Neurol Med Chir (Tokyo) 50, 845 ~ 852, 2010

Neuroethics of Deep Brain Stimulation for Mental Disorders: Brain Stimulation Reward in Humans

Hideki OSHIMA and Yoichi KATAYAMA*

Departments of Functional Morphology and
*Neurological Surgery, Nihon University School of Medicine, Tokyo

Abstract

The theoretical basis of some deep brain stimulation (DBS) trials undertaken in the early years was the phenomenon of “brain stimulation reward (BSR),” which was first identified in rats. The animals appeared to be rewarded by pleasure caused by the stimulation of certain brain regions (reward system), such as the septal area. “Self-stimulation” experiments, in which rats were allowed to stimulate their own brain by pressing a freely accessible lever, they quickly learned lever pressing and sometimes continued to stimulate until they exhausted themselves. BSR was also observed with DBS of the septal area in humans. DBS trials in later years were undertaken on other theoretical bases, but unexpected BSR was sometimes induced by stimulation of some areas, such as the locus coeruleus complex. When BSR was induced, the subjects experienced feelings that were described as “cheerful,” “alert,” “good,” “well-being,” “comfort,” “relaxation,” “joy,” or “satisfaction.” Since the DBS procedure is equivalent to a “self-stimulation” experiment, they could become “addicted to the stimulation itself” or “compulsive about the stimulation,” and stimulate themselves “for the entire day,” “at maximum amplitude” and, in some instances, “into convulsions.” DBS of the reward system has recently been applied to alleviate anhedonia in patients with refractory major depression. Although this approach appears promising, there remains a difficult problem: who can adjust their feelings and reward-oriented behavior within the normal range? With a self-stimulation procedure, the BSR may become uncontrollable. To develop DBS to the level of a standard therapy for mental disorders, we need to discuss “Who has the right to control the mental condition?” and “Who makes decisions” on “How much control is appropriate?” in daily life.

Key words: deep brain stimulation, neuroethics, addiction, reward, self-stimulation

Introduction

Deep brain stimulation (DBS) in humans has a long history lasting more than half a century since the work reported by Delgado in 1955 and by others. The theoretical basis of some DBS trials undertaken in the early years was the phenomenon of “brain stimulation reward (BSR),” which was identified in rats. Olds and Milner in 1954 noted that rats preferred to return to the experimental environment in which the septal area of their brain was stimulated. They inferred that stimulation of the septal area gives pleasure to rats. This hypothesis was proven in experiments which demonstrated that rats could be trained to execute novel behaviors by stimulation of the septal area. Novel behavior is learned efficiently when it is followed by the presentation of an operant reinforcer, which is usually a natural reward, such as food and water. Since the effect of stimulation of the septal area is equivalent to that of a natural reward as an operant reinforcer, it is reasonable to conclude that the stimulation is rewarding to the rats. Similar studies were performed by Sidman et al. in 1955 and by others. Subsequent research revealed that stimulation of a broad range of areas, including the lateral hypothalamus, could be rewarding to rats. Such areas were termed the “reward system.” BSR is a phenomenon in which the stimulation of a certain area is rewarding and can serve as an operant reinforcer, similar to natural rewards.

Further studies demonstrated that the reward system represents areas which could be activated by natural rewards. Such natural rewards motivate and shape behavior through the peripheral senses of vision, sound, smell, taste, or touch. However, BSR bypasses the peripheral senses to directly activate the reward system and establishes novel behaviors more powerfully than natural rewards.

Experiments in which rats are allowed to stimu-
late their own brain by pressing a freely accessible lever are called “self-stimulation.” In such self-stimulation experiments, rats quickly learn lever pressing.32) Natural rewards tend to inhibit any further need for the same reward through satisfaction. For example, rats stop eating, once they have become satisfied through eating food. In contrast, BSR does not inhibit further stimulation, so that the rats sometimes continue self-stimulation until they exhaust themselves. This suggests that rats could be addicted to the pleasure caused by self-stimulation.

