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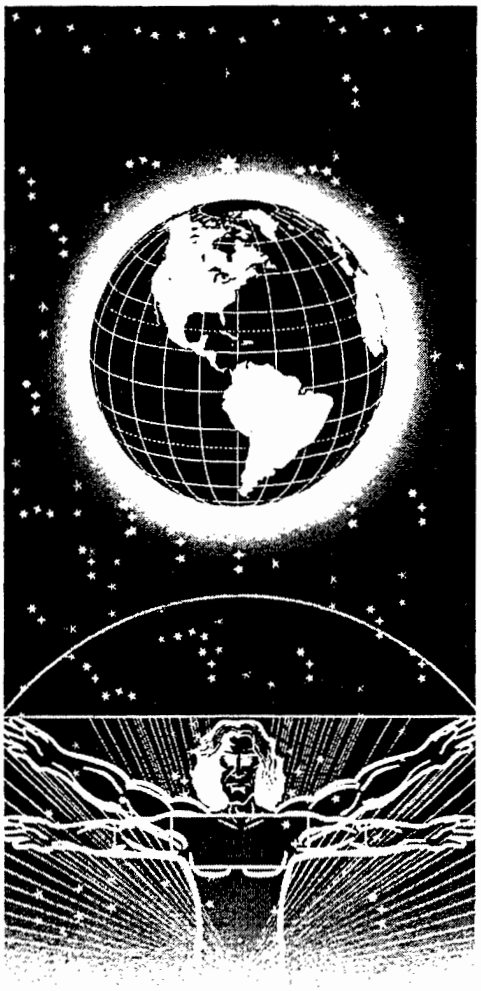

UNITED STATES AIR FORCE RESEARCH LABORATORY

BIOLOGICAL EFFECTS OF DIRECTED ENERGY

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The Office of Public Affairs has reviewed this paper, and it is releasable to the National Technical Information Service, where it will be available to the general public, including foreign nationals.

This report has been reviewed and is approved for publication.

JAMES MERRITT
Contract Monitor

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14. ABSTRACT
This Final Report summarizes the biological effects research conducted by Veridian Engineering personnel under contract F41624-96-C-9009 in support of the Air Force Research Laboratory's Radio Frequency Radiation Branch from April 1997 to April 2002. Biological effects research and consultation were provided in five major areas: Active Denial System (also known as Vehicle Mounted Active Denial System), radio frequency radiation (RFR) health and safety, non-lethal weapon biological effects research, the newly formed Joint Non-Lethal Weapons Human Effects Center of Excellence, and Biotechnology. The report is organized by research efforts within the major research areas, providing title, objective, a brief description, relevance to the AF or DoD, funding, and products.

15. SUBJECT TERMS
Acoustic Energy Biological Effects, Biotechnology, Directed Energy Biological Effects, Electromagnetic Field Biological Effects, Radio Frequency Biological Effects, Non-Lethal Weapons Technology

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1.0 INTRODUCTION AND HISTORY

Veridian Engineering, (originally Systems Research Laboratory), began work on contract F41624-96-C-9009, "Biological Effects of Directed Energy," in April 1997. The overall goal of this effort was to provide an experienced, qualified research team to work alongside government scientists to conduct biological effects, to include human effects, research of directed energy. To accomplish this, Veridian was to provide effective research program management, establish integrated research teams of contractor, subcontractor, and government scientists and technicians with experience in the field of directed energy biological effects, and perform meaningful, quality research in conformance with pertinent regulations. Veridian scientists provided scientific and technical support in five areas: Active Denial System (also known as Vehicle Mounted Active Denial System), radio frequency radiation (RFR) health and safety, non-lethal weapon biological effects research, the newly formed Joint Non-Lethal Weapons Human Effects Center of Excellence, and Biotechnology.

As needed, Veridian acquired scientific and technical staff, hired consultants, designed and built special fixtures and equipment to conduct both laboratory and field experiments in support of these five research areas. The assembled scientific staff represent an interdisciplinary research team with both knowledge of the literature on the biological effects of RFR and a working knowledge, including physiological and behavioral effects, long-term effects, and dosimetry. The scientific staff possessed the experience needed to perform physiological and behavioral effects research on a number of diverse non-lethal technologies, beginning with Active Denial Technology (ADT) and then extending to acoustics, kinetics, and TASERS. This subject matter expertise was valuable as the ADT program transitioned to the acquisition stage. Increased requests for evaluations of other non-lethal technologies were received from customers inside and outside the Department of Defense (DoD), as well as the consultation support required by the Human Effects Center of Excellence (HECOE) located at Brooks. Veridian responded to a number of special projects and needs of the customer; providing expertise in electrophysiology to investigate the response of excitable tissue to ultrawide band RFR; designing, modifying, and constructing unique test fixtures and equipment for lab and field experiments of non-lethal weapons; and working with operational units and warfighting labs to demonstrate the feasibility and utility of advanced technology concepts. Veridian also provided critical expertise to conduct research involving bioagent detection, protection, and neutralization, as well as RFR bio-dosimetry.

The Veridian/Air Force Research Laboratory (AFRL) team made a significant contribution to the non-lethal capabilities of the DoD by successfully demonstrating the robust utility of ADT to warfighters and senior level DoD officials in FY01. The Veridian team continued to perform thorough, relevant biological effects and safety-related research for the current active denial

concept, Vehicle Mounted Active Denial System (VMADS). In 1997, the Veridian/Radio Frequency Radiation Branch (HEDR) team planned and executed the first successful field demonstration for the concept which would become known as VMADS at Kirtland Air Force Base, NM. Veridian scientists designed protocols, equipment, and experimental setups for the field experiments and collected data during the field experiments to prove the utility of ADT to the warfighter.

As the need for, and the interest in, non-lethal technologies grew, Veridian was funded to plan and execute experiments investigating the effectiveness and risks of other non-lethal technologies, such as acoustics (to include infrasound), kinetic projectiles, and TASERS. In many instances, the bioeffects research programs were initiated to collect effectiveness data for systems already in development. Special sources, data collection equipment, and test fixtures were constructed, particularly for acoustics and kinetics; examples of these are the Infrasound Test System, a tunable infrasound chamber, and a compressed air-driven kinetic launcher. For the acoustic research, some sources could not be brought to the lab, so the research team had to design experiments to collect data in the field and then travel to remote locations to collect the data.

