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FINAL NARRATIVE REPORT

1. Principal Investigator: **Barry R. Komisaruk, Ph.D.**

2. Institution: **Rutgers, The State University of New Jersey**
Department of Psychology
101 Warren Street
Newark, NJ 07102

3. Grant Title: **Using fMRI Online as a Biofeedback Signal for Brain and CNS Rehabilitation.**

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NJ COMMISSION ON SPINAL CORD RESEARCH

4. Grant Number: **NJCSCR Grant # 01-3004-SCR-S-0**

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1. Original aims of the project:

The main aim of the project was to develop a method of brain imaging, using fMRI ("functional Magnetic Resonance Imaging") by which the person in the scanner would be shown his/her brain activity in near-real-time and asked to modify the activity voluntarily by cognition in the absence of physical sensory stimulation. The goal was to ascertain whether this "neurobiofeedback" procedure would enable a person with spinal cord injury who is experiencing chronic pain to "cool down" hotspots of brain activity that are correlated with the pain and whether this would attenuate the pain. Furthermore, because of compromised sexual response in persons with spinal cord injury, we also proposed to ascertain the brain regions whose activity is normally correlated with sexual response and ascertain whether activity in these brain regions could be activated voluntarily by persons with spinal cord injury, using our neurobiofeedback methodology, and whether doing so would provide pleasurable feelings, thereby improving the quality of life of those women and men.

2. Project successes:

We have succeeded in developing the near-real-time neurobiofeedback methodology and applying it to pain attenuation and sexual response induction, both via the subjects' use of cognition in the absence of physical sensory stimulation. Our evidence for both this pain attenuation and sexual response induction is characterized below.

A. How the near real time activity appears to the subject in the fMRI scanner

The attached digital CD motion picture (80-second duration) shows the near-real-time activity that the subject in the scanner sees. The 3 Powerpoint slides should start automatically upon clicking on the CD drive. The third slide contains the

movie. **Figure 1** shows the beginning of the movie. In this example, the subject is tapping the fingers of her right hand together in rapid succession. The brain images show the induced activity in her left-side sensory cortex (the 2 brain images are serial transaxial views of her brain as if her head is oriented toward the observer and her feet oriented away from the observer, looking upwards). The green light seen in the movie is a green laser that we shine on the monitor screen showing the area of interest to the subject in the scanner. It is registered on the camcorder and thereby projected to the subject who views it in near-real-time in the scanner.

