Arousal by stimulation of deep-brain nuclei

Arising from: N. D. Schiff *et al.* *Nature* 448, 600–603 (2007)

Schiff *et al.*[1] show that deep-brain stimulation of the unspecific thalamocortical system through certain midline thalamic nuclei produces an alerting effect in a patient in a minimally conscious state. Such nuclei include the central lateral nucleus, paralaminar regions of the median dorsalis, and the posterior–medial aspect of the centromedian/parafascicularis nucleus complex.

Hassler and colleagues published a similar study, with certain methodological differences, in 1969[2,3]. Their aim was similar, namely the alerting of consciousness by activation of anatomically undamaged neurons in the unspecific thalamocortical system. McLardy *et al.*[4] were also motivated by the same concept, but gave little detail of methodology and failed to produce a result. Several reports followed, but that by Schiff *et al.*, though it concerns only a single case, is the most detailed and is strengthened by its internal statistical control.

Hassler's subject[2] is described as having a post-traumatic apallic state. This term derives from the original description by Kretschmer[5] of a state of waking either without awareness (as seen in the vegetative state), or with minimal awareness (as in the minimally conscious state). Hassler stimulated pallidum on the basis that it feeds into the unspecific system as well as the specific system. This view was supported at the time by the elicitation of recruiting responses (incremental high-voltage synchronizing waves, usually, though not always, of long latency, carried over the unspecific thalamocortical system[6]) by stimulation of pallidum[7]. The dipole for such laminar field potentials is in the superficial layers of the cortex[8]. This is perhaps concordant with the later demonstration of the ubiquitously distributed matrix of calbindin-immunoreactive neurons, which project to the superficial layers of wide areas of cortex[9,10]. Hassler also chose the basal portion of, using his terminology, the latero–polar nucleus of the thalamus on the opposite side.

As a neurologist, a neuroanatomist who wrote the anatomy of the thalamus for the Schaltenbrand stereotactic atlas, and someone with a wide experience of stereotaxy, Hassler was well placed to make the foregoing contribution.

Hugh Staunton[1]

[1]Department of Clinical Neurological Sciences, Royal College of Surgeons in Ireland, Beaumont Hospital, Dublin 9, Ireland.

email: hugh@iol.ie

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Schiff et al. *reply*

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Staunton[1] highlights prior work applying deep-brain stimulation (DBS) in related thalamic and other subcortical structures in vegetative-state patients. We focused on patients who have plateaued at the upper end of the minimally conscious state at least one year after injury[2], a group distinct from patients remaining in or just above vegetative state within the low end of the minimally conscious state. Patients remaining in a chronic vegetative state have anatomic pathology consistent with widespread neuronal death and cerebral disconnection[3]. In these patients, forebrain structures within the corticostriatopallidal–thalamocortical systems have been overwhelmingly damaged .

The paper by Hassler *et al.*[4] cited by Staunton is one of several early studies that culminated in a large multicentre series of vegetative-state patients implanted with DBS systems in the centromedian thalamus[5,6]. Those studies found that acute arousal responses occurred in the majority of patients, who nonetheless did not improve. Arousal responses *per se*, including wide eye-opening, changes in autonomic function and shifts to higher-frequency content ('desychronization') of the electroencephalogram reflect a basic and broad activation of forebrain, brainstem and spinal cord systems[7]. Notably, these earlier studies demonstrated that acute arousal responses alone are not predictive of an effect on outcome, nor do they imply a role for DBS in the sustained recovery of higher integrative brain function.

The prior literature must be examined for two distinct aspects of study design. The first is that in earlier studies of DBS in vegetative-state patients, the patient-selection criteria did not ensure that patients were unlikely to recover function spontaneously. The few patients with traumatic brain injuries labelled as 'responders' were studied 3 to 6 months into their recovery course[5]. The probability of recovery of consciousness for these patients (and the Hassler patient[4]) ranged from 35% to 16%[8,9]. Moreover, these few patients have since been reclassified by the investigators as having been in minimally conscious state[10]. Smaller prospective studies of such patients indicate that the likelihood of recovery of consciousness by one year from minimally conscious state at 3–6 months after traumatic injury is significantly higher[11,12].

The second design issue is that evaluation of the effects of DBS were not carried out in a formal, blinded fashion to allow assessment of the effects on behaviour, even within a single patient. To assess a causal influence of DBS on recovery, formal neurobehavioural assessments are essential to establish baseline diagnosis, assure that natural recovery has plateaued, and to track emergence of cognitively

mediated behaviours induced by DBS. That further recovery was incidental to the application of DBS in these earlier studies has remained statistically likely. In contrast, our patient had been formally assessed, with stable behavioural profiles for more than 6 years, making spontaneous recovery from minimally conscious state very unlikely; also, DBS effects were tracked and shown to be causal to behavioural recovery[2].

Although other thalamic and subcortical structures produce arousal responses when stimulated, we chose our targets because of their specific anatomical and physiological properties, not shared by the globus pallidus or centromedian nucleus (which does not have strong projections to the cortex). The central lateral nucleus and surrounding regions have reciprocal monosynaptic connections with the medial frontal regions supporting arousal regulation, receive very dense innervation from brainstem arousal systems, and have diffuse inputs to the striatum, among other unique specializations supporting the use of this target[13].

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], T. Biondi[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]

[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.
e-mail: nds2001@med.cornell.edu

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