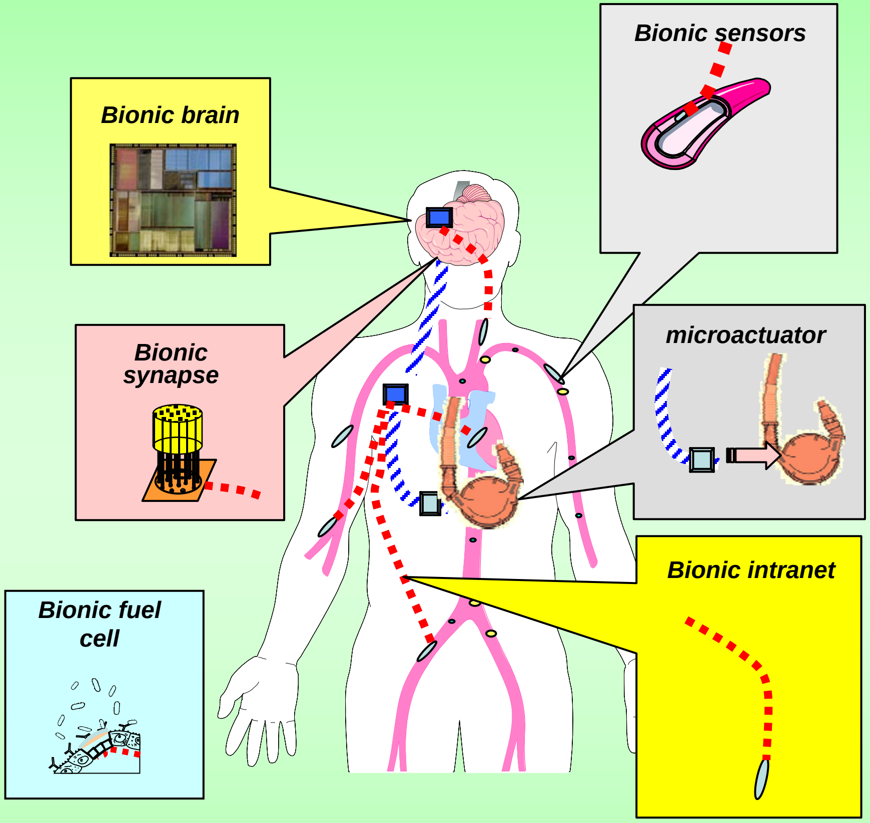
バイオニック医療はもはやSFではない

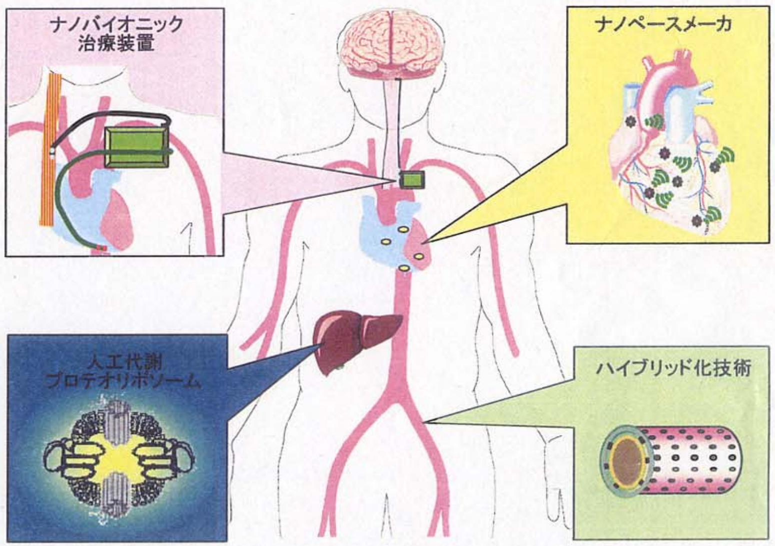


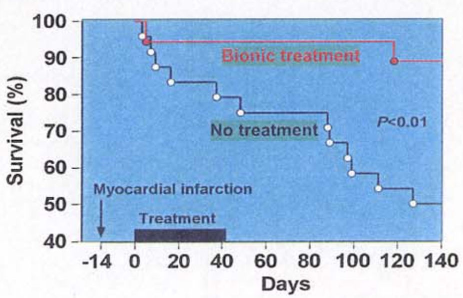
ナノテクの進歩に伴い21世紀はバイオニック医療が飛躍的な進歩を遂げる。

バイオニックナノメディシンによる生体機能代替デバイスの開発

- ナノバイオニック治療装置は電子的かつ知的に生体調節系を代替しその異常を是正する装置である。この装置により現代医療で救命できない重症心不全の生命予後を劇的に改善した（下図）。バイオニック中枢、センサや、神経電極の超LSI化、ナノ化によって実現した。
- 超微細回路、生体内通信、生体燃料電池技術を駆使し、カテーテルにより植え込み可能なナノペースメーカの基盤技術を開発している。
- 人工血管やステントの表面を分子レベルで修飾することにより抗血栓、抗炎症性が格段に向上したデバイスを実現した。
- 能動輸送や解毒などの生体特有の機能を人工プロテオリポソームによって実現し、夢の人工肝臓・人工腎臓に向けて開発を行っている。

＜萌芽的先端医療技術推進研究（ナノメディシン）事業＞





医療機器による代替え医療と再生医療

機械工学的アプローチ	生物細胞学的アプローチ
知的医療機器・神経工学	細胞工学
埋込み型センサー 電気刺激	遺伝子改変 幹細胞、ES細胞の分化・体外増殖・移植
視覚	網膜再生
聴覚	内耳細胞再生
筋力	筋細胞再生
脊髄損傷	神経再生
パーキンソン病	ドーパミン生産細胞
心臓ポンプ力（人工心臓）	心筋細胞再生
心臓リズム（ペースメーカー）	ペースメーカー細胞

医学・医療発展
車の両輪

Brain-Machine Interface

脳とコンピュータの接合

視床下部電極 ------------------------------------ パーキンソン病
ジストニア

聴覚電極（人工内耳） ----------------------- 聾唖者をなくす

網膜視覚野電極（人工眼） --------------- 視覚の回復

Cg25（悲しみ中枢）電極 -------------------- うつ病の治療

人の感情の神経工学的コントロールが可能
→ 人の行動をコントロールしうる

人工感覚器(聴覚)

Auditory Brainstem Implant (ABI)
Cochleal Implant（人工内耳）

1990 Bionics社（米国）

Cochlea社（オーストラリア）

MED-EL社（オーストリア）