The report that follows is intended to summarize the research conducted under the five research areas. The format to be followed for each write-up is as follows:

- Research Area Overview
    - Title of Work
    - Description of work (the objectives)
    - Funding
    - Relevance
    - Products (journal article, technical report, abstract, presentation, proceedings) Note that not all the publications have Veridian authors; these publications are listed to show all relevant publications in one place. Veridian (to include subcontractor and consultant) authors are in bold.

2.0 ACTIVE DENIAL TECHNOLOGY (ADT) RESEARCH

Veridian Engineering scientists have been on the forefront of the research investigating the use of radio frequency radiation as a non-lethal technology since 1990. Several concepts emerged from the exploratory research efforts of the Veridian-Government research team in the early 90s. Veridian efforts over the past several years have concentrated on performing the required research to help prove the operational utility and public acceptability of the concept known for the Vehicle Mounted Active Denial System (VMADS). Numerous animal and human laboratory research efforts established effectiveness parameters with which an operational demonstrator could be designed and built. Other experiments determined damage thresholds to establish a safety index and carefully and thoroughly investigated the long-term effects of millimeter wave RF exposure. All of these effectiveness and safety data were collected to feed into the design of a demonstration system that could be demonstrated on human subjects at operationally relevant parameters. Veridian and AFRL/HEDR researchers teamed up with AFRL/DEH scientists/engineers to successfully demonstrate both the operational utility and technical feasibility of the VMADS concept to the Joint Non-Lethal Weapons Directorate, the AF Force Protection Battlelab, and other joint service customers through a series of field demonstrations and human experiments. Preparation for these remote demonstrations/experiments took three years; Veridian scientists participated in the design of the VMADS demonstration unit and in the design of the test site. Transition of the VMADS program out of the lab and into the acquisition stage will occur within the next year and may be on a fast track; ongoing lab and field experiments will need to continue through the transition. A substantial amount of critical research remains to be performed such as whole body frontal exposures, effects of environmental conditions on the effectiveness of VMADS, identification of countermeasures, development of optimum exposure parameters for system operation modes, and conduct of additional safety and long-term studies.

Special equipment and techniques were developed and/or modified to collect data required to establish dose response curves. Early in the contract period, millimeter waves (MMW) source power limited the research to investigate exposure levels that had operational utility; spot size was greatly restricted due to the use of a focusing lens to increase exposures to effective levels. Special restraint devices for animals and enclosures for humans had to be built to conduct the research. Due to space restrictions and exposure configurations, reflecting systems had to be built in labs. Dosimetry of such small spot sizes was challenging to both Veridian and government RF technicians; counsel was sought from AFRL/High-Power Microwave Division, Directed Energy Directorate (DEH) to develop an acceptable technique. Attempts were made to acquire other higher power MMW sources and get them operational but to no avail. Finally, the arrival of a higher power system from AFRL/DEH allowed experimenters to increase both spot size and power density to better answer operational utility questions. Infrared (IR) thermography was employed by

experimenters to develop temperature rise curves and to establish thresholds for effectiveness (ED50); however, data analysis was cumbersome until Veridian scientists developed software to automate the analysis of the IR camera. For field experiments, structures were designed to allow for controlled acquisition of data and to mitigate confounding environmental and procedural problems.

2.1 Use of Animal Models

2.1.1 Description of Work

Veridian personnel have participated in a variety of studies using a variety of animal models to understand the consequences of ADT exposures. We have supported primate studies by the Naval Medical Research Detachment including multifrequency effects in monkeys (D'Andrea et al., in progress), effects of repeated, low-level exposure to MMW on visual acuity in monkeys (D'Andrea et al., in progress), threshold for MMW-induced corneal lesions in monkeys (Chalfin et al.1999, 2002; D'Andrea & Chalfin, 2002), facial detection thresholds for MMW in monkeys (D'Andrea et al., 1999), and eye aversion thresholds in monkeys (D'Andrea et al., in progress). We have conducted studies comparing skin-heating rates in several species (Walters et al., 1998a, 2000). We have studied brain heating and changes in exercise capacity associated with microwave exposure (Walters et al. 1997; 1998e). We have collaborated in a variety of work on brain markers resulting from MMW exposure in rats (Mason et al., 2000; Ryan et al. 1998a,b; Walters et al., 1996; 1998e; 1999; 2001), and in work on plasma catecholamines in response to MMW exposures (Ryan et al. 1999a,b). We have compared microwave-induced heating patterns in the brains of rats to predictions from computational models (Walters et al., 1998d; Gajšek et al, 2002), as well as to patterns induced by conventional heating and exercise (Walters et al., 1997; 1998b). We have also examined the induction of thermal tolerance by microwave exposure (Mason et al., 1998), and collaborated in studies of circulatory shock induced by MMW exposures (Ryan et al., 2000). Work that Veridian personnel initiated on thermal injury is continuing (Mason et al., in progress).

2.1.2 Funding

These efforts were funded by the Joint Non-Lethal Weapons Directorate (JNLWD) (USMC), AFRL 7757 project funds, and limited Navy funding.

2.1.3 Relevance

DOD Directive 3000.3 identifies three conditions that must be met to successfully field a non-lethal technology - technical feasibility, operational utility, and policy acceptability. To satisfy these conditions, the biological effects of ADT, both intended and unintended, must be determined

through lab and field experiments. Research investigating the effects of MMW RFR on the eyes and skin (i.e., damage thresholds, aversion levels, repeated low-level exposures, spot size or scaling effects, etc.) is critical to addressing both operational utility and policy acceptability.

2.1.4 Products

The work described above has resulted in the publications and presentations listed below.

Chalfin, S., D'Andrea, J. A ., Comeau, P. D., Belt, M. E., and Hatcher, D.J. 35 GHz and 94 GHz microwave absorption in the primate eye. *Health Physics*, 2002, in press.

Chalfin, S., D'Andrea, J. A ., Comeau, P. D., Belt, M. E., and Hatcher, D.J. 35 GHz and 94 GHz microwave absorption in the primate eye. *Investigative Ophthalmology and Visual Science* 40(4):S447, 1999.

D'Andrea, J. A. and Chalfin, S. Effects of microwave and millimeter wave radiation on the visual system. In: B.J. Klauenberg and D. Miklavic (Eds.), *Radio Frequency Radiation Dosimetry*, Dordrecht, The Netherlands: Kluwer Academic Publishers 2002, pp. 395 - 407.

D'Andrea, J.A. Microwave effects on the visual system. Invited review paper presented at *XXVIth General Assembly, Of The International Union, Of Radio Science (URSI)*, University of Toronto, Toronto, Canada, August 13-21, 1999.

