reaching movements, the considerable trial-to-trial variability in hand trajectory[9]. Todorov and Jordan[1] capture this hand path variability for a throwing task using a model based on optimal feedback control. Such variability in hand trajectory is tolerated because it does not interfere with task performance, but it is inconsistent with explicit trajectory planning. Optimal feedback control does not plan the hand trajectory, which instead simply emerges from the optimal control law for the task. What has often been interpreted as a sign of sloppy control by the brain may actually reflect the optimal strategy for controlling body movements.

In effect, Todorov and Jordan argue that the feedback control law is not fixed, but is malleable and can be set based on the motor task. If this is true, a major question becomes how the motor system can learn these optimal control laws for myriad motor behaviors performed by an individual.

The new article[1] provides a cohesive framework for interpreting motor coordination and provides interesting examples of how optimal feedback control can explain many observations on coordinated movement. However, use of stochastic optimal feedback control as a model of motor control comes with a large computational price, requiring challenging mathematical contortions to solve even the simplest of linear control problems. As a result, the musculoskeletal system in some cases must be modeled as point masses providing only motion along a single direction. It seems a bit ironic that a theory illustrating the importance of considering the properties of the musculoskeletal system for motor control must use incredibly simplistic models of the motor periphery! This should not be seen as a downside of the theory proposed by Todorov and Jordan[1]. Rather, this limitation simply reflects the lack of existing mathematical tools to apply optimal feedback control to complex non-linear systems, like our motor system. However, the intuitive value of the many examples presented in this paper cannot be ignored.

Although it may be comforting to assume that emergent patterns of motor behavior reflect the optimal strategy for a given task, that conclusion may not apply to all cases. The neural circuits to control movement are very distributed and complex, and they presumably are based in part on evolutionary baggage. The Todorov and Jordan optimal control theory tends to ignore this inherent hierarchical organization[10]. It seems reasonable to believe that motor circuitry itself can influence strategies for a given task, perhaps because the motor circuitry cannot be entirely optimized for each individual task. Instead, certain features of the circuit may be optimal only when the complete motor repertoire of humans is considered, much like the conclusion that the distribution of muscle spindles may be optimal only by considering the complete behavioral repertoire of the animal[11]. However, optimizing for such global cost functions is likely to be quite a challenge.

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Chickens, eggs and hippocampal atrophy

Robert M. Sapolsky

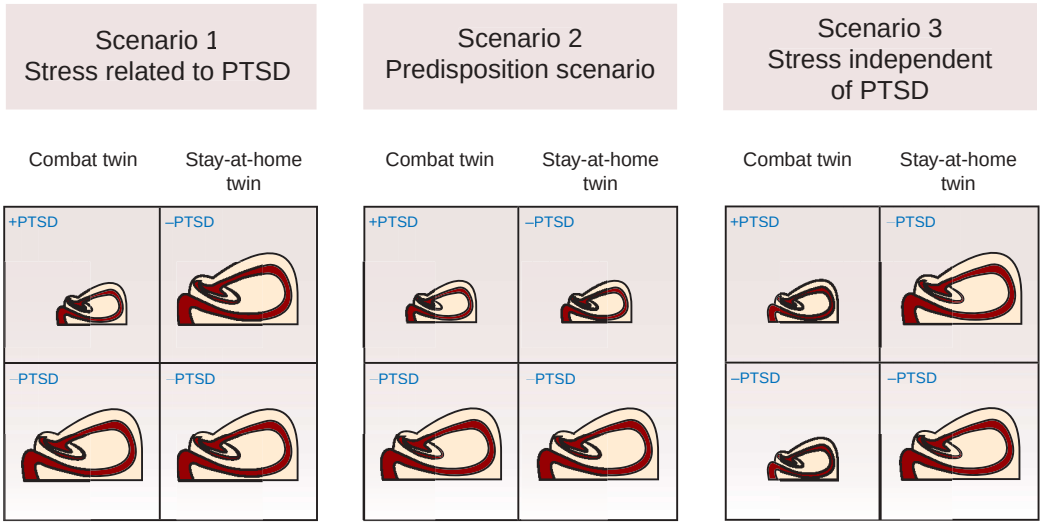
A new study provides the strongest evidence yet that a smaller hippocampus may be a predisposing factor toward, rather than a consequence of, post-traumatic stress disorder.

Experience can alter the brain. The dark side of this truism is that adverse experience can damage it. Perhaps one of the most unsettling examples of this idea is post-traumatic stress disorder (PTSD), a psychiatric disorder with symptoms including flashbacks, nightmares and sleep problems, emotional numbness or outbursts, loss of pleasure, an inappropriate startle reflex, and problems with memory and concentration. Many studies indicate that PTSD arising from combat trauma or prolonged childhood abuse is associated with atrophy of the hippocampus. This finding is striking because glucocorticoids, the adrenal hormones secreted during stress, can damage the hippocampus of experimental animals through a number of mechanisms[1,2]. In combination, these results gave rise to a perception that the hippocampal atrophy in PTSD was stress related[3,4].

Much discussion has ensued as to how this might occur[2]. Is it the trauma or the post-traumatic period that gives rise to the atrophy? Are glucocorticoids responsible? (This question is contentious, insofar as reports differ as to whether glucocorticoid levels in PTSD are above or below normal). Is the atrophy due to death of neurons and/or glia, shrinkage of cells, or failure of new ones to be born? The mechanism that explains trauma-related hippocampal atrophy must also explain why such shrinkage only occurs in a subset of individuals. Amid these debates, an alternative idea has occasionally been aired, namely that the hippocampal atrophy is not a consequence of either the trauma or the post-traumatic period[5]. Instead, perhaps a small hippocampus precedes trauma and predisposes an individual toward developing PTSD. In this issue, Gilbertson and colleagues[6] provide powerful data supporting this possibility.

