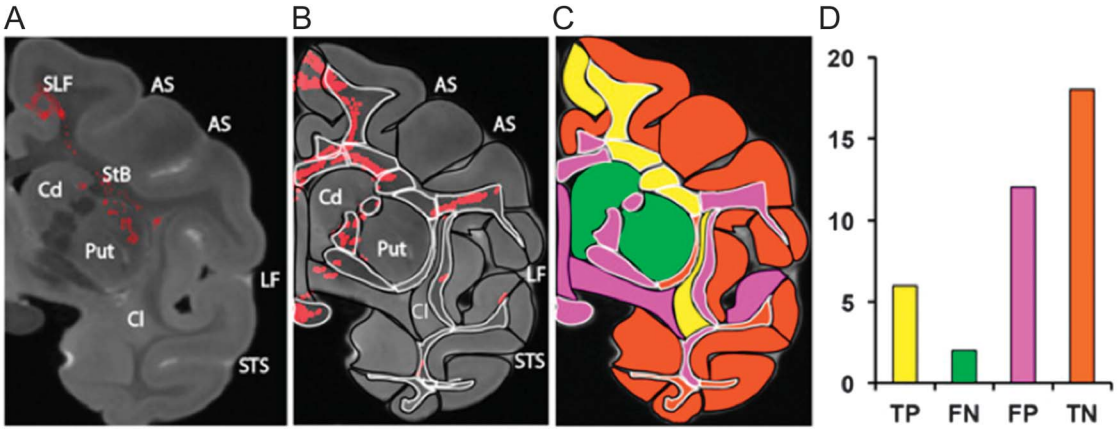

Figure. Representative illustration of the procedure used for assessing the anatomic accuracy of various diffusion tractography approaches. **A**, *the red dots indicate the topography of axonal pathways after the injection of an anterograde tracer in the left PCG.* **B**, *for each diffusion-weighted imaging slice that was anatomically matched with the histology slice from the reference atlas, the gray matter (black lines) and white matter (white lines) regions were manually segmented and parcellated into discrete regions of interest. The red dots in* **B** *represent the location of axonal pathways as determined with the Q-ball tractography method based on the left PCG as the seed region and an angular threshold of 80°.* **C**, *agreement between tracer and tractography results was computed for each slice. The colors indicate regions of interest that were categorized as true positive (TP), false negative (FN), false positive (FP), and true negative (TN).* **D**, *histogram showing the TP, FN, FP, and TN for the specific slice.* From Thomas et al.[4]

anatomy is the combined use of magnetic diffusion histology and microtractography to reveal mesoscale features of human brain.[6] The spatial resolution used in this technique is orders of magnitude more than that in DTI, allowing the disentangling of connections that might have been grouped together in a single window with DTI. In the meantime, it is important to recognize the subjective nature of tractography results, especially at the resolution required for addressing fundamental questions in neuroscience.

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Progesterone Is Not Effective in the Treatment of Traumatic Brain Injury

Read the introduction of any given traumatic brain injury (TBI) study, and the staggering impact of the condition will be clear. The statistics paint a bleak picture of the effect of TBI on individuals, families, and society as a whole. Neurosurgeons and neurologists are intimately familiar with the effects of TBI, and many have dedicated their careers to improving outcomes. One principal goal of this research has been to identify a pharmacological intervention that will mitigate the effects of TBI. Thus far, a multitude of compounds and studies have failed. Early animal studies using progesterone, however, have demonstrated a neuroprotective effect. Translation to humans showed improved outcomes in phase I and II trials in progesterone-treated acute TBI patients, but unfortunately, the phase III trial produced negative results.

The Neurologic Emergencies Treatment Trials (NETT) Group has recently published in *The New England Journal of Medicine* a multicenter, double-blind, placebo-controlled phase III trial titled "Very Early Administration of Progesterone for Acute Traumatic Brain Injury," which did not show an improvement in TBI outcome after treatment with progesterone compared with placebo.[1] Also known as the Progesterone for the Treatment of Traumatic Brain Injury (PROTECT III), the trial was conducted at 49 trauma centers in the United States. The study enrolled adult patients with a Glasgow Coma Scale (GCS) score of 4 to 12. Exclusion criteria included a nonsurvivable injury; bilateral dilated, unresponsive pupils; the need for cardiopulmonary resuscitation or physiological findings of hypoxemia, hypotension, active myocardial infarction, ischemic stroke, pulmonary embolism, deep vein thrombosis, spinal cord injury, or status epilepticus; pregnancy; status as a prisoner or ward of the state; severe intoxication (ethanol level, >249 mg/dL); history of reproductive cancer; allergy to progesterone or a fat-emulsion vehicle; and a blood-clotting disorder.

