



Editorial

Whole brain transplantation in man: Technically feasible

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The unavailability of technologies that can successfully rejuvenate an aged body suggests that it is time to explore other options. BRAVE, the BRain Anastomosis Venture^[3] is part of a larger scope project – PERSEUS – that aims at moving an old brain into a young immunoconditioned body (or a nonsentient clone *tout court* when this becomes available) and kick off rejuvenation of the brain, as afforded by Progressive Brain Replacement (J Hebert, accompanying editorial). The anchor of this project is the successful achievement of whole brain transplantation (BT).

Cephalosomatic anastomosis^[2] might be construed as a form of BT, but the fact remains that – rejuvenation-wise-the aged face and other head tissues are left *in situ*, which defeats the purpose of enjoying a pristine body.

According to contemporary thinking, a full brain transfer from one living individual (Body Recipient, R) to another (Body Donor, D), a.k.a. cerebrovascular anastomosis, is unachievable.

Four primary reasons are adduced: ^[3]

1. Impossibility to extract the brain proper from the dura mater, given the intimate relationship between the brain's venous and cerebrospinal fluid (CSF) outflow and the dural cranial sinuses
2. Impossibility to resuture the internal carotid and vertebral arteries (ICAs/VAs) and the internal jugular veins (IJV) once the brain is laid on the donor's skull base
3. Lack of an efficient technology to functionally reconnect the 12 pairs of cranial nerves
4. Lack of a technology to reconnect the severed spinal cord
5. Undetermined neuroprotective measures to deploy between the moment of physical separation of the brain from R's skull and re-establishment of circulation after positioning on D's skull base
6. Possible immune rejection if BT is carried out on a heterologous body rather than R's clone.

The last three points are covered elsewhere. In particular, the spinal cord – once sharply severed – can be functionally reconnected in primates (GEMINI protocol: Fully reviewed in Canavero and Ren;^[2] see also Canavero *et al.*,^[4] Ren *et al.*^[7]) Brain protection through profound hypothermia has been demonstrated by Dr. White 50 years ago in primates and more recently confirmed in China.^[3,6] Other techniques can boost hypothermia's effects.^[3] The brain is a partially immunoprivileged organ. BT on a clone would not require immunosuppressants; at the same time, tolerogenic protocols are being developed that may be tapped for heterologous brain transfers.^[2,3]

In this paper, I summarily address the first three points in that order. More technical details and extensive discussion and referencing are found elsewhere.^[3]

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THE BRAIN IS TRANSPLANTED ALONG WITH THE DURAL SAC

Sparing the dural venous sinuses along with all the veins and arachnoidal granulations is currently unachievable. Besides, the subdural circulation of CSF would be totally disrupted. The solution is transplanting the brain *inside the dural sac*.

Briefly, both individuals are trachetomized and ventilated and installed in the upright position. Heads are secured on both sides with a fixation apparatus adapted from the maxillofacial equivalent^[9] and centered on the mastoids. A standard fixation is of course to no avail given the wide dural exposition necessary for a BT and the associated ultraextensive craniectomy.

Predicated on the complete expendability of R's body, the approach in R starts with a nasion-C7 spinous process linear incision followed by full thickness scalping of the head down to the orbital ridges. The skull cap is removed in standard fashion, with multiple burr holes on the two sides of the superior longitudinal sinus and other holes, including along the basal circumference. A standard wide craniectomy frees the cerebellum [Figure 1].

A slightly modified LeFort III osteotomy follows.^[9] The entire splanchnocranium (including the orbital ceiling) and both pterygoid and styloid processes are removed. This is deemed necessary as the dura mater tightly clings to the cranial base and detaching it without tears from the inside represents a veritable

tour de force. Moreover, delicate neural and vascular structures might be damaged in the process. Instead, it seems preferable to gain direct access to the dura of all three cranial fossae from the outside, especially through the clivus. This also allows complete visualization of exiting cranial nerves and vessels [Figure 1].