DBS is a procedure which is basically equivalent to a “self-stimulation” experiment. Richardson and Akil38) in fact employed the term “self-administration” in their paper published in 1977, which reported pain relief by DBS. It seems surprising, therefore, that some DBS trials in the early years10,12,15,28,42,43) were undertaken in an attempt to induce BSR. If BSR is induced in patients, they can obtain pleasure from the DBS to whatever extent they wish at any time. Therefore, we need to be rather cautious not to induce inappropriate BSR by DBS, to avoid a situation in which the patient becomes addicted to the pleasure caused by the DBS.

The present paper reviews the literature, including our own experience, concerning BSR induced by DBS. We are not simply opposing DBS of the reward system. Appropriate modulation of the activity of the reward system is probably of clinical significance. We believe, however, that BSR represents a topic which could help to clarify the potential problems of DBS, and should be taken into consideration when discussing the neuroethics of DBS for mental disorders.

**Intended BSR Induced by DBS**

BSR has been demonstrated in all vertebrate species so far tested. Heath and Mickle15) reported a reward-like effect of stimulation of the septal area for the first time in humans in 1960. They stimulated the septal area for therapeutic purposes in a total of 52 patients with intractable pain, schizophrenia, or epilepsy. Other regions, including the caudate nucleus, hippocampus, amygdala, and globus pallidus, were also stimulated. Only when the septal area was stimulated did the patients express feelings which could be accounted for by a reward-like effect. Heath and Mickle stated: “With stimulation of the septal region, the patients appear alerted, speak more rapidly, and generally state that they feel good. Several have expressed the desire for repeated stimulation to this region.”

They came to the conclusion that stimulation of the septal area was a worthwhile therapeutic tool for some patients with intractable pain. Although their paper is frequently quoted as the first attempt to induce BSR in humans, the BSR identified by Olds and Milner in humans was not specifically mentioned as a theoretical basis. While they titled their paper as 7-year experience, they may have been influenced by the report of Olds and Milner first published in 1954 at some point during their work.

The paper of Heath and Mickle was published together with a discussion between Sem-Jacobson and Heath. In this, Sem-Jacobson questioned15): “Do you think that the reason for the relief of pain was that the area stimulated gave so much pleasure that he forgot about the pain? In other words, do you think this area is a pleasure area or do you think it is just that the stimulation in your case is blocking all pain?” Heath replied: “They certainly do have a pleasurable-like response and report feeling good. It would have to be an interpretation from this point on. Whether the stimulus masks pain or whether it blocks pain impulses in some way, we don’t know.”

Sem-Jacobson reported his experience with stimulation of the ventromedial frontal lobe, the temporal lobe, the region of the third ventricle and the mesencephalon in 1959.42) He stated: “We have been able to obtain feelings of comfort, relaxation, joy, and intense satisfaction ... The responses of relaxation and comfort obtained from stimulation of the frontal lobe are so intense that psychotic episodes have been broken up in less than one minute on several occasions ...”

In addition, according to Gol,12) Sem-Jacobson and Torkildsen43) stated in their paper published in 1960: “... emotional responses were repeatedly encountered consisting of ease, relaxation, joy or satisfaction. Desire for repeated stimulation was expressed by some patients. In some cases, deep stimulation was given over a period of days without ill effects and obvious evidence of rewards from stimulation. When allowed to stimulate themselves, some patients stimulated themselves into convulsion.”

Gol12) described the results of stimulation of the septal area in 6 patients with intractable pain, due mostly to terminal malignancy in 1967. He clearly stated that the theoretical basis of his DBS trial was BSR. He was unable to induce a distinct pleasure sensation but encountered a patient who demonstrated a reward-like effect. He reported: “... the patient stated that he felt more cheerful and more alert during stimulation. When smoking cigarettes, he noted that the cigarettes tasted stronger and his pleasure from smoking was increased during stimulation.”