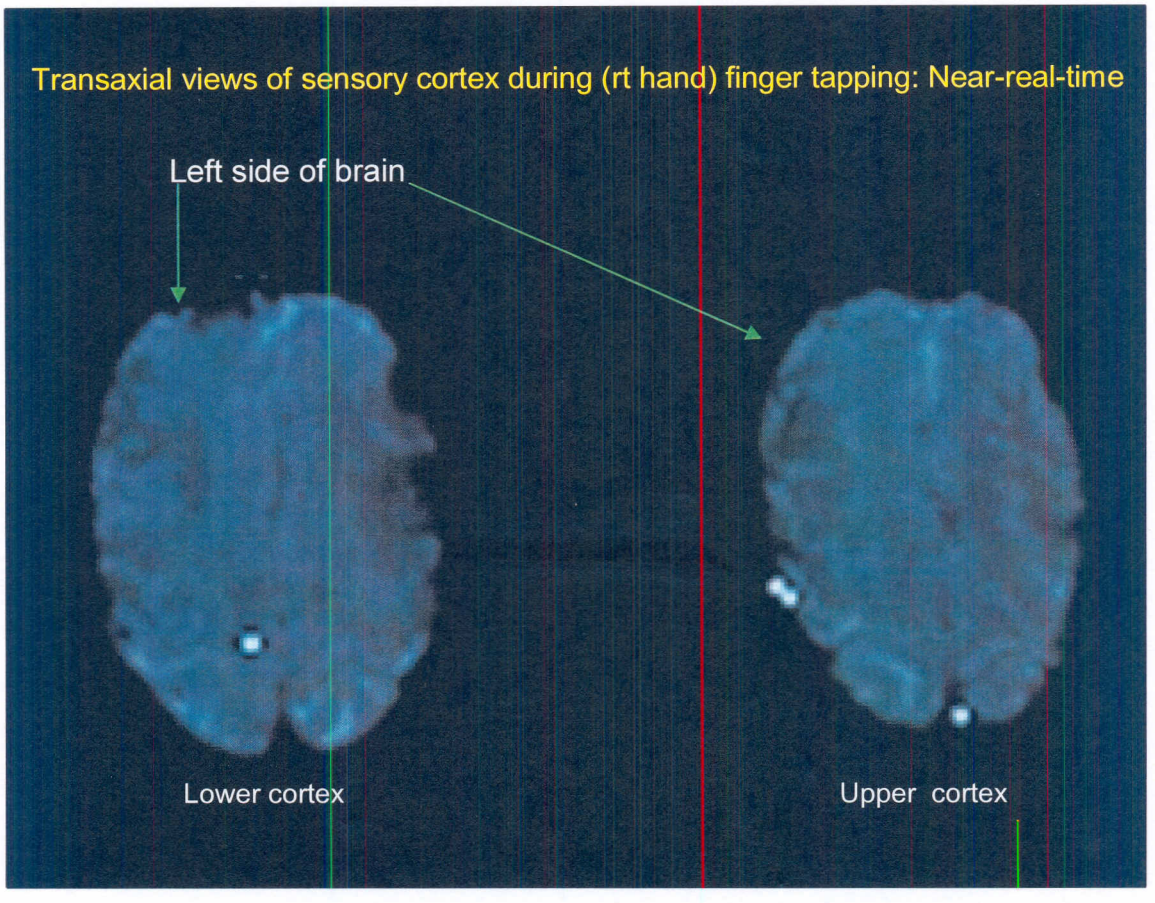

Figure 1

In Section D, below, we describe the arrangement of our equipment and an example of the results we have achieved using our methodology, specifically: a) pain blockage produced by suppressing the brain activity in the sensory cortex that normally responds to noxious stimulation of the finger and b) activation of sensory cortex that normally responds to genital stimulation, just by thought in the absence of actual genital stimulation.

B. Pain blockage produced by suppressing the brain activity in the sensory cortex that normally responds to noxious stimulation of the finger