In D, a standard coronal incision is followed by a linear incision from the bregma through theinion down to C7 (T incision). The frontal skin flap is rolled forward in classic fashion, while the two hemihalves of the posterior teguments are retracted sideways. The skull cap is removed *en bloc* after a single linear high-speed saw cut through the skull bone proper along its basal circumference and set aside for repositioning at the end of the surgery. D's brain can be removed *en bloc* (hypophysis included) along with the hemispheric dural sac and the upper metameres of the cervical cord, without fear of damage. However, *the basal dura is left in place*, as this will not interfere with the whole process. Bilateral anterior and posterior clinoidectomies are carried out to facilitate later hypophyseal repositioning, nerve fusion, and vascular anastomosis in the sella turcica region.

In both R and D, the cervical spinal cord is accessed in standard fashion with removal of the C1-5 spinous processes (in D, these are repositioned after GEMINI spinal cord fusion). However, longitudinal durotomy is delayed until the final process of spinal fusion.

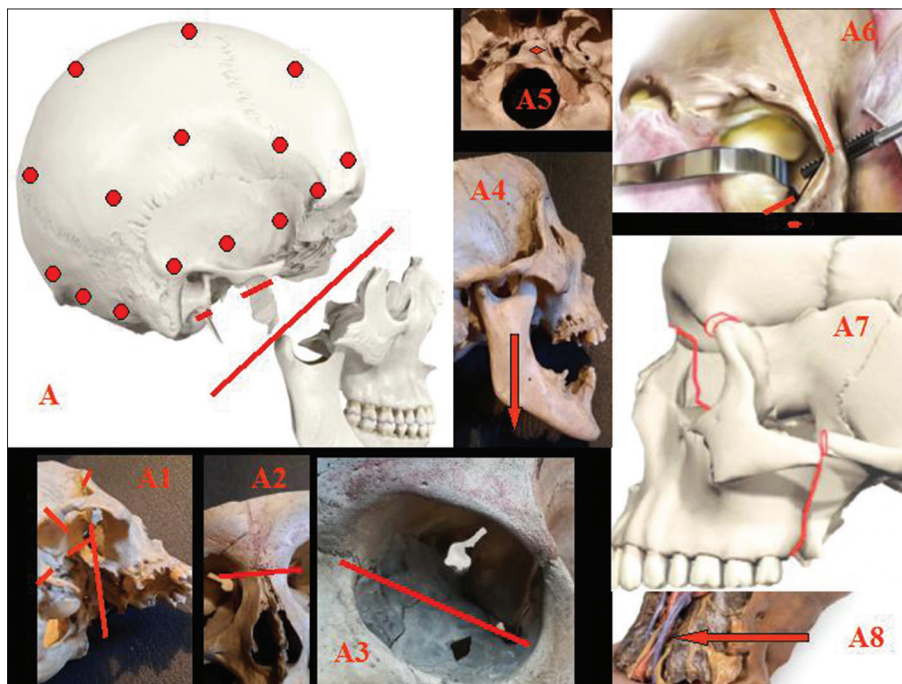


Figure 1: A: Burr holes (red circles) for skull detachment from dura; splitting of splanchnocranium (red line); removal of pterygoid process; and styloid process (red segments). A1-4: LeFort III osteotomy (red lines). A5: The clivus is removed (red circle). A6: Orbital step of LeFort III osteotomy (red lines). A7: Lines of fracture for full splanchnocranium detachment (red lines). A8: Unrestricted view of the neurovascular bundle in the neck that can be followed up to cranial entry (arrow).

In both R and D, the ICA is severed above the point of origin of the ophthalmic artery (whose branches include the central retinal artery) and temporarily clamped. The IJV is severed distally as it emerges from its bulb. Cranial nerves are severed beyond the points of later actual fusion, so as to have fresh interfaces after further trimming.