D'Andrea, J.A., Hatcher, D.J., **Walters, TJ.**, Ziriax J.M., Hurt, W.D., Kosub, K.R., and **Weathersby, F.** Facial detection of 94 GHz millimeter waves by the nonhuman primate. Presented at *21st Annual Meeting of the Bioelectromagnetics Society*, Long Beach, CA June 20-24,1999.

Gajšek, P., D'Andrea, J.A., Mason, P.A., Ziriax, J.M., **Walters, T.J.,** and Hurt, W.D., Mathematical modeling of EMF absorption in biological systems. Chapter 3 in: *Biological Effects of Electromagnetic Fields*, Peter Stavroulakis, ed., IEEE Press, In press.

Kalns, J.E., Ryan, K.L., Mason, P.A., and Kiel, J.L. Can exposure to thermal levels of millimeter waves (MMW) alter cell behavior. Presented at *Seventh Annual Michaelson Research Conference*, Gig Harbor, WA, 2000.

Mason, P.A., Blystone, R.V., **Kalns, J.E., Ryan, K.L., Walters, T.J.,** and Kiel, J.L. Biomarkers of radio frequency radiation exposure. Presented at

Seventh Annual Michaelson Research Conference, Gig Harbor, WA, 2000.

Mason, P.A., Walters, T.J., Lehnert, H.M., **Mahajan, K.,** Skitek, E.B., Scholin, T.L., Taylor, R.L., and **Ryan, K.L.** Thermal tolerance induced by 2.06-GHz microwave heating. *Experimental Biology Abstract*, San Francisco, CA, 1998.

Ryan, K.L., Kains, J.E., Mason, P.A., and Kiel, J.L. Protein nitration precedes circulatory shock induced by millimeter wave (MMW) exposure. Presented at *Seventh Annual Michaelson Research Conference*, Gig Harbor, WA, 2000.

Ryan, K.L., Mahajan, K., Lehnert, H.M., Tehrany, M.R., Jauchem, J.R., and **Mason, P.A.** Brain c-fos induced by 35-GHz radio frequency radiation (RFR) exposure in ketamine- and pentobarbital-anesthetized rats. *20th Annual Meeting of the Bioelectromagnetics*, St. Petersburg Beach, Florida, 1998a.

Ryan, K.L., Mahajan, K., Lehnert, H.M., Tehrany, M.R., Jauchem, J.R., and **Mason, P.A.** Brain c-fos induced by 35-GHz microwave (MW) heating, environmental heating (EH), and cutaneous noxious thermal stimulation. *Experimental Biology Abstract*, San Francisco, CA, 1998b.

Ryan, K.L., Taylor, R.L., Lehnert, H.M., **Mahajan, K., Walters, T.J.,** and **Mason, P.A.** Plasma and adrenal catecholamines during 35-GHz microwave (MH) heating. *Experimental Biology Abstract*, Washington, D.C., *FASEB J.*,13:A743, 1999a.

Ryan, K.L., Taylor, R.L., Lehnert, H.M., **Mahajan, K.,** and **Mason, P.** Effects of 35-GHz microwave (MW) heating on catecholamine content in specific regions of the rat brain. *21st Annual Meeting of the Biolelectromagnetics Society*, Long Beach, CA, June, 1999b.

Ryan, K.L., Walters, T.J., Paulus, L.A., and **Mason, P.A.** Determination of regional brain heating using biological indicators. Presented at *Fifth Annual Michaelson Research Conference*, Montana, August 1998.

Walters, T.J., Mason, P.A., Lehnert, H.M., **Mahajan, K.,** Scholin, T.L., and **Ryan, K.L.** HSP expression in the CNS may be dissociated from whole-body thermotolerance. *Experimental Biology Abstract*, Washington, D.C., *FASEB J.*13:A743, 1999.

Walters, T.J., Nelson, D.A., Blick, D.W., Johnson, L.R., and D'Andrea, J.A. The rate of skin heating in response to 94 GHz mm-wave irradiation

in humans, rhesus monkeys, and rats. Presented at *20th Annual Meeting of the Bioelectromagnetics Society*, St. Petersburg, FL, June 7-11, 1998

Walters, T.J., Nelson, D.A.**, Ryan, K.L.**, J.D'Andrea, J., **Blick, D.W.**, Johnson, L.R., and **Mason, P.A.** Surface heating from millimeter wave irradiation: Modeling inter-species variations. Presented at *22nd Annual Bioelectromagnetics Society Meeting*, Munich, Germany, June 2000.

Walters, T.J., Ryan, K.L., and **Mason, P.A.** The influence of brain and core temperature on endurance performance. *Experimental Biology Abstract*, San Francisco, CA, 1998.

Walters, T.J., Ryan, K.L., and Mason, P.A. Regional CNS distribution of hsp70 in the CNS of young and old food-restricted rats following hyperthermia. *Brain Research Bulletin* 55:367-374, 2001.

Walters, T.J., Ryan, K.L., Scholin, T.L., and **Mason, P.A.** Neuronal damage following thermal stress. *Experimental Biology Abstract*, San Diego, CA, 2000.

Walters, T.J., Ryan, K.L., Tate, L.M., and **Mason, P.A.** Microwave-induced regional heating as a function of orientation: Relationship to FD-TD predictions. Presented at *Fifth Annual Michaelson Research Conference*, Montana, August 1998.

Walters, T.J., Ryan, K.L., Tehrany, M.R., Jones, M.B., Paulus, L.A., and **Mason, P.A.** HSP70 expression in the CNS in response to exercise and heat stress in rats. *J. Applied Physiol.* 84:1269-1277, 1998.

2.2 Human Studies for ADT

2.2.1 Description of Work

Building on previous animal work which demonstrated that MMWs did create an effect potentially useful as a non-lethal technology and which determined effective, yet safe, range of exposure parameters for humans, several human studies were conducted. The objective of these studies was to (1) measure sensory and behavioral effects of exposure to MMWs to show that the system is both effective and safe as a non-lethal antipersonnel weapon; (2) determine pain thresholds as a function of duration and area of stimulus, as well as environmental conditions (e.g., ambient temperature, initial skin temperature); and (3) determine pain intolerability level in the laboratory, as well as in the field with a prototype system.