Patients were randomly assigned to either the progesterone group or the placebo group. In both groups, the TBI was managed according to standardized protocols, and adherence to these protocols was monitored on a daily basis in all centers. The progesterone group received an initial loading dose (progesterone 0.05 mg/kg body weight), a maintenance dose (14.3 mL/h for 1 hour, then 10 mL/h for 71 hours), and a tapering dose (tapered by 2.5 mL every 8 hours). This resulted in a total treatment duration of 96 hours, and treatment was initiated within 4 hours of injury. The primary outcome was functional recovery determined by the Extended Glasgow

Outcome	Progesterone (N=442)	Placebo (N=440)	Overall (N=882)	Unadjusted Difference (95% CI)
				percentage points
Primary outcome — no. (%)				
Favorable outcome	213 (48.2)	232 (52.7)	445 (50.5)	−4.5 (−11.1 to 2.1)
Missing data	28 (6.3)	24 (5.5)	52 (5.9)	—
According to initial injury severity — no./total no. (%)				
Moderate injury				
Favorable	35/129 (27.1)	45/125 (36.0)	80/254 (31.5)	−8.9 (−20.3 to 2.5)
Missing data	10/129 (7.8)	11/125 (8.8)	21/254 (8.3)	—
Moderate-to-severe injury				
Favorable	133/234 (56.8)	133/238 (55.9)	266/472 (56.4)	1.0 (−8.0 to 9.9)
Missing data	13/234 (5.6)	9/238 (3.8)	22/472 (4.7)	—
Severe injury				
Favorable	45/79 (57.0)	54/77 (70.1)	99/156 (63.5)	−13.2 (−28.1 to 1.8)
Missing data	5/79 (6.3)	4/77 (5.2)	9/156 (5.8)	—
Death — no. (%)	83 (18.8)	69 (15.7)	152 (17.2)	—
Cause of death — no./total no. (%)				—
Neurologic	53/83 (63.9)	49/69 (71.0)	102/152 (67.1)	—
Not neurologic	28/83 (33.7)	20/69 (29.0)	48/152 (31.6)	—
Unknown	2/83 (2.4)	0	2/152 (1.3)	
According to initial injury severity — no./total no. (%)				—
Moderate	19/129 (14.7)	14/125 (11.2)	33/254 (13.0)	—
Moderate to severe	37/234 (15.8)	39/238 (16.4)	76/472 (16.1)	—
Severe	27/79 (34.2)	16/77 (20.8)	43/156 (27.6)	—
Disability Rating Scale score†	2.9±4.6	3.3±5.1	3.1±4.9	—

Figure. Outcome at 6 months after injury. CI, confidence interval. From New England Journal of Medicine, Wright DW, Yeatts SD, Silbergleit R, et al. Volume 371, Page No. 2457-2466. Copyright © 2014 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

Outcome Scale measured at 6 months from the time of injury (Figure).

A favorable outcome was determined by stratifying patients according to the severity of their initial injury so that patients with a less severe initial injury had to have a better recovery than those with a more severe injury to have a favorable outcome. A total of 882 patients were randomized between April 2010 and October 2013. The progesterone and placebo groups were balanced in terms of demographics and injury severity; 53.5% of patients had an initial GCS score of 5 to 8, with the remainder divided between a GCS score of 4 (severe injury) and a GCS score of 9 to 12 (moderate injury). Favorable outcomes were achieved in 51.0% of progesterone-treated patients and 55.5% of placebo patients. A secondary analysis in which a favorable outcome was simply considered to be an Extended Glasgow Outcome Scale score ≥5 (equating to moderate disability or better) provided similar results. There was also no significant difference in mortality between the 2 groups. Additionally, adverse events were similar between the groups with the exception of phlebitis and thrombophlebitis (considered a nonserious adverse event) occurring significantly more often in the progesterone group. Thus, although progesterone maintains a good safety profile, it does not appear to have an effect on functional outcome when administered to patients with acute TBI.

Despite data from multiple animal studies, 2 human trials preceding it, and a high-quality study design, the PROTECT III trial was not able to establish a role for progesterone in the treatment of TBI. The authors cite the heterogeneity of injuries, patient pre-existing conditions, and the characteristics of individual patients as potential confounding factors. Although these negative results are disappointing, the study paves the way for the investigation of future compounds.

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Closed-Loop Deep Brain Stimulation Successfully Modulates Hippocampal Activity in an Animal Model

Recent research in brain stimulation techniques (in the context of a variety of neurological conditions, including movement disorders, psychiatric disorders, and epilepsy) has turned toward understanding the