As R's brain encased in its dura (hypophysis included) is being freed from the cranial vault and base, a robotic scoop with retractable tines is brought into the operating field. This envelops the brain and supports it as the dural detachment proceeds, and facilitates the final transfer onto D [Figure 2].

It goes without saying that the surgeries in R and D must be synchronized so that transfer of R's brain can occur even as D's brain is removed.

In sum, BT should be understood as a *meningo-cerebro-somatic anastomosis*.

VASCULAR RECONNECTION

BRAVE requires a rapid restart of the circulation to R's brain. However, anatomical (in particular, the highly constrained surgical space of the cranial fossae) and technical considerations^[3] rule out standard manual sutured anastomosis of neurovascular structures. Instead, BT exploits *sutureless vascular anastomosis* (SVASTOM).

A pretransplant angiography in both R and D is mandatory to assess the entire vasculature, including anatomic variations (e.g., absence/hypoplasia of the ICA and IJV) and size mismatches.^[3]

Briefly, the ICA enters the skull through the carotid canal (diameter in adults: 6–7 mm on the right, 6–8 mm on the left)

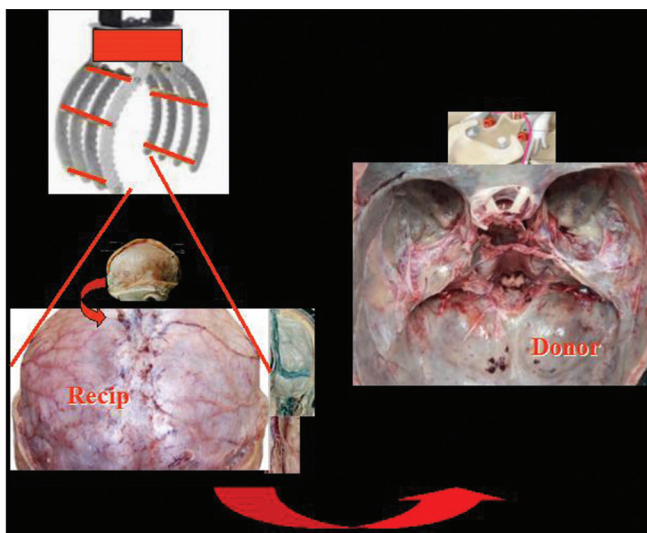


Figure 2: Once the skull cap has been removed down to the occipital foramen, a robotic scoop secures the brain for transfer from recipient to donor.

along with the venous plexus and veins surrounding it and the sympathetic nerves. The ICA leaves the cavernous sinus before and medial to the anterior clinoid. The subarachnoid segment has a width of 2.8–3.3 mm and is 13.4 (8–18) mm long; it then bifurcates into the middle and anterior cerebral arteries. The IJV's diameter is 9.1–10.2 mm, but in a minority, it can be <5 mm. The VA – with the left being dominant – has a mean diameter (C3 level) of 3.5–3.6 mm in males and 3–3.4 mm in females.^[3] These diameters are fully compatible with a sutureless vascular anastomosis approach.

Several scenarios are possible, including *stent-assisted vascular anastomosis* (SAVATOM) and *Magnetic Anastomosis* (MAGSTOM) [Figure 3]. These afford, among others, ease of deployment, durability, and resistance to high pressure. This technology is noninferior to standard sutured anastomosis and may in fact be superior (details in Canavero^[3]).

CRANIAL NERVE RECONNECTION

Similarly to vascular reconnection, sutured anastomosis is ruled out for cranial nerve reconstruction. Besides the constrained operative space, microsuturing cannot reestablish cranial nerve function rapidly, being exclusively dependent on regeneration. In addition, microsuturing is traumatizing to the nerve (reviewed in De Medinaceli^[5]). It goes without saying that BT is acceptable exclusively under condition that rapid recovery of neural transmission ensues. The patient is expected to emerge from post transplant-induced coma with cranial nerve function already present or rapidly recovering. *Neural fusion* (NF) and *sutureless nerve anastomosis* (SNATOM) aim at solving this problem. NF would reestablish immediate transmission of electrical impulses, while SNATOM firms up the coaptation.^[3]

Importantly, R's and D's cranial nerves are severed beyond the actual point of final connection so that any Wallerian degeneration that usually starts within minutes of section is offset by severing the initially degenerating extra-length once the brain has been placed on D's skull base and fusion initiated (see in Canavero and Ren^[2]).