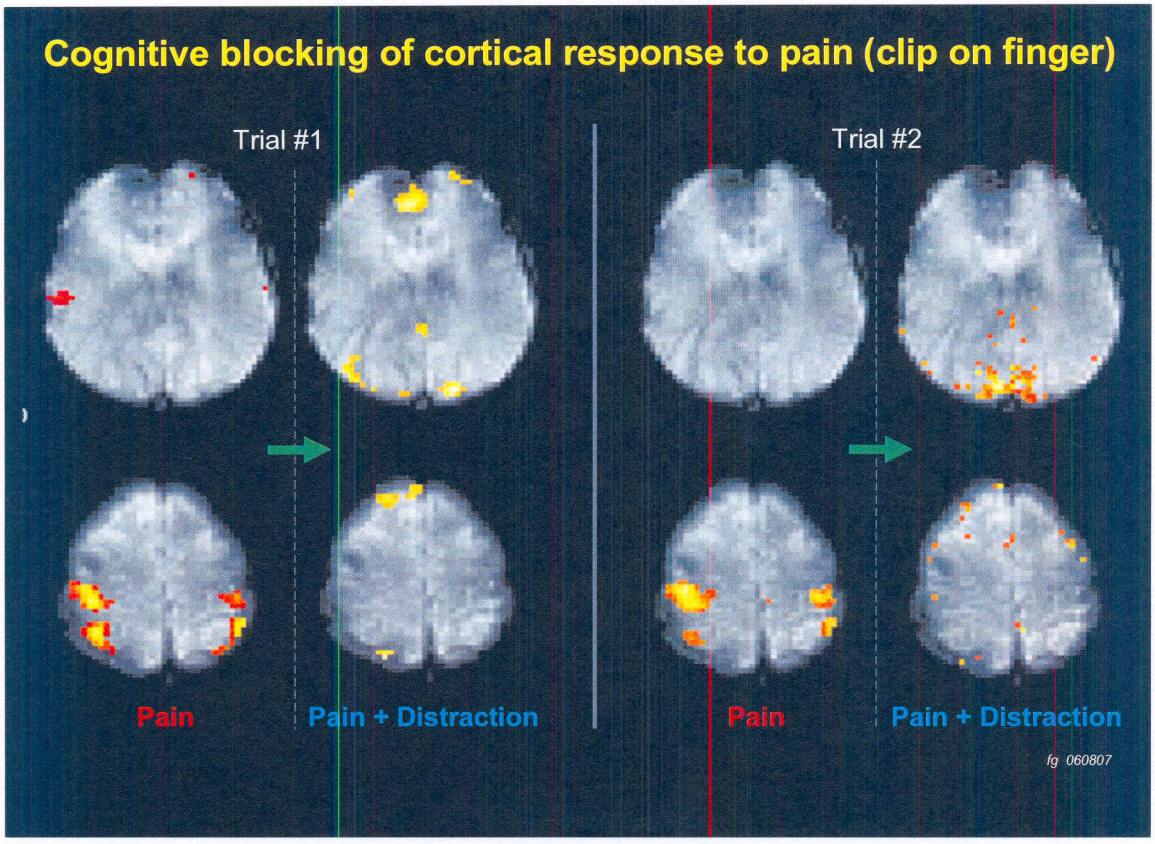

Figure 2
In Figure 2, the research subject placed a small plastic cable clamp on her left forefinger and squeezed it, locking it at the tightest ratchet step, which was painful. Note the activation of both the left and right motor and sensory cortex hand regions (lower left image in Trial #1). Then, seeing this activation on the projected image of her own fMRI, she tried various strategies and soon was able to eliminate the activation, while the clamp was at the same tightest ratchet step, by distracting herself by multiplying imagined numbers (lower right image in Trial #1). Note also the change in activation in the upper left and right images. During the distraction procedure in which she performed multiplication of imagined numbers, the visual association cortex became activated (yellow pixels). After a rest period of 5 minutes, the procedure was repeated with similar results. The subject reported that she did not feel the pain when she was distracting herself.

Thus, with the fMRI near-realtime neurobiofeedback methodology that we have developed under the support of the NJCSCR grant, we see that modifying one's own brain activity by observing it in near-realtime and attempting different strategies until finding the one that produces the clearest effect (in this case, eliminating the brain response to an applied painful stimulus), can modify one's sensory perception (in this case, eliminating experimentally-induced pain).

C. Activation of sensory cortex that normally responds to genital stimulation, just by thought alone, in the absence of actual genital stimulation.

In addition to our strategy of using the neurobiofeedback method to enable men and women with spinal cord injury to attenuate pain, we have also sought to enable women with spinal cord injury to intensify their sexual response. In this regard, we have used the neurobiofeedback method to have women either intensify or attenuate voluntarily their genital-related brain activity. We have observed that, similar to the ability to voluntarily attenuate brain activity that is activated by painful stimulation, women are able to voluntarily (i.e., by thought only, in the absence of physical stimulation) activate brain regions that are normally activated by physical genital stimulation. This makes feasible the possibility that women with spinal cord injury could, by neurobiofeedback, learn to activate their genital sensory brain regions, activation of which could then generate sexual pleasure in the absence of actual genital sensory activity.

