small hippocampus. For example, small hippocampal volume has only been observed with PTSD arising from the chronic traumas of combat or childhood abuse, but not from PTSD arising from a singular trauma, such as a bad car accident[2]. In line with this heterogeneity, the authors' note that "pre-existing decreased hippocampal volume may only be related to severe and unremitting forms of post-traumatic stress responses."

As a minor glitch, the rate of PTSD in this combat population (42%) is considerably higher than is typical of most combat PTSD studies[12]. Thus, this PTSD population may be unrepresentative, perhaps having been exposed to particularly severe combat trauma. The importance of this difference is unclear.

Two issues are worth mentioning. First, it is possible that stress resulting in hippocampal atrophy might still be pertinent to the development of combat-associated PTSD. A powerful role for stress in causing hippocampal atrophy would come from a particular version of a stress scenario (Scenario 3 in **Fig. 1**). This scenario would predict that independent of the incidence of PTSD, the more severe the combat trauma that veterans are exposed to, the smaller their hippocampi. Such a relationship was not observed in the present report, and this negative finding is pivotal to acceptance of the predisposition model. However, a relationship between the extent of combat trauma and hippocampal volume, independent of PTSD status, was reported by this same group in a prior study of different Vietnam War veterans[13]; the reason for this difference is not clear.

Second, to the extent that a small hippocampus can be a predisposing risk factor for PTSD, the present data suggest that it is not an extraordinarily strong predictor. Figure 3 of Gilbertson *et al.*[6] is a scatterplot diagram of hippocampal volumes in the four groups. Although hippocampal volume in the 'PTSD twins' was significantly smaller than in the 'non-PTSD twins', the overlap was enormous, with 36/40 data points from the latter group overlapping with those of the former.

Obviously, more research is needed, including a replication of this finding, which would help answer some critical questions. For example, should a small hippocampus be viewed as a risk factor for PTSD and thus, like a heart murmur, be an exclusionary factor for some types of military service? Alternatively, does trauma start a race against a clock to prevent the emergence of brain damage once we understand the underlying mechanism? And how is a small hippocampus actually linked to the symptoms of PTSD? Although scientists are sometimes criticized for "knowing more and more about less and less" and losing themselves in intricate puzzles of no use to anyone, these questions are not merely academic. It is therefore satisfying to see such a dramatic intersection of the scientifically fascinating with the scientifically important.

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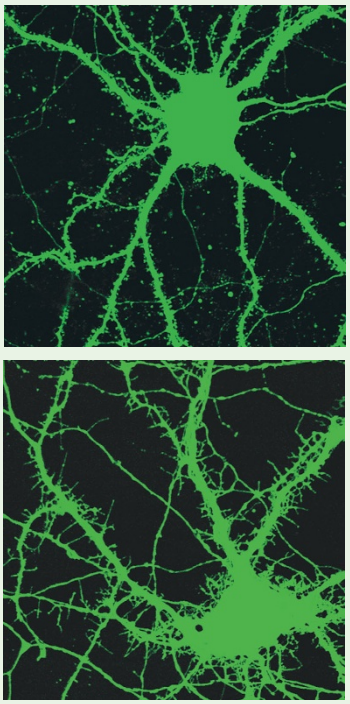
How ephrins sculpt dendritic spines

Originally identified as repulsive axon guidance cues, ephrins and their Eph receptors have since been implicated in many aspects of neural development, including tissue morphogenesis, cell migration, synapse formation and the development of dendritic spines. Shaping of spines requires rearrangement of the underlying actin cytoskeleton, and although cell biologists have identified many of the molecules involved in regulating this process, the link between cell surface receptors and the cytoskeletal machinery is not well understood. On page 1117 of this issue, Yamaguchi and colleagues identify the molecular mechanism linking Eph receptors to dendritic spine morphogenesis.

The crucial output of the cascade initiated by EphB receptor ligands is the activation of a Rho family GTPase, CDC-42, which controls the initiation and branching of actin filaments. The authors found that intersectin, a guanine nucleotide exchange factor (GEF) that activates CDC-42, associates with the EphB2 receptor and that this association activates the GEF activity of intersectin. Another activator of CDC-42, N-WASP (neural Wiskott-Aldrich syndrome protein), which links CDC-42 to actin filament initiation, also associates with this complex. The combined association of intersectin and N-WASP with the EphB receptor synergistically activates CDC-42.

CDC-42 is known to induce a complex branching pattern of actin filaments, consistent with the formation of the bulbous structure of dendritic spines (the punctate protrusions on dendrites in the hippocampal neuron shown at top). Expression of a dominant-negative CDC-42 would be predicted to result in a loss of branched actin filaments, and does indeed lead to the loss of dendritic spines in hippocampal cultures (bottom). In the presence of this inhibitor, spines are replaced by long, thin filopodia, consisting of a linear core of filamentous actin, consistent with the loss of CDC-42's actin branching activity.



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