Digisonic社（フランス）

300〜400万円　保険収載済み

日本製なし

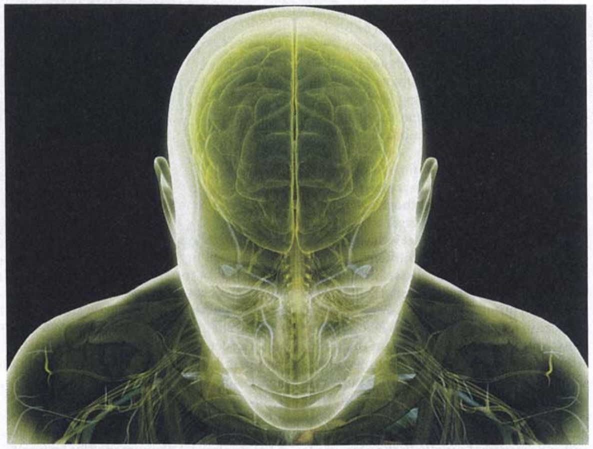
NEWS & VIEWS

NEUROLOGY

An awakening

Michael N. Shadlen and Roozbeh Kiani

Neuroscientists and engineers are developing ways to help patients overcome paralysis and stroke. But what about mental function itself? Can medical intervention restore consciousness?


3D4MEDICAL.COM/GETTY

Jean-Paul Sartre wrote[1]: "In one sense choice is possible, but what is not possible is not to choose." To the neurologist, however, gaining consciousness is a decision of the unconscious brain to make choices. Philosophers and scientists may argue about the definition of consciousness[2,3], but neurologists have little trouble identifying its absence. Now, physicians are beginning to understand how it can be restored in some patients with severe brain damage. A case report by Schiff *et al.* (page 600 of this issue[4]) raises hope in this area, and sheds light on the neurobiological underpinnings of consciousness. Schiff and his colleagues treated a patient who had been in a 'minimally conscious state' (Box 1, overleaf) for several years after a serious brain injury.