These observations indicate that stimulation of the reward system can induce a pleasure-like response and also accentuate pleasure derived from natural rewards, which is consistent with the find-
ings obtained in rats.27) He commented that, although a pleasurable state can be induced, the stimulation itself does not necessarily suppress all pain.

Richardson36) also reported his experience with stimulation of various areas in 1982. He stimulated the septal area in 5 patients. He found that pain relief was obtained in 4 of the 5 by stimulation of the superior septal area and in 3 of the 5 by stimulation of the inferior septal area, although no reward-like effect was mentioned.

Schvarcz41) described in 1985 his experience with stimulation of the septal area to control intractable pain in 10 patients. He stated: "... just above threshold, a feeling of generalized warmth was often felt. Also a sensation of well-being and relaxation was frequently mentioned."

Since the effect of DBS varies substantially depending on the area to which the stimulation is actually delivered and on the stimulation parameters, these somewhat conflicting results are not surprising. Gol12) emphasized the very circumscribed nature of the area associated with BSR, reporting that the reward-like effect was induced by only one of 24 electrodes implanted within the septal area of a single patient.

Based on the above reports, we can conclude at least that stimulation of certain particular areas with appropriate stimulation parameters can induce a pleasure-like response which is expressed as feelings described as "cheerful," "alert," "good," "well-being," "comfort," "relaxation," "joy," or "satisfaction," and a reward-like effect which causes "a desire for repeated stimulation" to a varying extent. Moan and Heath28) reported one patient who experienced sexual pleasure through stimulation of the septal area in 1972. The pleasure was so overwhelming that self-stimulation had to be discontinued, although the patient did protest strongly.

**Unintended BSR Induced by DBS**

Most DBS trials in later years were undertaken with the theoretical basis for the DBS unrelated to BSR. DBS trials carried out during the 1970s and 1980s were based on or at least influenced by the concept of the "gate control theory" proposed by Melzak and Wall,20) or the theory of the "descending pain inhibitory pathway" proposed by Mayer and Liebeskind,25) both of which were derived from experiments in rats.

Although the original gate control theory hypothesized that pain inhibition could be elicited by non-pain sensation within the spinal cord, a similar mechanism of pain inhibition was assumed to exist also at higher levels of the central nervous system. The somatosensory thalamus was stimulated in DBS trials for the activation of such a mechanism in patients with intractable pain. The theory of the descending pain inhibitory pathway hypothesizes that activity at higher levels of the central nervous system can inhibit pain at the spinal cord. The periventricular or periaqueductal gray matter was stimulated in DBS trials for activation of the descending pain inhibitory pathway in patients with intractable pain.19,37,38) Dieckmann and Witzmann10) reported their experience with stimulation of either the somatosensory thalamus or the periventricular gray matter for controlling intractable pain in 52 patients in 1982. A patient who demonstrated an unexpectedly strong reward-like effect was encountered. They stated: "One patient who appeared to have relief of pain from stimulation seemed to have become addicted to the stimulation itself. He tried to stimulate himself during the entire day and demanded an additional stimulator and batteries. After withdrawal treatment, the addiction-like behavior disappeared ..."

It is unclear from their description whether the somatosensory thalamus or the periventricular gray matter was stimulated in this patient. It seems likely, however, that this patient underwent stimulation of the periventricular gray matter, since there is no evidence indicating that the somatosensory pathway is involved in the reward system. We have never experienced an addiction-like effect, although in our work we have performed stimulation of the somatosensory thalamus in more than 100 patients for pain control.

The descending pain inhibitory pathway originates in the periventricular or periaqueductal gray matter and is relayed by the raphe magnus and locus coeruleus complex.11) There are several lines of evidence to indicate that stimulation of these areas can inhibit pain in rats and cats.9,17,20,22,25,35) We reported that stimulation of the parabrachial region, which is part of the locus coeruleus complex, was useful for controlling intractable pain in 2 patients caused by terminal malignancy in 1985.21) The anatomical target was situated 13 to 15 mm below the anterior commissure-posterior commissure line, 1 to 5 mm posterior to the posterior commissure, and 6.5 to 8.5 mm lateral to the midline (Fig. 1).

