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Editorial

HEAVEN: The Frankenstein effect

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Abstract

The HEAVEN head transplant initiative needs human data concerning the acute restoration of motor transmission after application of fusogens to the severed cord in man. Data from two centuries ago prove that a fresh cadaver, after hanging or decapitation, can be mobilized by electrical stimulation for up to 3 hours. By administering spinal cord stimulation by applied paddles to the cord or transcranial magnetic stimulation to M1 and recording motor evoked potentials, it should be possible to test fusogens in fresh cadavers. Delayed neuronal death might be the neuropathological reason.

Key Words: Delayed neuronal death, electrical stimulation, fusogens, spinal cord fusion

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INTRODUCTION

Cephalosomatic anastomosis is made possible by the GEMINI Spinal cord Fusion protocol.[3,5] GEMINI exploits, among others, fusogens [e.g., polyethylene glycol (PEG)], namely, substances that have the ability to reconstitute severed or damaged cell membranes.[3-5] Published animal experiments employed several molecular weights of PEG to achieve spinal fusion, and data show that molecular weight may have an influence on the final result.[3,4,11,18] Human data are needed in order to clarify this issue and confirm transmission of impulses across the treated stump interface. The HEAVEN initiative aims at acquiring this data by acute tests on brain dead organ donors before explantation. This is considered ethical since only 3–6 hours would pass between testing and organ harvesting for transplants.

Another possibility exists, namely, testing the fusogens on fresh cadaveric specimens. This exploits the phenomenon of delayed neuronal death and is supported by observations made two centuries ago in which electric jolts induced complex motor responses in fresh cadavers.

ELECTRICAL INDUCTION OF MOVEMENTS IN FRESH CADAVERS

In 1802, at the height of the controversy on the existence of animal electricity between Alessandro Volta (con) and Luigi Galvani (pro),[7,8] Giovanni Aldini, Galvani's nephew,[18] in order to prove his uncle right, applied electrical stimulation ("galvanism") to three criminals who had been decapitated about 1 hour earlier. Employing (ironically) Volta's battery ("Pila") in Bologna (Northern Italy), he produced all manner of muscular contractions by applying an electric arc at different points along the head and bodies. Such effects persisted up to 3 hours after death. He then stimulated

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various regions of the human brain: massive facial muscle contractions were generated by stimulating the callosal fibers; similar effects followed the stimulation of the cerebral cortex. In January 1803, Aldini[1] conducted similar experiments in London on George Foster who had been hanged and left in the cold for 1 hour. The movements induced were "so much increased as almost to give the appearance of reanimation."[1,18] The news was reported by The Times on January 22, 1803, and strongly and enduringly impressed scientists and ordinary people alike, many coming to believe that electricity might be the long-sought vital force. This belief later inspired Mary Shelley and her novel Frankenstein in 1818. Actually, other physicians repeated these experiments and confirmed the 3-hour window.[17]

These data prove that electrical stimulation up to 3 hours after death can engage the CNS and produce movements, in agreement with Aldini's predictions: "*convey an energetic fluid to the seat of all sensations; distribute its force throughout the different parts of the nervous and muscular systems; produce, reanimate and, so to speak, control the vital forces: this is the object of my research…from the theory of galvanism.*"[1]

In other words, it appears that a fresh cadaver might act as a proxy for a live subject as long as a window of opportunity is respected (a few hours). It also implies that the process of deathly disintegration is not an immediate process (see below). We name this effect the "Frankenstein effect." We believe this has a neuropathological basis.