Sadly, the vast majority of coma patients do not recover consciousness. The prognosis is determined by the type of injury to the brain, its extent, and the findings from serial neurological examinations[5]. For example, a trained neurologist can predict with near certainty that meaningful recovery will not occur for many patients who remain in a coma for days after a cardiac arrest, in which the brain is deprived of blood flow and oxygen. For other patients, however, the outcome is less certain.

Even after severe brain injury, some patients retain enough of the cerebral cortex to raise hopes that some degree of organized mental function might one day recover. Indeed, some show intermittent signs that are clearly distinguishable from coma, despite an overall level of function that is effectively unresponsive. For these patients, we do not have reliable indicators of prognosis, and we lack treatments that might help the brain restore consciousness.

But advances in basic neuroscience are beginning to reveal the brain systems that are responsible for monitoring and sustaining engagement with the world around us. A key component is the thalamus, which lies between the brainstem and the cerebral hemispheres, and forms the gateway to the brain's cortex.

The thalamus is organized as a set of nuclei. The best understood of these nuclei are those containing the neurons that relay information from the eyes, ears and skin to the appropriate sensory cortex. But much of the thalamus is poorly understood. Anatomical studies in non-human primates have identified a class of thalamic neuron that might operate more generally in activating cortical networks[6]. These neurons, which stain positively for the calcium-binding protein calbindin, are found in all thalamic nuclei. Although we know little about the physiological properties of these calbindin-positive cells, they tend to exhibit a different pattern of connections with the cortex compared with the relay cells. Their axons terminate more broadly both across cortical areas and in layers that the relay cells miss. These calbindin-positive cells comprise a large percentage of the intralaminar nuclei of the thalamus — nuclei that have long been thought to have a role in arousal.

Schiff *et al.*[4] hypothesized that their patient might express a minimal level of consciousness because of a primary impairment of the arousal system itself. The patient had suffered irreparable damage to much of the cerebral cortex, but many essential areas were preserved. By stimulating the intralaminar nuclei, the authors hoped to switch on the undamaged areas of cortex. Neurologists and neurosurgeons have previously used electrodes to monitor brain activity in patients with epilepsy and to stimulate deep-brain regions in the treatment of severe Parkinson's disease. Because the brain itself lacks sensory receptors (after all, it is normally protected by a cranium), these electrodes cause no discomfort. This insight, and extensive experience with stimulation electrodes in animal experiments[7], made the procedure feasible and relatively safe. Such considerations probably helped to guide the complex ethical debate preceding this experimental trial on a human patient.

The results were dramatic. Within 48 hours of the surgery to place the electrodes, the patient, who had remained in a minimally conscious state for 6 years, demonstrated increased arousal and sustained eye-opening, as well as rapid bilateral head-turning

LETTERS

Behavioural improvements with thalamic stimulation after severe traumatic brain injury

N. D. Schiff[1], J. T. Giacino[2,3], K. Kalmar[2], J. D. Victor[1], K. Baker[4], M. Gerber[2], B. Fritz[2], B. Eisenberg[2], J. O'Connor[2], E. J. Kobylarz[1], S. Farris[4], A. Machado[4], C. McCagg[2], F. Plum[1], J. J. Fins[5] & A. R. Rezai[4]

Widespread loss of cerebral connectivity is assumed to underlie the failure of brain mechanisms that support communication and goal-directed behaviour following severe traumatic brain injury. Disorders of consciousness that persist for longer than 12 months after severe traumatic brain injury are generally considered to be immutable; no treatment has been shown to accelerate recovery or improve functional outcome in such cases[1,2]. Recent studies have shown unexpected preservation of large-scale cerebral networks in patients in the minimally conscious state (MCS)[3,4], a condition that is characterized by intermittent evidence of awareness of self or the environment[5]. These findings indicate that there might be residual functional capacity in some patients that could be supported by therapeutic interventions. We hypothesize that further recovery in some patients in the MCS is limited by chronic underactivation of potentially recruitable large-scale networks. Here, in a 6-month double-blind alternating crossover study, we show that bilateral deep brain electrical stimulation (DBS) of the central thalamus modulates behavioural responsiveness in a patient who remained in MCS for 6 yr following traumatic brain injury before the intervention. The frequency of specific cognitively mediated behaviours (primary outcome measures) and functional limb control and oral feeding (secondary outcome measures) increased during periods in which DBS was on as compared with periods in which it was off. Logistic regression modelling shows a statistical linkage between the observed functional improvements and recent stimulation history. We interpret the DBS effects as compensating for a loss of arousal regulation that is normally controlled by the frontal lobe in the intact brain. These findings provide evidence that DBS can promote significant late functional recovery from severe traumatic brain injury. Our observations, years after the injury occurred, challenge the existing practice of early treatment discontinuation for patients with only inconsistent interactive behaviours and motivate further research to develop therapeutic interventions.