Young et al.50) attempted to reproduce our findings and reported that good pain control was achieved in 3 of 6 patients tested in 1992. They described their stimulation site as the Kölliker-Fuse nucleus, which is a name that is also given to part of the locus coeruleus complex. Their anatomical target was situated 12 to 22 mm below the anterior
Fig. 1 Schematic representation, lateral view (A) and axial view (B), of a parabrachial region stimulation site according to Katayama et al.\textsuperscript{21}) AC: anterior commissure, BC: brachium conjunctivum, DX: decussation of the brachium conjunctivum, IC: inferior colliculus, LC: locus coeruleus, NPB: nucleus parabrachialis, NTTP: nucleus tegmentalis pedunculopontinus, PC: posterior commissure, III: third ventricle, IV: fourth ventricle. \textit{Line a}: line connecting AC and PC, \textit{line b}: line showing the contour of the base of the fourth ventricle. \textit{Lines 1 and 2} on Fig. 1A indicate the levels of the sections in Fig. 1B.

commissure-posterior commissure plane, 2 to 6 mm posterior to the posterior commissure, and 7 to 10 mm lateral to the midline. Comparison of the anatomical targets suggests that both we and Young et al. stimulated a similar part of the locus coeruleus complex.

Mapping of the stimulation sites associated with pain inhibition in cats suggests that the area we called the parabrachial region includes variously named nuclei,\textsuperscript{1,48,49} including the nucleus of the brachium conjunctivum of Winkler and Potter, the nucleus parabrachialis of Taber, the marginal nucleus of the brachium conjunctivum of Berman, the caudal part of the nucleus tegmenti pedunculopontinus and the nucleus subcoeruleus of Taber as well as the paralemniscal tegmental field and the Kölliker-Fuse nucleus of Berman.

Young et al.\textsuperscript{50}) encountered a patient who unexpectedly demonstrated a reward-like effect. They stated: "The patient began to use stimulation for progressively longer periods of time and at higher amplitude. After several months, she was stimulating virtually continuously at the maximum stimulus strength of 10 V. She became compulsive about the stimulation, refused requests to decrease stimulation, and avoided her husband who attempted to assist her in decreasing stimulation. Increased tone of contralateral limb muscles was noted during stimulation at maximum amplitude and this appeared to be very gratifying to the patient. After inactivating the Kölliker-Fuse nucleus stimulation, the patient's compulsive stimulation ceased."

It is not entirely certain if this patient's compulsive behavior was caused by BSR. The stimulation was at least pleasurable to her, however, even though her limb muscle tone increased. We actually experienced a similar patient in 1986, although the details remain unpublished. He was suffering from intractable pain after surgery for spinal cord tumor. We tested the effects of DBS of the parabrachial region in this patient, and a DBS lead was then internalized since the effect of stimulation appeared to be satisfactory for pain control. Soon after the surgery, he began to stimulate himself continuously during the entire day. While his pain was partially controlled by the DBS, his desire to continue stimulation appeared to be unrelated to pain control. We requested that he discontinue the stimulation for a while. He never agreed, stating that the stimulation made him feel quite good and comfortable. This suggested that the stimulation was pleasurable to him. Since he eventually came to stimulate himself at maximum intensity and demanded additional batteries, we took his Xtrele (Medtronic, Inc., Minneapolis, Minn., U.S.A.) type pulse generator away. After this experience, we ceased to employ DBS of the parabrachial region.