Rodent studies show that, at least for healthy sciatic nerves, stretching up to 30% is not harmful: this is important for surgical maneuvering.^[5]

All cranial nerves have <100,000 axons each, with the optic nerve being the outlier (1,200,000 fibers).

Fusion exploits so-called fusogens, such as PolyEthylene Glycol (PEG) and chitosan (reviewed in Ryan and Henderson^[8]). *Within minutes*, successful PEG-fusion restores gross anatomical and electrophysiological continuity across severed nerves. At 6 weeks, many fused axons are morphologically similar to intact axons, that is, do not undergo Wallerian degeneration and remain connected to a nerve cell body. Survival of successfully PEG-fused axons

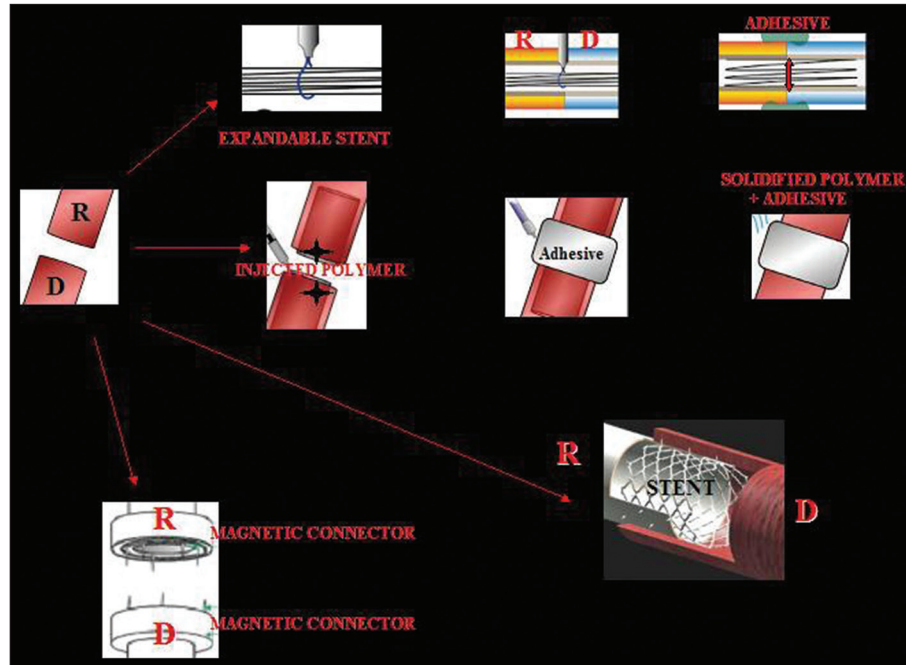


Figure 3: The vessels (here are shown the carotids) of both recipient (R) and donor (D) can be anastomosed with sutureless vascular anastomosis technology. Four options are illustrated: 1 – an expandable stent can be inserted in both stumps, the stumps are then approximated, the stent is fully expanded; an adhesive adds stability to the coaptation (stent-assisted vascular anastomosis, SAVATOM 1); 2 – a polymer can be injected into the lumen of the vessels; an adhesive stabilizes the complex while the polymer solidifies (SAVATOM 2); 3 – a nonresorbable stent with pins, once deployed, effects the anastomosis (SAVATOM 3); 4 – magnetic connectors inserted into the two stumps ensure immediate coaptation Magnetic Anastomosis. 3D printing is ideal for personalized stents (From Canavero and Ren,^[2] with permission).