In December 1997, a classified human use protocol (F-BR-1998-0003-H) was approved, allowing testing of pain threshold responses to MMW under a variety of conditions (different durations, areas, etc.). Previously, Dr. Dennis Blick (Veridian) had tested pain threshold for 3-sec duration under a protocol (AL-ACHE 95-25) by Dr. Clifford Sherry (Veridian) that had been approved earlier. Work began immediately on the classified protocol, but was suspended in March, 1998, under a presidential directive to revise the "Common Rule" as it affected federally sponsored classified research using human subjects. Dr. Blick then wrote and got approval of an omnibus health and safety protocol (F-BR-1998-0026-H) to measure pain thresholds at a number of different frequencies (including MMW and IR). This allowed continuation of the work that would have been done under the classified protocol. Under this protocol, testing of pain threshold and pain intolerability continued until March 2001 when the MMW transmitter failed. Considerable effort on the part of Dr. Zibignew Wojcik (Veridian) resulted in a program that provided automated processing of IR thermographic data, saving thousands of person-hours of data analysis. Data processing continued, in parallel with work on a new, classified protocol to permit testing with the prototype system at Kirtland AFB. Work on the new classified protocol began in November 1999. In May 2000, Dr. Blick met with the Institutional Review Board (IRB) at Wright-Patterson AFB; the protocol was approved, and the process of getting the approval of the Secretary of Defense (SECDEF) began. Since this was the first classified human use protocol to seek approval under the new Common Rule, procedures for staffing it up to SECDEF were not in place, and it failed to get the necessary approval within the required time (30 days after IRB approval). In hope that the DoD approval process was now established, Dr. Blick met with the IRB at Wright-Patterson AFB again in August, 2000. The classified protocol was again unanimously approved, and forwarded to the USAF Surgeon General's Research Oversight Committee (SGROC), which approved it immediately, and sent it on. In

spite of a memo from SECAF to Director, Defense Research and Engineering, Office of the Secretary of Defense (DDR&E) strongly recommending approval, the protocol again failed to receive timely SECDEF approval. Shortly thereafter, it was decided that declassification of parts of the program would allow the work to be done under an unclassified protocol. Dr. Blick prepared an amendment to the omnibus health/safety protocol which was approved by the AFRL IRB on 17 January 2001; it received final SGROC approval on 22 January 2001. Human subject testing at Kirtland AFB began 04 May 2001. Between 4 May 2001 and 27 September 2001 full body exposures for the repel effect were conducted. The data have been analyzed, and the results presented to the customer. A Technical Report summarizing the effects is in preparation. The IRB approved extension of the protocol for 1 year at its meeting in January 2002. A protocol "Effects of Skin and Environmental Conditions on Sensations Evoked by Millimeter Waves" (F-WR-2002-0016-H) was approved by the AFRL IRB at its meeting 21 February 2002; SGROC approval was received 27 February. Two more protocols: "Facial Sensitivity and Eye Aversion Response to Millimeter Waves" and "Effects of Ethanol on Millimeter-Wave-Induced Pain" have been submitted by Dr. Blick for approval. Work on these 3 protocols will be conducted under the follow-on contract.

2.2.3 Funding

JNLWD (USMC) and AFRL 7757 project funds.

2.2.4 Relevance

Initial laboratory results with humans helped prove initial operational utility and were fed into the prototype system design, as they indicated the power levels needed for effectiveness at range. Later field tests in humans were necessary to demonstrate both operational utility and policy acceptability.

2.2.5 Products

Summaries of the data have been provided to the system developers for their use in system design and evaluation. Numerous graphs, charts, and pictures have been prepared for use in classified briefings, both by the investigators and the Government. Since nearly all of the results are either sensitive or classified, few open-literature papers or presentations have resulted. Data from our MMW studies have been used to develop an empirical model of thermal response of the skin. The resulting publications are:

Mason, P.A., Hurt, W.D., Ziriax, J.M., **Walters, T.J.**, **Ryan, K.L.**, **Nelson, D.A.**, Smith, K.I., Townsend, D.S., and D'Andrea, J.S. Models used to determine the bioeffects of directed energy exposure. *Proceedings of the NATO Research and Technology Agency Symposium on Countering the*

Directed Energy Threat: Are Closed Cockpits the Ultimate Answer? April, 1999, Antalya, Turkey, NATO-RTO-MP-30: Chapter 7.

Nelson, M.T., **Nelson, D.A., Walters, T.J.,** and **Mason, P.A.** Thermal effects of millimeter wave irradiation of the primate head: Model results. *IEEE Transactions on Microwave Theory and Techniques* 48(11):2111-2120, 2000.

Nelson, D.A., Walters, T.J., Mason, P.A., and **Nelson. M.T.** Modeling thermal effects of millimeter wave exposure in primate head. Presented at *21st Annual Meeting of the Biolelectromagnetics Society*, Long Beach, CA, June 1999.

Walters, T.J., Blick, D.W., Johnson, L.R., Adair, E.R., and **Foster, K.R.** Heating and pain sensation produced in human skin by millimeter waves: Validation of a simple thermal model. *Health Physics* 78(3):259-267, 2000.

Other Papers and Presentations Related to Human Testing

Adair, E.R., **Blick, D.W., Walters, T.J., Mylacraine, K.S.**, and Johnson, L.R. Laser doppler imaging of skin blood flow is a useful adjunctive tool for RF research. Presented at *21st Annual Meeting of the Bioelectromagnetics Society*, Long Beach, CA, June 20-24, 1999.

Blick, D.W. The sensory effects of millimeter waves in humans. Presented at *U.S.A.F. Special Session: Biological Effects of Millimeter Waves, 23d Annual Meeting of the Bioelectromagnetics Meeting,* St. Paul, Minnesota, June 10, 2001.

Blick, D.W., Foster, K.R., Riu, P.J., **Walters, T.J.**, and Adair, E.R. Skin heating and sensations of warmth and pain produced by microwaves: data and thermal modeling. Presented at *20th Annual meeting of the Bioelectromagnetics Society*, St. Petersburg, FL, June 7-11, 1998

Blick, D.W., Foster, K.R., Walters, T.J., and Adair, E.R. Millimeter waves, sensation, and thermal models: Implications for safety standards. Presented at *Sixth Annual Michaelson Research Conference*, Cloudcroft, NM, August 16, 1999.

Blick, D. W., Foster, K. R., Walters, T. J., and Adair, E. R. Sensory and Thermal Effects of Microwaves in Human Skin: Implications of Thermal Models. Presented at *AFRL/Association of Old Crows Ninth National High-Power Microwave and Radio frequency Electromagnetics Symposium*, May 11-13, 1999, Sandia National Laboratories, Kirtland AFB, NM.

Blick, D. W., Walters, T. J., and Johnson, L. R. Effects of ambient temperature on the heating of human skin by millimeter-waves. Presented at *Seventh Annual Michaelson Research Conference*, Gig Harbor, WA, August 11-15, 2000.