The periventricular gray matter belongs to the region of the hypothalamus. The lateral hypothalamus is the area in which BSR is consistently induced in rats.\textsuperscript{3,33,34} The locus coeruleus complex is also one of the areas associated with BSR in rats.\textsuperscript{4,16,46,47} The above-mentioned experience suggests that DBS in the proximity of these areas could induce BSR unexpectedly, in which patients would be "addicted to the stimulation itself" or "compulsive about the stimulation itself".
We have performed DBS in more than 1000 patients with various diseases, such as intractable pain and movement disorders since 1979. The stimulation sites employed for DBS include the somatosensory or ventrolateral thalamus, periaqueductal gray matter, midbrain reticular formation (cuneiformis nucleus), parabrachial region, basal forebrain nucleus, globus pallidus, subthalamic nucleus, and zona incerta, as well as the motor cortex and other cortical areas. The patient described above is fortunately the only one in whom BSR occurred unexpectedly. We need to recognize, however, that any DBS has the possibility of inducing BSR, and this must be considered when we develop new DBS procedures.

**Discussion**

**I. Characteristics of BSR in humans**

Although little is yet known concerning the detailed effects of stimulation of the reward system in humans, the experience in patients so far reported (Table 1) is consistent with the BSR described in rats, and can be summarized as follows. Firstly, the stimulation produces pleasure-like responses which have been described as “cheerful,” “alert,” “good,” “well-being,” “comfort,” “relaxation,” “joy,” or “satisfaction.” Secondly, stimulation of the reward system accentuates the pleasure caused by natural rewards, as reported for “pleasure from smoking.” However, the pleasure described from smoking is of course dependent on many variables, so that value of this observation remains uncertain. On the other hand, Schlaepfer et al. recently reported detailed examinations showing that DBS of the reward system at the accumbens nucleus can accentuate reward-oriented behavior. Finally, the stimulation can serve as an operant reinforcer. No attempt has been made in humans to modify specific behavior by BSR. Nevertheless, the self-stimulation procedure employed for DBS is equivalent to the self-stimulation experiments undertaken in rats. In such self-stimulation experiments, pressing a freely accessible lever activates a circuit for stimulation of the reward system of the animals, so that lever pressing represents a specific behavior and BSR is an operant reinforcer. Statements like “addicted to the stimulation itself” and “compulsive about the stimulation,” can thus be viewed as evidence indicating that BSR can induce novel behavior and act as an operant reinforcer in humans as well as rats.

**II. Addiction to DBS by BSR in humans**

Two important characteristics are evident in BSR. Firstly, the pleasure associated with BSR appears to be much greater than that afforded by natural rewards such as the satisfaction of appetite or sexual drive. If rats are given a choice between BSR and natural rewards, they tend to choose BSR. Secondly, the satisfaction associated with BSR does not inhibit further stimulation, unlike natural rewards. This suggests that the pleasure caused by BSR does not result in satisfaction in the real sense of the word.

In self-stimulation experiments in rats, BSR sometimes leads the animals to continue stimulation until they exhaust themselves. When BSR is induced by DBS in patients with the self-stimulation procedure, some may stimulate “for the entire day” or “at maximum amplitude.” In other instances, some may stimulate themselves “into convulsions.” This resembles the addiction observed in other situations. We need to bear in mind that, once BSR is induced by DBS with the self-stimulation procedure, the stimulation may become uncontrollable. We should not allow patients to engage in self-stimulation procedures under such circumstances.

**III. Clinical significance of BSR in humans**

If DBS is performed for the purpose of inducing specific behavior by using BSR as an operant reinforcer, this could be regarded as direct mind control. Such a procedure certainly requires ethical or neuroethical discussion. DBS could be employed just to adjust the patient’s feelings and reward-oriented behavior within the normal range. This may be of clinical significance as a method for controlling certain mental disorders such as depression.

In addition, we do not yet know whether DBS can stabilize abnormal activity of the reward system with certain stimulation parameters. All previous authors except Gol performed DBS with relatively low frequency pulses of no more than 60 Hz (Table 1). DBS with high frequency pulses of more than 100 Hz is assumed to stabilize abnormal activity within the extrapyramidal motor system in movement disorders. Therefore, DBS of the reward system may be useful to control symptoms by stabilizing reward-oriented behavior in certain mental disorders such as compulsive eating, drug addiction, and abnormal gambling.