leads to behavioral recovery starting at 3 days postoperatively up to 1–4 weeks. This recovery is sustained over time. Not all axons undergo fusion, as this requires precise alignment, but those that do so are enough to ensure return of function, also supported by CNS reorganization. Alternatives to chemical fusion are possible, including electrofusion and electroacoustic fusion (see in Canavero *et al.*,^[3] De Medinaceli^[5]). Importantly, parts of De Medinaceli's protocol are deployed to protect the cranial nerves from the deleterious effects of transection.^[3,5] in particular, a custom-made circular-snare blade that first sections the tougher outer layer of a nerve and only then the axonal proper is key to avoid crush damage of the axons to be fused.

Multiple approaches enable nerve approximation, including *Photochemical Tissue Bonding* and *MAGSTOM*.^[3]

A caveat should be added. Unless performed in a clone, variation of the diameter of cranial nerves must be assessed with high-resolution MRI before BT in D.

It is worth mentioning how the entire surgery might be adapted so that the eyes are also transplanted without damaging the neurovascular bundle. However, the eyes also degenerate with age.^[1]

CONCLUSION

Contrary to common lore, a full BT is achievable, at least theoretically. Of course, further extensive cadaveric rehearsals will be necessary, followed by tests in brain-dead organ donors (as e.g., done recently in kidney xenotransplants). New surgical tools will have to be developed. With appropriate funding, a long-held dream may finally come true.^[10]

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Commentary

Kidney, Liver, Lung, Hand, Heart, and Face Transplantation. Brain transplantation?

This concept of a brain transplant is an advanced plan based on Dr. Canavero's previous experience with acute spinal cord repair which has been fully confirmed to succeed in animals from rats to cats, dogs, and monkeys. That work was never believed possible until Dr. Canavero assembled a team of scientists worldwide to solve the many aspects of that achievement. The work was based on a fundamental misunderstanding of the mechanisms involved in spinal neuron regrowth. His revelation that the short neurons regrow to re-establish primitive motor pathways present in species from their origins is a breakthrough in science.

Now, Dr. Canavero is challenging science and humanity with the possibility of a brain transplant. Kidney, liver, lung, hand, heart, and face transplants have all been done in the late 20th century. Yet, the scientific success was delayed in these major advances by the emotional, ethical, and religious objections which were raised. This project of a brain transplant will not doubt undergo similar criticism. Yet, the scientific question remains as to whether such a transplant can be achieved. That is the major focus of Dr. Canavero's work.

Humans have discovered the manipulation of atoms and molecules which can be used for the good or bad purposes in benefitting civilizations, as in work with fusion and fission and the development of atomic weapons that can kill millions of people or produce energy benefiting all. That is a human problem in the use of knowledge with good or evil intent which extends to many aspects of life. Prejudgment of the experiments misses the point of this work, as it did with the discovery that the spinal cord can be repaired, which Dr. Canavero and his colleagues proved. The ultimate goal was to reestablish a functional life.

This brain transplant program is also complex, the results of which are not known to questions not yet asked. There are many aspects of the giant project which Dr. Canavero is considering which will need to be tested and validated. However, assume for a moment that the project is successfully done. What will we learn? Can a brain of a nonathletic person be transplanted to an athletic one and how will that brain function? What reorganization will we see? What further secrets to an understanding of the human body will emerge for us to learn more about the brain-body interactions? This work can only be fully understood in its use in humans after its validation in animals. Can a person born without arms undergo regeneration of those appendages? That does happen in animals. Imagine the impact of such a discovery on humans now and in the future.

In science, asking the proper questions leads to more knowledge of the solution of disease states and longevity. Already, as a result of the advances in science, the life expectancy of humans has tripled in the past 150 years, a monumental accomplishment of humans. Such ideas challenge our traditional views and should be accepted and properly tested. To reject questions on the basis of traditional or emotional views will only stop the advances in science and an understanding of our place in the universe and inhibit our progress as a civilization in the future in all fields.

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