Blick, D. W., Walters, T. J., and Johnson, L. R. Millimeter-wave heating of human skin: effects of ambient temperature. Presented at *22d Annual Meeting of the Bioelectromagnetics Society Annual Meeting*, Munich, Germany, June 9-16, 2000.

Mason, P.A. and Walters, T.J. IR mapping for greater radiation safety. *NASA Tech Briefs* 23(4):1a-4a, 1999.

Murphy, M. R., **Blick, D. W.**, Mason, P. A., Merritt, J. H., and **Beason, C. W.** Recent research on the biological effects of millimeter waves. Presented at *European Bio Electromagnetics Association Annual Meeting*, Helsinki, Finland, September 6-8, 2001

Walters, T. J., Ryan, K. L., Nelson, D. A., Blick, D. W., and **Mason, P. A.** Effects of Cutaneous Bloodflow on 94 GHz Microwave Induced Skin Heating in Humans: Preliminary Studies. U.S. Air Force Special Session, "Dosimetry," Presented at *21st Annal Meeting of the Bioelectromagnetics Society*, Long Beach, CA, June 20-24, 1999.

Walters, T. J., Ryan, K. L., Nelson, D. A., Mason, P. A., and **Blick, D. W.** Critical avenues for heat transfer during 94-GHz irradiation in humans. Presented at *Sixth Annual Michaelson Research Conference*, Cloudcroft, NM, August 16, 1999.

2.3 Cancer Study (subcontract with Trinity University)

2.3.1 Description of Work

In collaboration with HEDR and Trinity University, Veridian personnel (Kavita Mahajan, Dr. Patrick Mason, Dr. Thomas Walters) and a Veridian Consultant (Dr. J. DiGiovanni) designed and conducted an exhaustive study to determine whether exposure to 94 GHz MMW could promote or co-promote carcinogenesis in a scientifically accepted animal model of skin cancer.

The SENCAR mouse model of skin carcinogenesis was chosen, based on the recommendation of our consultant, a leading expert in the study of skin cancer. Both single (1.0 W/cm², 10 sec.) and repeated (0.33 W/cm², 10 sec., 2 exposures per week, 12 weeks) exposures were tested for their ability to promote (in animals initiated with 7, 12-Dimethylbenz (a)-anthracene (DMBA) or co-promote (in animals initiated with DMBA and promoted with Tetradecanoylphorbol Acetate (TPA) the formation or growth of papillomas. Controls included similar skin heating with infrared, sham exposure, and a positive control (promotion with TPA) to demonstrate the sensitivity of the model.

2.3.2 Funding

JNLWD (USMC)

2.3.3 Relevance

There is no evidence in the literature to suggest that MMWs at high power can cause skin cancer. However, to address an important policy acceptability question sure to be asked, a well-thought out, scientifically sound experiment needed to be designed using accepted models and in consultation with outside experts. This study provides the best possible scientific evidence to support the safety of ADT.

2.3.4 Products

Findings (i.e., exposure to 94 GHz MMW under the conditions tested does not promote or co-promote papilloma development in this accepted animal model of skin carcinogenesis) were published in the peer-reviewed literature.

Peer-reviewed publication:

Mason, P.A., Walters, T.J., DiGiovanni, J., Beason, C.W., Jauchem, J.R., Dick, Jr., E.J., **Mahajan, K,** Dusch, S.J., Shields, B.A., Merritt, J.H., Murphy, M.R., and **Ryan, K.L.** Lack of Effect of 94-GHz radio frequency radiation exposure in an animal model of skin carcinogenesis. *Carcinogenesis* 22:701-1708, 2001.

2.4 Dosimetry (subcontract with Trinity University)

2.4.1 Description of Work

Veridian personnel, in collaboration with Trinity University, San Antonio, Texas, conducted a number of studies aimed at understanding and modeling the effects of MMW on the skin and eyes. The development of the techniques using infrared thermography and data analysis (Mason and Walters, 1999) was critical to the success of these efforts, which included studies of the effects of ambient conditions (Blick et al., 2000) and skin blood flow (Walters et al., 1999) on MMW-induced skin heating. We also worked with computational models to predict heating effects in the eye (D'Andrea et al., 2000) and skin (Hurt and Mason, 1997; Mason et al., 1999). Some of our data were also used in thermal modeling efforts for human skin (e.g., Nelson et al., 1999; Nelson et al., 2000, Walters et al., 2000), and for comparing heating rates of human skin and skin of common laboratory animals (Walters et al., 2000). Finally, we contributed to a published review of health and safety issues related to MMW exposure (Ryan et al., 2000).

2.4.2 Funding

JNLWD (USMC) and AFRL 7757 project funds.

2.4.3 Relevance

Detailed understanding of the effects of MMW absorption in tissues is critical to the design and operation of ADT. Since not all exposure orientations can be tested in the lab or in the field, one must have a data-based model to predict energy absorption. The ability to predict the outcomes of various exposure scenarios will contribute greatly to future efforts in the Concept of Operations (CONOPS) area.

2.4.4 Products

The results of our studies were presented in the publications and presentations listed below.

Blick, D. W., Walters, T. J., and Johnson, L. R. Millimeter-wave heating of human skin: effects of ambient temperature. Presented at *22d Annual Meeting of the Bioelectromagnetics Society*, Munich, Germany, June 9-16, 2000.

D'Andrea, J.A., Ziriax, J.M., Hurt, W.D., **Mason, P.A.,** and Chalfin, S. Modeling microwave absorption in the eye. *Proceedings of the Millennium Workshop on Biological Effects of Electromagnetic Fields*, Crete, Greece, 2000.

Hurt, W.D. and **Mason, P.A.** Dosimetry at millimeter wavelengths. *Proceedings of the Dosimetry of Lasers and Millimeter Waves Meeting,*

Technical Report AFRL-HE-BR-PC-1999-0002, Brooks AFB, TX, p. 79-82, 1997.

Mason, P.A., Hurt, W.D., Ziriax, J.M., **Walters, T.J.**, Ryan, K.L, **Nelson, D.A.**, Smith, K.I., Townsend, D.S., and D'Andrea, J.A. Models used to determine the bioeffects of directed energy exposure. *Proceedings of the NATO Research and Technology Agency Symposium on Countering the Directed Energy Threat: Are Closed Cockpits the Ultimate Answer? April 1999, Antalya, Turkey,* NATO-RTO-MP-30: Chapter 7.