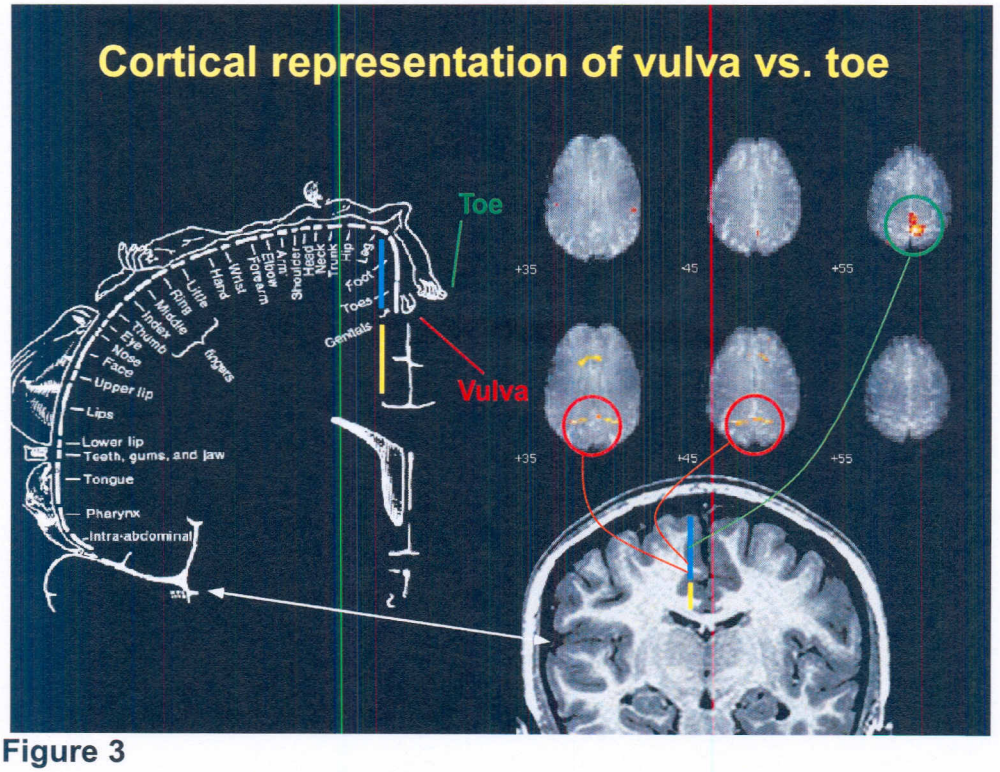

Figure 3

Figure 3 is a control procedure showing that the sensory "homunculus" first mapped by W. Penfield and T. Rasmussen (1950) ["*The Cerebral Cortex of Man*" New York: Macmillan] using electrical stimulation of the cortex in awake humans prior to brain surgery (using local anesthesia) is confirmed in our study using fMRI. That is, in the top row showing three transaxial serial "sections," tapping the toe activated the topmost (i.e., closest to the cortical surface) serial section (upper right, circled in green), whereas self-tapping the vulva activated the deeper sections (lower row, circled in red).

Figure 4 shows that the same genital sensory cortex can be activated not only by physical stimulation, but by thought alone, using our neurobiofeedback methodology.