The authors studied 40 pairs of identical twins in which one member of each pair went to Vietnam and experienced combat, while the other stayed home. Of those in combat, 42% developed PTSD. Using magnetic resonance imaging, the authors found that those with PTSD had smaller hippocampi than combat veterans without PTSD when expressed as a

The author is in the Departments of Biological Sciences, Neurology and Neurological Sciences, Stanford University, MC 5020, Stanford, California 94305, USA.
email: sapolsky@stanford.edu



Ivelisse Robles

Fig. 1. Three possible scenarios for the relationship between hippocampal size and PTSD. In scenario 1, development of PTSD in the combat-exposed twin results in atrophy of the hippocampus. In scenario 2, both siblings already have smaller hippocampi, which predisposes the combat-exposed twin to developing PTSD. In scenario 3, hippocampal size is reduced by the stress of being in combat, regardless of whether PTSD develops or not. The current study by Gilbertson *et al.*[6] supports scenario 2.

percentage of total brain volume. As a control typical in such studies, the amygdala did not differ in size between these groups. More severe PTSD was associated with an even smaller hippocampus. Importantly, the two veteran groups did not differ in the severity of their combat exposure, and both groups had higher cumulative trauma exposure than their stay-at-home siblings.

The punchline of the study, however, was that the stay-at-home siblings of the PTSD combat-veterans also had small hippocampi. Stated more quantitatively, hippocampal volumes of stay-at-home and combat siblings were equally predictive of the severity of the combat siblings' PTSD. One population went through combat trauma, while their siblings were not in the war, yet both groups had small hippocampi. Therefore, instead of a scenario of atrophy as a consequence of the stress of trauma and PTSD (Scenario 1 in **Fig. 1**), a small hippocampus seemingly preceded the war and increased vulnerability to PTSD (Scenario 2 in **Fig. 1**).

In retrospect, this finding was not completely unexpected, in that certain factors are known to increase vulnerability to PTSD. For example, in the first wave of studies examining which New Yorkers succumbed to PTSD after the World Trade Center attacks, lower socioeconomic status and lower degrees of social support following the attack increased risk (after controlling for factors such as proximity to Ground Zero)[7,8]. Prior history of trauma increases the likelihood of PTSD following rape[9]. And studies of combat veterans (by the authors of the present report) indicate that for the same degree of combat trauma, increased risk of PTSD is associated with low IQ and a history of 'soft' neurological signs (attention deficit, hyperactivity, learning problems, enuresis)[10,11]. To quote a psychiatrist I once met who oversaw a ward full of PTSD sufferers in an American Veteran's Administration hospital, "You have to understand that these boys had a lot of mileage under the hood before they ever set foot in Vietnam."

The design of the Gilbertson *et al.* study[6] also controlled for some of the more vexing confounds in trying to understand this phenomenon. Not surprisingly, combat veterans with PTSD have extremely high rates of alcohol use and clinical depression, both of which are independently associated with hippocampal atrophy[2]. Investigators have tried to circumvent this, both with complex statistical analyses meant to dissociate those risk factors from PTSD itself, as well as with control groups having similar histories of those risk factors. These efforts have not satisfied all critics. In the present report, the combat veterans with PTSD did indeed have far higher rates of alcohol consumption than the other groups. However, if the combat veterans with PTSD had significantly higher rates of substance abuse than did their stay-at-home siblings, yet they had statistically identical hippocampal volumes, this suggests that alcohol abuse was not a contributing factor.

What caused these men to have small hippocampi? Despite the involvement of identical twins in the study, the effect may not be genetic. (For example, identical twins can have much more similar fetal environments than do dizygotic twins.) And why should small hippocampi increase vulnerability to PTSD? The authors offer some speculations. The hippocampus has a neuroendocrine role of inhibiting glucocorticoid secretion, and small hippocampi can be associated with impairment of such inhibition, raising glucocorticoid levels. Perhaps this results in an exaggerated stress response, somehow increasing the risk of PTSD. (However, this idea is difficult to reconcile with reports of lower, rather than higher than normal glucocorticoid levels in some cases of PTSD.) Alternatively, given the role of the hippocampus in learning and memory, perhaps a small hippocampus somehow alters aspects of cognition involved in buffering against PTSD.

Naturally, there are a few holes in this revisionist picture of a small hippocampus preceding and predisposing toward PTSD. The disorder is a heterogeneous one; the type of trauma can alter psychiatric symptoms, glucocorticoid profile and whether PTSD is associated with a

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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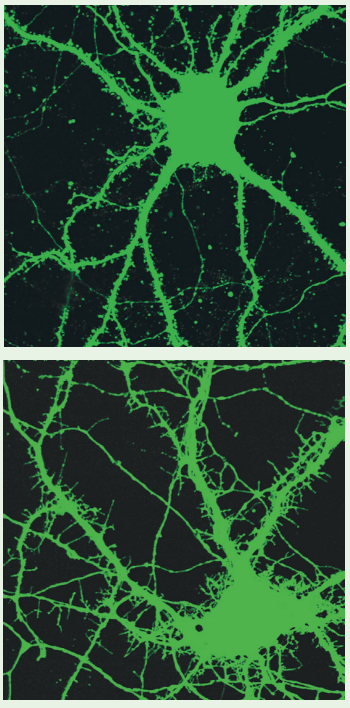
How ephrins sculpt dendritic spines



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.

Jack Horne