Mason, P.A. and **Walters, T.J.** IR mapping for greater radiation safety. *NASA Tech Briefs* 23(4):1a-4a, 1999.

Nelson, D.A., Nelson, T.J., **Walters, T.J., Mason, P.A.**, and Nelson, M.T. Modeling thermal effects of millimeter wave exposure in primate head. *21st Annual Meeting of the Bioelectromagnetics Society,* Long Beach, CA, June 1999.

Nelson, M.T., **Nelson, D.A., Walters, T.J.**, and **Mason, P.A.** Thermal effects of millimeter wave irradiation of the primate head: Model results. *IEEE Transactions on Microwave Theory and Techniques* 48(11):2111-2120, 2000.

Ryan, K.L., D'Andrea, J.A., Jauchem, J.R., and **Mason, P.A**. Radio frequency radiation of millimeter wave length: Potential occupational safety issues relating to surface heating. *Health Physics* 78(2):170-181, 2000.

Walters, T. J., Blick, D. W., Johnson, L. R., Adair, E. R., and **Foster, K. R.** Heating and pain sensation produced in human skin by millimeter waves: Validation of a simple thermal model. *Health Physics* 78(3):259-267, 2000.

Walters, T. J., Blick, D. W., Johnson, L. R., and Hurt, W. D. Specific absorption rates of human skin during 94 GHz mm wave irradiation. Presented at: *Fourth Annual Michaelson Research Conference*, Canandaigua, NY, August 15-18, 1997.

Walters, T.J., Nelson, D.A., Ryan, K.L., D'Andrea, J., **Blick,** D.W., Johnson, L.R., and **Mason, P.A.** Surface heating from millimeter wave irradiation: Modeling inter-species variations. Presented at *22d Annual Meeting of the Bioelectromagnetics Society*, Munich, Germany, June 9-16, 2000.

Walters, T. J., Ryan, K. L., Nelson, D. A., Blick, D. W., and **Mason, P. A.** Effects of Cutaneous Bloodflow on 94 GHz Microwave Induced Skin

Heating in Humans: Preliminary Studies. Presented at *U.S. Air Force Special Session, "Dosimetry," 21st Annual Meeting of the Bioelectromagnetics Society*, Long Beach, CA, June 20-24, 1999.

3.0 NON-LETHAL WEAPONS RESEARCH

Veridian's experience in testing the effectiveness of directed energy non-lethal technologies led to the testing other potential non-lethal technologies, such as acoustic, blunt impact, and TASERS. Effectiveness data for these technologies was sparse to non-existent. Since these technologies were already in the field or about to be fielded, the luxury of conducting a thorough research program like ADT was not afforded. Veridian researchers designed and conducted pilot studies to provide quick answers as to the effectiveness of these technologies. Veridian's involvement in acoustics began in 1996 when the U.S. Army Armament Research, Development, and Engineering Center, Picatinny Arsenal, NJ, funded research into the effectiveness of continuous wave and pulsed sonic devices. The acoustics work was extended into the infrasound region at the request of the National Institute of Justice; a special test device known as the Infrasound Test System was designed and built. The Veridian team investigated every acoustic device it could find to thoroughly cover the acoustic parameter space searching for an effect; numerous lab tests and field tests were conducted to collect data. A tunable resonance chamber had to designed and constructed to perform experiments with high intensity infrasound. The result of all the testing was that no robust effect was shown and the development of acoustic Non-Lethal Weapons (NLWs) stopped by the Joint Non-Lethal Weapons Directorate (JNLWD). Veridian scientists submitted a proposal to the JNLWD for funding to conduct initial effectiveness testing on small, high velocity projectiles, beginning with the 0.32 caliber PVC balls used in several fielded blunt impact munitions. As with acoustics, research data to support effectiveness of the impact of the balls or the potential for injury did not exist. Experiments on the projectiles will continue into the next contract to study multiple impacts and other size and mass projectiles, supported by the JNLWD. As the interest from the NIJ, the DOD, and FAA in the incapacitating effects of TASERs grows, the existence of effects research is drawing interest. The NIJ funded Veridian through AFRL/HEDR to conduct experiments to determine the effectiveness of existing TASER devices. This effort is spanning the old and new contract so the report has not yet been written. Research with TASERs continues into the next contract with JNLWD funding to look at optimizing the output of the TASER devices. Building on the effects data from ADT, Veridian researchers developed and conducted a series of experiments to determine how well a hand-held MMW device could be aimed. A program was written to integrate aiming data to determine the spot size needed on target to produce an effect. Thus, effects data and human factors data collected in the lab will help the hardware developers design the man-portable system.

3.1 Acoustic Research

3.1.1 Description of Work

Beginning in 1996 (and ending in 2000), Veridian Engineering was asked to assess the biological impact of an array of acoustic weapon prototypes in a number of scenarios employing various bio-behavioral endpoints. Bio-behavioral endpoints examined were equivalent to a robust, immediate (or a fast acting) effect on the target. The possibility of a subtle effect of acoustic energy may have some military utility; however, the charge from the Government was to look at the acute incapacitating or behavioral disruption effects of acoustic energy absorption. Startle is a useful first exposure effect; that was acknowledged but not studied.

3.1.2 Funding

U.S. Army's Armament Research, Development, and Engineering Center (ARDEC), National Institute of Justice (NIJ).

3.1.3 Relevance

Both military and law enforcement agencies have a compelling interest in non-lethal weapons technology designed to disorient, incapacitate, confuse, or repel individuals or groups, without causing acute or long-term injury. Such weapons offer the potential of a more appropriate response in support of certain peacekeeping and tactical combat operations. A strong effects research base must underlie and support the operational requirements of the user and withstand the scrutiny of policymakers.

3.1.4 Products

The results of our studies were presented in the publications and presentations listed below

Cook, M.C., Sherry, C.J., Brown, G.C., and Jauchem, J.R. Lack of effects on goal-directed behavior of high-intensity infrasound in a resonant reverberant chamber: U.S. Air Force Research Laboratory; Technical Report: AFRL-HE-BR-TR-2001-0154, Brooks Air Force Base, TX, Nov. 2001.

Murphy, M.R., Jauchem, J.R., Merritt J.H., **Sherry, C.J., Cook, M.C.**, and **Brown, G.C**. Acoustic bioeffects research for non-lethal applications. In: *Fraunhofer Institut Chemische Technologie, ed. New options facing the future. Proceedings of the First European Symposium on Non-Lethal Weapons; 2001 Sep 25-26, Ettlingen, Germany*. Karlsruhe, Germany: DWS Werbeagentur und Verlag GmgH; 2001:9.1-9.13.