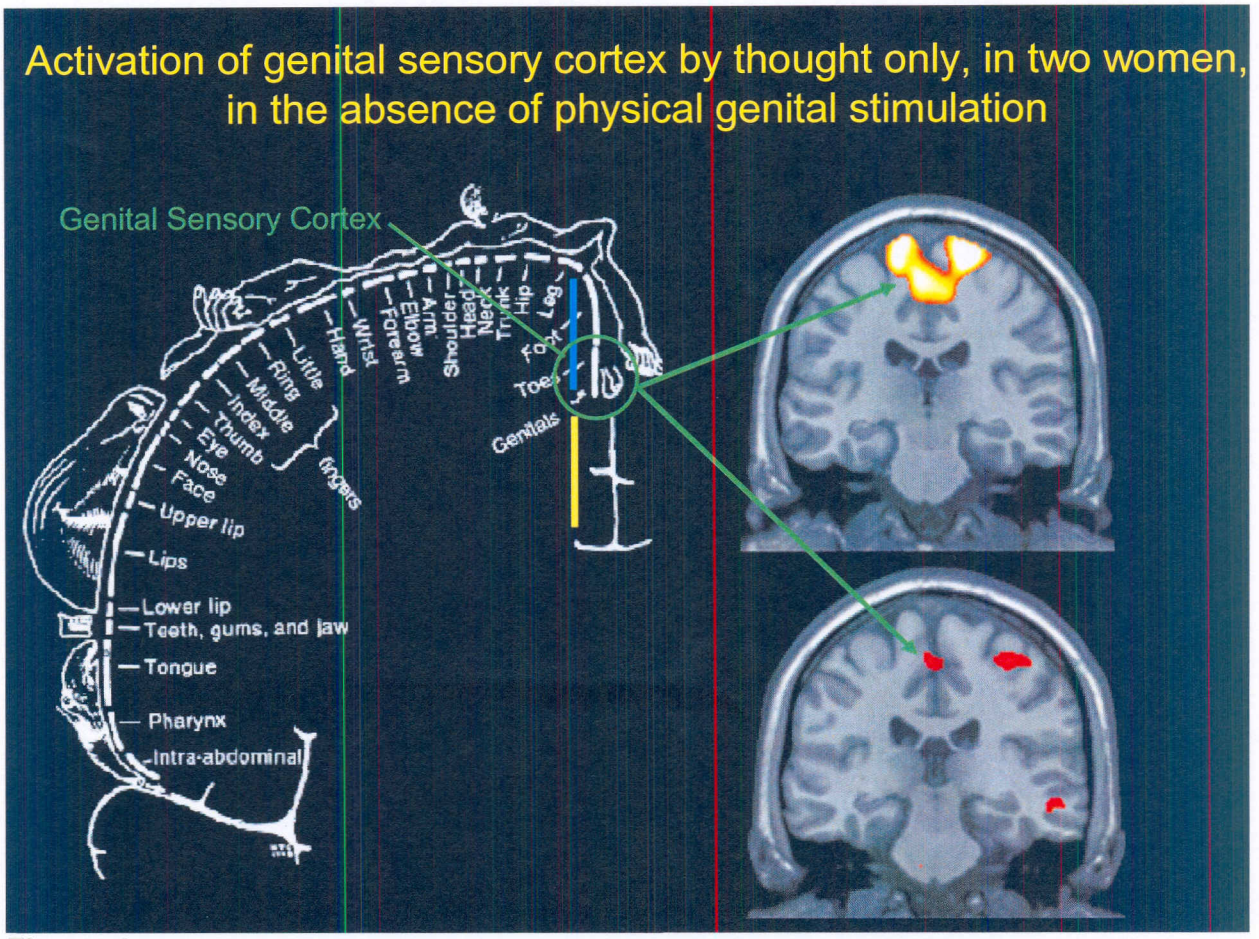

Figure 4

D. fMRI near-realtime neurobiofeedback methodology

1) Hardware and Software:

The functional imaging takes place at the Joint Rutgers-Newark – UMDNJ-NJMS Advanced Imaging Center on the Medical School campus in Newark. Our existing near-realtime system includes: a Siemens Allegra 3T "head-only" scanner with the following software: Siemens Advanced Neuro Package version NUMARIS-4, Syngo MR 2004A DHHS; a SONY video camcorder DCR-PC110-NTSC; and a Sanyo PLC-X21N LCD video projector & screen.

2) Working mechanism:

Based on this package, we have developed a protocol that allows us to visualize the initial functional maps as soon as 15 sec after the start of the imaging acquisition. The continually updated maps are calculated, generated, and

displayed on the MRI operation console monitor according to the cross-correlation algorithm on every TR (time of repetition) until the end of the data acquisition.

At the beginning of scanning, T1-weighted high resolution anatomical images are acquired using the MPRAGE sequence. These anatomical images serve as the template onto which the functional information is superimposed.

The near-real-time fMRI employs a gradient echo EPI sequence with the following scanning parameters: TR/TE=2000/40, FOV=220, matrix size=64 x64, slice thickness = 7 mm, and16 slices, which covers most of the brain. The near-real-time fMRI utilizes the "Advanced Neuro Package" of Siemens. In this utility, we specify the number of images to be considered as stimulation and baseline. Once the scanner starts to acquire the images, the near-real-time program reads the collected images, performs a motion correction, runs a simple statistical test of correlation for the BOLD signals of each voxel in the images based on the information provided previously, and displays the detected activation superimposed on the previously-acquired T2 weighted EPI anatomical brain images. This program has a turnaround time of one cycle initially and continuously updates every TR (time of one imaging acquisition unit under our specified conditions is 2 sec). The displayed images with continuously updated functional changes are viewed simultaneously by the investigators and the participant in the fMRI scanner.

As shown in the following figures, in front of the MR console monitor, there is a camcorder arranged to capture and transmit the updated functional information that appears on the console monitor. The camcorder can zoom in on a single brain "slice" or zoom out to show several "slices, depending on the regions of interest. This is transmitted continuously onto our LCD computer projector that is located at the back of the MRI area outside the scanning room. A 6" inch diameter wave-guide was constructed to allow the projector to project back into the scanning room onto a translucent screen that is positioned at the end of the open lumen of the magnet. The research subject in the scanner views the display on the screen via an adjustable angled mirror that is attached to the standard head coil. For the research subjects who may be nearsighted but without corrective contact lenses, we provide a varied diopter package of MRI-compatible correction lenses (Pennsylvania Optometrics Vision Center Inc, Philadelphia, PA).