Severe traumatic brain injury typically results in *en passant* injuries to thalamic and midbrain structures that are essential parts of the forebrain arousal regulation system[6–11]. We sought to determine whether DBS in the central thalamus could promote behavioural responsiveness in a patient in a chronic MCS by approximating the normal role of mesial frontal cortical and brainstem inputs, which adjust firing rates in central thalamic neurons to regulate cognitive effort and maintain brain metabolic activity during normal wakefulness[10,11].

As part of a multi-institutional, FDA- and IRB-approved clinical trial, we implanted DBS electrodes bilaterally within the central thalamus of a 38-yr-old male who remained in an MCS following a severe traumatic brain injury (see Supplementary Information). Over a two-year course of inpatient rehabilitation and four subsequent years in a nursing home, he failed to recover consistent command-following or communication ability and remained non-verbal. Six-and-a-half years after the injury, the patient was re-admitted to an inpatient rehabilitation unit for comprehensive re-evaluation and rehabilitation. Although he remained unable to communicate reliably, functional MRI showed preservation of a large-scale, bi-hemispheric cerebral language network, indicating that a substrate for further recovery might exist[4]. Additional studies using positron emission tomography showed that the patient's resting global cerebral metabolism was markedly reduced. These observations supported our hypothesis that the patient's inconsistent behavioural responsiveness and communication reflected a global reduction in neuronal activity resulting from widespread de-afferentation and compression injuries to the thalamus and midbrain[4].

We used a single-subject, multiple baseline design to investigate the effects of DBS using a priori statistical evaluation of preselected behavioural metrics. A presurgical baseline established the patient's level of responsiveness before surgery. Post-surgical assessments were conducted within 48 h and during a 2-month period preceding a DBS titration phase in which the patient was exposed to varying patterns of stimulation, to allow us to identify optimal behavioural responses. After the titration phase, a six-month double-blinded crossover phase began, in which DBS was alternated between being turned on and turned off every 30 days (Fig. 1). A multidisciplinary neurorehabilitation team performed all evaluations using standardized assessment procedures.

To assess the effects of DBS, we prospectively chose the JFK Coma Recovery Scale — Revised (CRS-R), a measure of neurobehavioural function that has been validated in patients with disorders of consciousness[12,13] (Supplementary Fig. 1). We also developed three secondary outcome measures that assessed object naming, purposeful upper extremity limb movement and oral feeding to characterize behavioural changes more fully (see Supplementary Information). A comprehensive inpatient rehabilitation program was initiated four months before surgery and continued without modification throughout the study (Figs 1, 2a,b). This program consisted of physical, occupational, speech and recreational therapies and did not differ from the patient's initial course of rehabilitation, which had been completed four years earlier.

CRS-R evaluations conducted over a three-week presurgical baseline verified that the patient's neurobehavioural status was stable. Three subscales of the CRS-R were subsequently selected as the primary outcome measures. Scores on the Arousal subscale indicated that the patient could not consistently respond to basic verbal commands.

[1]Department of Neurology & Neuroscience, Weill Cornell Medical College, New York, New York 10021, USA. [2]JFK Johnson Rehabilitation Institute, Edison, New Jersey 08818, USA. [3]New Jersey Neuroscience Institute, Edison, New Jersey 08818, USA. [4]Center for Neurologic Restoration, Cleveland Clinic Foundation, Cleveland, Ohio 44195, USA. [5]Division of Medical Ethics, Weill Cornell Medical College, New York, New York 10021, USA.