Sherry, C.J., Cook, M.C., Brown, G.C., Jauchem, J.R., Merritt, J.H., and Murphy, M.R. An assessment of the effects of four acoustic energy devices on animal behavior: U.S. Air Force Research Laboratory;

Technical Report: AFRL-HE-BR-TR-2000-0153, Brooks Air Force Base, TX, Oct. 2000.

Sherry, C.J., Cook, M.C., Jauchem, J.R., **Brown, G.C.**, and Edris, R. The effects of infrasound on rhesus monkey performance of a continuous compensatory tracking task. *Aviation, Space and Environment Medicine* (In press)

3.2 Blunt Impact Research

3.2.1 Description of Work

Recognizing the need to establish a human effects database for blunt impact munitions, the JNLWD funded an initial study to determine the effective impact velocity required to change the behavior of a goal-directed target. The study was entitled "Bio-Behavioral Effects of Kinetic Munitions on Swine (Sus scofa)." The swine were trained to bar-press for a food reward; the objective of the study was to determine at what impact velocity 50% of the swine stop pressing for food (EV50) for at least 15 seconds after being impacted by a single 0.32 caliber PVC ball weighing 0.4 gram. The location of all impacts was just behind the front shoulder. Each swine was impacted just once to minimize any habituation. These same balls are the primary payload of two NLWs – the Modular Crowd Control Munition (MCCM) and the 66mm Non-Lethal Grenade. A custom-built compressed air driven launcher had to be constructed and chamber pressures calibrated to launch velocities. Maximum launch velocities were limited to approximately 120% (~625 ft/sec) of the reported launch (muzzle) velocities of the MCCM (~520 ft/sec). The up-down method of Dixon and Massey was used to estimate the EV50 with a relatively small group of animals. Particularly challenging was the selection of an initial velocity and an incremental velocity step in the absence of relevant literature; a pilot study was conducted to establish the initial velocity and incremental step size.

3.2.2 Funding

JNLWD (USMC).

3.2.3 Relevance

Research data on the effectiveness of blunt impact munitions with which to assess operational utility is sparse. Blunt impact weapon systems are being developed and fielded without any measures of effectiveness. This initial study (and follow-on studies) will form the basis upon which to develop meaningful measures of effectiveness.

3.2.3 Products

Single impacts did not produce the robust effects set as effectiveness criterion (i.e., stop behavior for 15 seconds or longer). Results and recommendations are documented in an unpublished report to the JNLWD ("Effects of the Impact of a Single .32 Caliber, Vinyl PVC Projectile at Various Velocities on Trained Behavior in an Animal Model," dated 17 July 2001); results of the study were briefed at the JNLW Director's Review and to the Human Effects Advisory Panel (HEAP).

3.3 TASER Research

3.3.1 Description of Work

The objectives of this study were to compare the effectiveness of existing TASER-like devices side by side in a simulated operational employment using the same behavioral task and to collect physiological data to enhance our understanding of the mechanisms which contribute to effectiveness and unintended consequences. Two models of TASER devices from both TASER International and Tasertron are being tested on each of ten swine trained to bar-press for a food reward. This conduct of this study spanned the old and new contract; data collection and analysis is ongoing. Interest in the results of this study has drawn more attention with the announcement that the Federal Aviation Administration is considering use of TASERs onboard aircraft. The DOD (in particular the USMC) has also shown an active interest in using TASERs as a non-lethal technology. Hence, future work has been funded to continue studying the biophysical mechanisms and optimizing the output parameters for improved effectiveness and minimizing risks.

3.3.2 Funding

NIJ

3.3.3 Relevance

Like other NLWs such as acoustics and kinetics, there is little coordinated research which forms the basis for determining the effectiveness and risk of injury of TASERs. Unlike acoustics and kinetics, though, there is an experience database for operational use of TASERs to subdue uncooperative targets. TASER-like devices have been used effectively by local law enforcement for a number of years. Hence, they must have some usefulness in subduing individuals.

3.3.4 Products

Informal presentations to the HEDR staff have been made. A formal report, requested by the HECOE, was prepared for the Human Effects Review Board (HERB) on the current understanding concerning effectiveness and risk of the use of TASERs. Preliminary results of the characterization of the outputs of each of the TASER devices being tested, using a standard test setup, were presented in the report. This report and a briefing to the HERB are archived in the HECOE database.

3.4 Radio Frequency Radiation NLW Research

3.4.1 Description of Work

Beginning in 2000, Veridian, working in concert with AFRL/HEDR, performed work that attempts to model one such potential non-lethal weapon. AFRL funded a collaborative effort to determine the design constraints for a handheld (or crew-served) RFR weapon with a defined spot diameter. Using effectiveness parameters from the ADT program, Veridian researchers investigated the effects of system shape and weight distribution on an operator's ability to hold the directed energy, speed-of-light device on the target delivering an effective energy exposure. The title of the study is "Aiming a Handheld Non-Lethal Weapon: Variables Affecting Hold Time on Target." The model employed is a modified, commercially available laser tag gun. Subjects were instructed to aim the gun at a target point 25 m away for a period of 1 minute under a variety of experimental conditions. Accuracy was monitored throughout the aiming session and the results digitized. Three phases have been completed to date, viz., varying weight, weight distributions of the gun and exercise on aiming accuracy. Conclusions reached thus far include: (a) mild aerobic exercise had a sustained negative impact on the ability of subjects to aim the weapon; (b) other factors such as weight of the weapon and randomly-presented loud noise had little or no impact; and (c) subjects' aerobic capacity (as indexed by estimated VO_2max) was only minimally related to their general success in aiming the weapon.

A computer program (HEATER) was written to simulate the resultant skin heating from a moving spot of MMWs. The HEATER code uses the results of the human aiming study as input for spot movement, and predicts skin temperature change with time. Peak power and 3 dB spot size are also used as input parameters. Currently, crude empirical skin heating and cooling models are used. Veridian will work with AFRL/DEH to develop better physics based models, which will allow HEATER to better predict system the effectiveness of a human carried and pointed ADT-type NLW.

After better skin heating and cooling models are inserted into HEATER, a prediction of skin temperature will be made for a moving spot on human skin. A human study with an RF source and mirror system that mimics aiming movements used in the prediction will then be performed, with the results used to verify both skin temperatures achieved, and intolerable pain thresholds. HEATER can then be used to design a human carried and pointed ADT-type NLW.