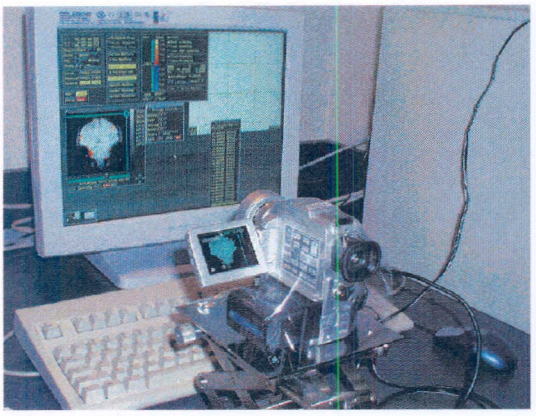

Figure 5

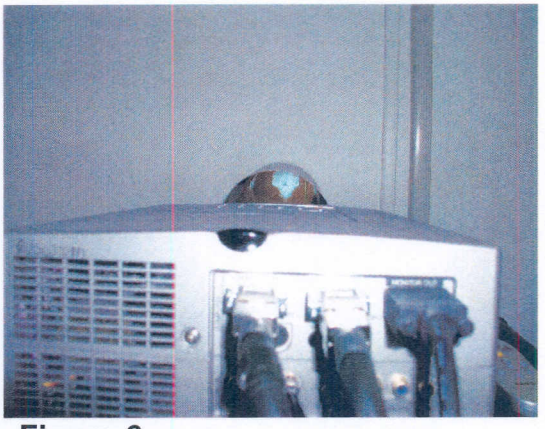

Figure 6

Figure 5: The camcorder takes a selected closeup video of one or several brain "slices" of interest.
A 50' shielded cable from the camera feeds into a video projector that projects the image onto a translucent screen placed behind the subject in the scanner (Figure 6). In **Figure 6**, note the brain image from Figure 5 projected onto the distant screen (seen just above the projector through the wave-guide tube).

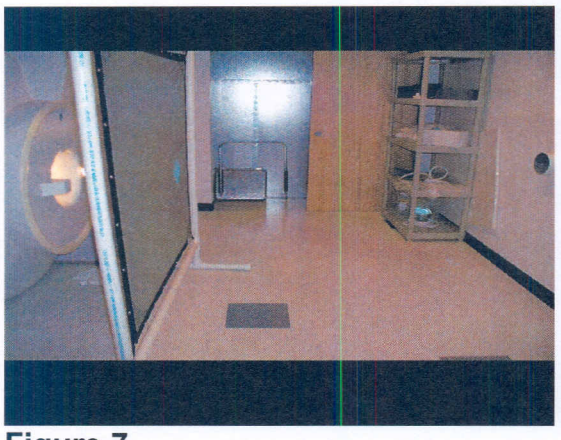

Figure 7

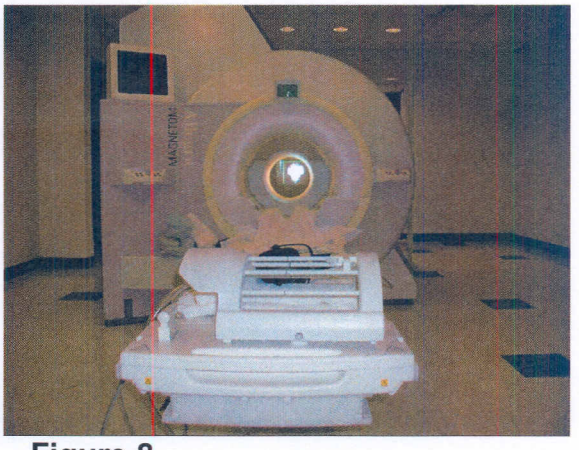

Figure 8

Figure 7 shows the brain image projected onto the translucent screen behind the fMRI scanner. The wave guide tube in front of the projector is seen at the far right side of the figure (small black oval; the projector, not visible in this image, is in the room behind the wall to the far right). The back of the fMRI scanner is seen at the far left of the figure. The brain image is seen projected onto the translucent screen. It is the small light blue oval spot on the screen located lined up between the back of the scanner and the wave guide tube.

Figure 8 shows the brain image (bright white spot seen through the lumen of the fMRI scanner) as it appears to the subject in the scanner. The head cage contains an angled mirror that enables the subject to view the image on the

screen while the subject is lying supine in the scanner. The head cage that contains the angled mirror is seen in the foreground. In this photo, it is oriented at right angles to that shown in the image when the subject is in the scanner.

3. Project challenges:
While we have succeeded in demonstrating the feasibility of cognitive control of both pain attenuation and sexual response induction in the neurobiofeedback paradigm, the technology is still to slow, in that the time lag between the performance of the neurobiofeedback and the appearance of the corresponding brain activity is 15 seconds. We believe that the subjects' ability to control their brain activity, and thereby their perceptions, would be significantly improved by reducing the time lag further. While there exists a *biological* response latency limitation of the fMRI "BOLD" [Blood Oxygen Level Dependent] signal of approximately 4 seconds that is not amenable to reduction, the other 10+ second latency is a function of the computer processing time. We are currently working with the scanner manufacturer, Siemens, to try to reduce that time lag.