**IV. Neuroethics of DBS for mental disorders**

However, one very difficult problem remains: who should act to adjust the patient's feelings and reward-oriented behavior within the normal range? If we allow patients to perform self-stimulation, the possibility arises that BSR may eventually lead to ad-
Table 1 Summary of reports on brain stimulation reward in humans

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Stimulation site</th>
<th>n</th>
<th>Feelings induced by stimulation (n)</th>
<th>Response to stimulation (n)</th>
<th>Stimulation parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sem-Jacobsen (1959)</td>
<td>frontal lobe</td>
<td>42</td>
<td>comfort, relaxation, joy, and intense satisfaction</td>
<td>desire for repeated and intense stimulation, desire for continuous and intense stimulation (into convulsions)</td>
<td>50 Hz, 1 msec</td>
</tr>
<tr>
<td>Sem-Jacobsen and Torkildsen (1960)</td>
<td>septal area</td>
<td>6</td>
<td>good, pleasure</td>
<td>desire for repeated stimulation</td>
<td>2-5 kHz, 0.02-0.06 msec, &lt;12 V</td>
</tr>
<tr>
<td>Heath and Mickle (1960)</td>
<td>septal area</td>
<td>52</td>
<td>more cheerful and more alert (1)</td>
<td>protesting against discontinuation of stimulation, desire for continuous stimulation (1)</td>
<td>30-60 Hz</td>
</tr>
<tr>
<td>Gol (1967)</td>
<td>septal area</td>
<td>6</td>
<td>more cheerful and more alert (1)</td>
<td>desire for continuous stimulation (1)</td>
<td>1 msec</td>
</tr>
<tr>
<td>Moan and Heath (1972)</td>
<td>thalamus or periventricular gray matter</td>
<td>26</td>
<td>overwhelming sexual pleasure (1)</td>
<td>addicted to the stimulation, desire for continuous stimulation (1)</td>
<td>50-60 Hz, &lt;10 V</td>
</tr>
<tr>
<td>Dieckmann and Witzmann (1982)</td>
<td>septal area</td>
<td>10</td>
<td>well-being and relaxation</td>
<td>compulsive about the stimulation, desire for continuous stimulation (1)</td>
<td>10-30 Hz</td>
</tr>
<tr>
<td>Schvarcz (1985)</td>
<td>septal area</td>
<td>10</td>
<td>quite good and comfortable (1)</td>
<td>desire for continuous and intense stimulation (1)</td>
<td></td>
</tr>
<tr>
<td>Young et al. (1992)</td>
<td>Köllicker-Fuse nucleus</td>
<td>6</td>
<td>gratifying (1)</td>
<td>desire for continuous and intense stimulation (1)</td>
<td></td>
</tr>
<tr>
<td>Oshima and Katayama (unpublished)</td>
<td>parabrachial region</td>
<td>3</td>
<td>must be under someone else's control</td>
<td>desire for continuous and intense stimulation (1)</td>
<td></td>
</tr>
</tbody>
</table>

References


Acknowledgments

The authors wish to thank Takamitsu Yamamoto, M.D., Ph.D. of the Division of Applied System Neuroscience, Ni-hon University School of Medicine; H. Oshima et al., for their invaluable comments and discussions.

References

9) DeSalles AAF, Katayama Y, Becker DP, Hayes RL: Pain suppression induced by electrical stimulation of the pontine parabrachial region: Experimental study

H. Oshima et al.
40) Shizgal P, Murray B: Neuronal basis of intracranial self-stimulation, in Lieberman JM, Cooper SJ (eds): The


Address reprint requests to: Hideki Oshima, M.D., Ph.D., Department of Functional Morphology, Nihon University School of Medicine, 30-1 Oyaguchikamimachi, Itabashi-ku, Tokyo 173-8610, Japan. e-mail: hoshima@med.nihon-u.ac.jp