人工神経器具市場の可能性は膨大だ。米国には推定1000万人のうつ病患者がいるほか，450万人はアルツハイマー病による記憶喪失に苦しんでいる。200万人以上が脊椎損傷や筋萎縮性側索硬化症，脳卒中によって麻痺を生じており，100万人以上が失明していると考えられている。（J. ホーガン）

次世代医療機器

1）intelligent device
賢い器械

2）integrated technology
総合技術

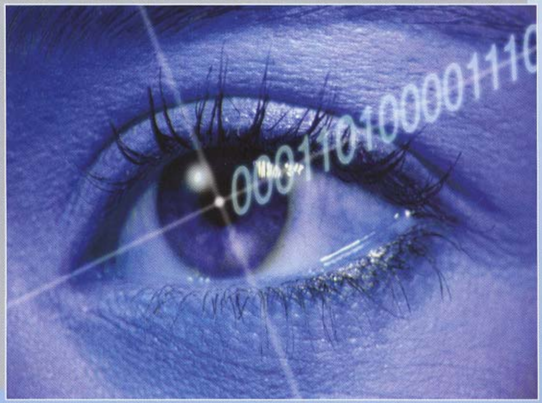
3）combination technology
医薬品と医療機器の融合

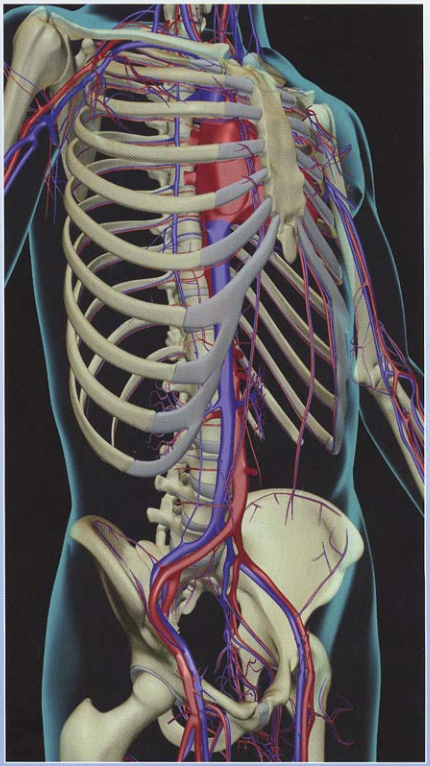
要素技術を医療機器として集積し、統合する組織が必要

UNIVERSITY OF MINNESOTA

Institute for Engineering in Medicine

Where Medicine Meets Technology





For Tomorrow's Innovation

研究開発機能拠点のイメージ【１】

Concept Word → Produce / Control / Coordinate / Assemble

研究開発機能拠点：求められる機能

革新的な医療機器の研究開発、実用化を支援する司令塔機能

産学医・異分野企業連携による共同研究開発の促進	○投薬＋手術では及ばない分野の治療技術・機器の研究開発 ○各種要素技術の集積とアセンブリ（センサー、モーター、ロボット技術等）
革新的研究開発の支援	○素材設計等の基盤研究 ○脳科学等先進分野の研究開発推進 ○開発資金の調達・確保
人材育成	○医工、産学連携人材の育成 ○コーディネータ人材の育成

連携 ⇔ **医療技術産業戦略コンソーシアム（METIS）**

連携 ⇔ **独立行政法人**
・医薬基盤研究所
・産業技術総合研究所　等

連携 ⇔ **ナショナル医療センター**
・国立循環器病センター
・国立がんセンター　等

司令塔 →

開発ターゲット

インテリジェント・デバイス

治療機器分野	人工心臓、人口肺、ペースメーカー　等
高度診断分野	バイオセンサー、ロボットセンサー　等
マテリアル分野	セラミック、ナノ、バイオ　等

BMI（ブレイン・マシン・インターフェース）

異分野連携コンソーシアム

医療機関、医薬・医療関連企業

⇕ 異分野連携

多彩なものづくり企業群
○先端素材開発・製造企業
○センサー技術等開発企業
○組立加工企業　等

⇕ 産学官連携

大学	研究機関
経済団体	自治体

研究開発機能拠点のイメージ【２】

■研究開発機能拠点を整備
～機能拠点をつなぐネットワーク型から、機能統合型拠点へ～