There was also a research hiatus of 3+ years (2002-2004) when I was asked to serve as a Program Director in the M.O.R.E. (Minority Opportunities in REsearch) Division of the National Institute of General Medical Science of the National Institutes of Health in Bethesda, MD, and then re-start my research activity on the project at Rutgers-Newark. Another delaying factor was that upon my return to Rutgers in January, 2005, I was asked by the Administration to serve as the Associate Dean of the Graduate School, a capacity in which I continue to serve at present.

4. Implications for future research and/or clinical treatment:
We believe that the real-time neurobiofeedback methodology has significant potential for therapeutic application, once the computational lag time is significantly reduced. We believe that this is a technologically soluble problem. This would make the methodology much more "user-friendly." We believe that chronic pain that is perceived below the level of spinal cord injury in men and women with complete spinal cord injury is primarily a cognitive brain process rather than a process that is initiated from the periphery. If that is the case, then we believe that it will be susceptible to control and attenuation by the neurobiofeedback method. Similarly, we believe that the neurobiofeedback method will make feasible the possibility that men and women with spinal cord injury could, by neurobiofeedback, and if they so desire, learn to activate their genital sensory brain regions, activation of which could then generate sexual pleasure under their conditions of reduced or absent genital sensory activity, thereby potentially improving their quality of life.

If the neurobiofeedback methodology is shown to be effective in treating the pain and sexuality problems, then it would be important to apply the methodology to other brain-cognitive problems, such as addiction, depression, post-traumatic stress disorder, and obesity. It may even be applicable to disorders such as

epilepsy, Parkinsonism, and attention deficit disorder, e.g., by voluntarily intensifying the activity of inhibitory neural systems such as the caudate nucleus.

5. Plans to continue this research, including applications submitted to other sources for ongoing support:

We are currently actively pursuing this line of research with men and women with spinal cord injury who have chronic pain or sexuality difficulties. In addition, we are currently studying a group of women who have been diagnosed with "Persistent Genital Arousal Disorder" (PGAD), which is characterized by distressing chronic genital awareness that is not amenable to treatment by medication or psychotherapy. We are seeking to ascertain whether these women can attenuate these unwelcome sensations voluntarily by observing the brain activity that is correlated with their sensations. We submitted an application to the 2007-2008 Clinical and Translational Science Pilot Awards (CTSPA) Program of the Robert Wood Johnson Medical School for the October, 2007 deadline, but it was not funded.

However, as evidence of official interest in the therapeutic potential of the fMRI neurobiofeedback methodology, in January, 2008, the National Institutes of Health issued a Request for Applications: RFA-DA-08-020 entitled, "Facilitating Self-Control of Substance Abuse Related Brain Activity Through Real-Time Monitoring of fMRI Signals (R21/R33)." I have prepared and submitted a grant proposal via this mechanism for the March 14, 2008 deadline. The proposals are scheduled to be reviewed in June, 2008.

6. Invited addresses in which I cited support by the NJCSCR grant:

University of Arizona Conference: "Toward a Science of Consciousness": 4/08.
Case Western Reserve University School of Medicine, Grand Rounds, 9/07
International Academy of Sex Research (IASR) (Symposium), Vancouver, B.C., 8/07
Venezuelan Society for Medical Sexology (Plenary address), Caracas,Venezuela (in Spanish), 7/07
World Association of Sexual Health (Plenary address), Sydney, Australia, 4/07
Int'l Society for the Study of Women's Sexual Health (Plenary address), Orlando, FL 2/07
American Association of Anthropology (Presidential Symposium), San Francisco, CA 11/06
Mexican Society for Reproduction Research (keynote address), Guanajuato, Mexico 5/05
Novartis Foundation: Conference on Gender and Pain, London, UK, 4/05
Mexican Physiological Society, Veracruz, Mexico, 8/04
Conference on Clinical Aspects of Human Sexuality, Shanghai, China, 5/04
Asociacion Mexicana de Neuropsiquiatria, Mexico City, MX, 7/03
SSSS 45th Annual Conference, Presidential Plenary, San Antonio, TX, 11/03
Kentucky Spinal Cord and Head Injury Research Trust Conference, Louisville, KY, 06/03