DELAYED NEURONAL DEATH AND RESISTANCE TO DEATH

It is generally believed that a neuron is highly sensitive to hypoxia or glucose deprivation, and that cerebral ischemia of more than several minutes results in irreversible brain neuron damage.[23] In fact, oxygen and glucose deprivation has almost immediate effects on brain function, typically causing symptoms in approximately 5–7 seconds followed by the electroencephalogram (EEG) going flat within 15–20 seconds (e.g., in decapitated rats).[23] After decapitation, some reserves of metabolic substrates and ATP can support a maximum of one minute of normal metabolism, but less if no oxygen is available.[9]

However, this belief seems to be negated by the above-reviewed data and modern evidence. The reality is that there is no well-accepted definition of the point at which a cell dies.[15] The only unequivocal definition of cell death is a morphological one, the elimination of the cell, which arises by unrecoverable cell disintegration (or phagocytosis).

Siemkowicz and Hansen[20] observed the return of EEG activity 15 minutes after a period of isoelectricity caused by complete ischemia. In fact, ischemic cell death is characterized by a long delay between the insult and manifestation of major cell damage. This delay varies greatly, depending on the nature of the insult and the brain region being affected. In some cases, it is as long as several days or even weeks whereas in others it is a few hours or less.[15] It is clear that, for any one region, the longer the insult, the shorter the delay. This is generally between 12 hours and 4 days.

As first characterized in 1982 by Kirino,[12] who named it delayed neuronal death (DND),[13] and Pulsinelli *et al.*,[19] neuronal death is a slow process taking 2–3 days before presenting the final morphologic outcome. Unlike simple destruction of the neuronal cell body, the cytoplasm and cellular organelles such as the mitochondria are well maintained for the first 2 days following ischemia. Afterwards, other changes set in and the cells are completely destroyed and disappear on the 3–4th day.[13] Physiologic and metabolic parameters during the process of DND are also maintained for a few days. The membrane potential of ca 50 mV is maintained and electrical excitation is also observed.[13]

These studies refer to stroke models in animals and humans.[15,16] Even more interesting is the evidence of neuronal survival in human cadavers, namely, resistance to death.[10] It is generally considered that autoptic brain tissue is not suitable for experimentation because of the deleterious effects of agonal state at death and postmortem delay on labile cellular constituents. However, evidence for survival of human brain neurons up to 8 hours after death such that they still had the potential to recover their functions of energy metabolism and axonal transport in 30+ postmortem (delay: 3–6 hours) human brains is on record.[6] The same group[21] removed the brain from cadavers 2–8 hours postmortem (mean: 4.2 hours). Tissue cultures of brain slices showed survival of viable neurons with normal morphology from both cortex (including the primary motor cortex, M1) and subcortical brain areas that could be manipulated experimentally. Neurons from M1 were maintained in culture for 1 up to 78 days! Material from nearly two-thirds of the patients could be used for experiments lasting at least 3 weeks whereas about half of the cultures could be used for more than 30 days.

EXPERIMENTATION ON FRESH CADAVERS

In view of many failed trials based on animal data, the need to acquire clinically relevant experimental data in neurology is urgent, and this also applies to spinal cord fusion protocols. Organoids ("minibrains") have been grown for exactly this purpose.[14] Testing on brain dead organ donors in the interval between declaration of brain death and initiation of organ harvesting is an ethical option. Reviewed data from two centuries

ago prove that another ethical option is available, that is, experimentation on fresh cadavers. As discussed, movements can be elicited in a fresh cadaver by electrical stimulation for up to 3 hours (and possibly more). This suggests that the cerebral cortex and its projections to the spinal cord and the cord itself remain viable for up to 3 hours postmortem. This includes both the cell bodies and the synapses. As far as GEMINI is concerned, spinal cord stimulation above the level of attempted fusion or transcranial magnetic stimulation to M1 followed by recording motor evoked potentials (MEP) should be enough to confirm neurophysiological conduction.

As a corollary, the same line of reasoning suggests that current protocols to rapidly (within the hour) freeze just-deceased heads (and/or whole bodies) for future reanimation might actually turn out to be successful, provided the de-thawing process does not damage cellular bodies.[2]

Both occurrences are likely due to the phenomenon of delayed neuronal death.

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