15:1152-63.
3. Gould E, McEwen BS, Tanapat P, Galea LA, Fuchs E. Neurogenesis in the dentate gyrus of the adult tree shrew is regulated by psychosocial stress and NMDA receptor activation. J Neurosci 1997;17:2492-8.
4. Palinkas LA, Suedfeld P. Psychological effects of polar expeditions. Lancet 2008;371:153-63.
5. van Praag H, Kempermann G, Gage FH. Neural consequences of environmental enrichment. Nat Rev Neurosci 2000;1:191-8.

DOI: 10.1056/NEJMc1904905

Five-Year Outcomes of a Randomized Trial of Treatments for Varicose Veins

TO THE EDITOR: Brittenden et al. (Sept. 5 issue)[1] conclude that disease-specific quality of life 5 years after treatment for varicose veins was better after laser ablation or surgery than after foam sclerotherapy. However, 31% of the patients who underwent laser ablation received one or more sessions of sclerotherapy.[2] Improvement in the condition of these patients was probably attributable to the combination of sclerotherapy and laser ablation and not to laser ablation alone. An analysis should be provided to separately address or exclude these patients in order to allow a clear conclusion.

Since the Food and Drug Administration approved radiofrequency ablation in 1999 and laser ablation in 2002,[3] treatment for varicose veins has shifted from surgery performed in hospitals with general anesthesia to less invasive procedures performed in outpatient clinics with local anesthesia.[4] Also, there has been a shift from the use of one procedure to the use of a combination of procedures tailored to the individual patient. Now, the more important question to answer is which combination of procedures, and not which procedure, gives each patient with varicose veins the best results.

Ayad Jindeel, M.D.
Essentia Health
Duluth, MN
aj1med@aol.com

No potential conflict of interest relevant to this letter was reported.

1. Brittenden J, Cooper D, Dimitrova M, et al. Five-year outcomes of a randomized trial of treatments for varicose veins. N Engl J Med 2019;381:912-22.
2. Brittenden J, Cotton SC, Elders A, et al. A randomized trial comparing treatments for varicose veins. N Engl J Med 2014;371:1218-27.
3. Niedzwiecki G. Endovenous thermal ablation of the saphenous vein. Semin Intervent Radiol 2005;22:204-8.
4. Gloviczki P, Comerota AJ, Dalsing MC, et al. The care of patients with varicose veins and associated chronic venous diseases: clinical practice guidelines of the Society for Vascular Surgery and the American Venous Forum. J Vasc Surg 2011;53:Suppl:2S-48S.

DOI: 10.1056/NEJMc1914045