Possible follow-on efforts include (a) modifying various characteristics of the weapon (e.g., adding additional weight, adding a stock, etc.); (b) imposing additional challenges on the subject during the aiming sessions

(e.g., wearing a weighted pack); (c) modifying the performance of human exposures in the laboratory with a Veridian-constructed, computer-controlled mirror system that mimics the average of all operators' aiming data. This will determine intensity and duration thresholds and verify the RFR effects model. The current RFR heating model used is empirical. The database used for this model is being expanded, which will allow use of the model across a greater range of system relevant parameters. This updated model will be compared with the physics based model being developed by Veridian and AFRL/DEH. These effects data will feed into the development of the hardware, source, and antenna.

3.4.2 Funding

AFRL 7757 project funds

3.4.3 Relevance

New directed energy non-lethal weapons are currently under development, including some that may eventually be handheld. For a directed energy weapon requiring energy on target for some duration to be effective, we must understand the effects of weapon design characteristics (e.g., weight) on both random and systematic errors in aiming.

3.4.4 Products

Brown, G.C., Scholl, D., Fines, D.A., Theis, C.F., Beason, C., and **Cook, M.C.** Aiming a model of a hand-held, non-lethal weapon: Variables affecting time on target. Interim Report to AFRL/HEDR, February 2002.

Brown, G.C., Scholl, D., Fines, D.A., Theis, C.F., Beason, C., and **Cook, M.C.** Aiming a model of a hand-held, non-lethal weapon: Variables affecting time on target. In preparation for submission to Military Psychology.

4.0 HUMAN EFFECTS CENTER OF EXCELLENCE (HECOE)

In 1999, the Joint Non-Lethal Weapons Directorate (JNLWD) funded AFRL/HEDR to establish the Joint Non-Lethal Weapons Program Human Effects Center of Excellence. In 2000, the HECOE was activated. The mission of the HECOE was to provide human effects support to the program managers of new and ongoing NLW programs and concepts. Veridian scientists were instrumental in activating the HECOE, providing subject matter expert consultation for a number of non-lethal technologies, and shaping the future direction of the HECOE.

4.1.1 Description of Work

Initial efforts of the HECOE and Veridian scientists focused on supporting legacy NLW programs, many of them Army and many of them blunt impact NLWs. Veridian scientists performed human effects analyses on two blunt trauma non-lethal weapon (NLW) systems, a TASER system, and a multi-sensory device for the Human Effects Review Board. Veridian's experience in conducting effectiveness testing on directed energy, kinetic, acoustic, and TASER technologies have proven valuable to the understanding of the available literature and the capability of related technologies. Veridian took the lead in organizing the first ever workshop on risk characterization of NLWs with worldwide experts in the field of risk assessment. The workshop was successful and the proposed risk characterization framework was presented at the Society for Risk Assessment 2001 annual meeting in New Orleans, LA, in addition to being published in a peer-reviewed journal on risk assessment. Veridian scientists served as subject matter experts in acoustics, radio frequency radiation, kinetics, and NLW modeling and simulation for the risk assessment expert panel. A second risk characterization workshop was conducted on a blunt impact system, the 66mm non-lethal hand grenade, currently in acquisition. Inadequacies of the predictive tools were identified. Monte Carlo methods for determining the probability of effectiveness and risk of injury were developed, however, accuracy of these methods depends upon dose response predictive models. Programs to improve the predictive tools were established; these programs include the Non-Penetrating Projectile (NPP) program and the Interim Total Body Model (ITBM). Blunt impact and TASER research efforts, sponsored by the Joint Non-Lethal Weapons Directorate, were initiated to fill research data gaps, establish effectiveness and injury criterion, and determine physiological mechanisms. The experience of

Veridian personnel in acquisition and in research and development test and evaluation (RDT&E) has allowed the HECOE to provide valuable inputs into the Master Test Plan for NLW systems in development.

4.1.2 Funding

JNLWD (USMC) and Marine Corps Systems Command (MARCORSYSCOM).

4.1.3 Relevance

The foundation for effective non-lethal weapons is the ability to predict both the probability of effectiveness and injury based upon relevant biological, psychophysical, and behavioral research data. JNLWD recognized the need for effects-based NLWs and established the HECOE to ensure that human effectiveness was addressed in each NLW system being developed or NLW concept being considered.

4.1.4 Products

The following Human Effects Analysis reports were prepared by HECOE/Veridian and HECOE/Conceptual Mindworks (CMI) staff: Modular Crowd Control Munition (MCCM), 40mm Non-Lethal Crowd Dispersal Cartridge, 66mm Vehicle-Launched Non-Lethal Grenade, Taser Area Denial Device, Clear-a-Space Concept Exploration Program – an assessment of flashbang devices. Other reports were prepared for the HECOE by the Toxicology Excellence in Risk Assessment (TERA), a non-profit corporation located in Cincinnati, OH – Proposed Non-Lethal Weapon Risk Characterization Framework, and by Battelle Labs – a Preliminary Human Effects Analysis of the MCCM.

Brence, A., Dayton, T.E., Sherry, C. J., Kosnik, D., Huantes, D., and Klauenberg, B.J. Use of flashbang devices to clear a space. Submitted to the Clear Spaces Concept Exploration Phase (CEP) program. April 25, 2002.

Gonzalez, D.L., **Dayton, T.E.,** Widder, J., Constable, R., and Klauenberg, B.J. The 66mm non-lethal grenade. August 20, 2001.

Gonzalez, D.L., **Sherry, C.J., Dayton, T.E.**, Constable, R., and Klauenberg, B.J. The TASER area denial device. October 11, 2001.

Sherry, C.J., Klauenberg, B.J., **Brown, G.C.,** and **Dayton, T.E.**, The TASER based electrical non-lethal weapons. May 15, 2002.

Simonds, J., Dayton, T.E., and Klauenberg, B.J. The 58 ft-lb Fragmentation Hazard Criterion. April 26, 2002

Simonds, J., Dayton, T.E., and Klauenberg, B.J. The XM-95 rifle launched munition. May 8, 2002.

Widder, J., **Dayton, T.E.,** Gonzalez, D.L., Constable, R., and Klauenberg, B.J. The non-lethal 40mm crowd dispersal cartridge. February 22, 2001.

5.0 HEALTH AND SAFETY EFFECTS RESEARCH

Veridian executed exploratory research into the mechanisms of RFR interaction with tissue and potential for affecting physiological functions. Three such studies, in which Veridian scientists are involved, are underway presently – the blood-brain barrier (BBB) study, the RFR biomarker study, and the ultrawide band (UWB) RFR study.

The RFR environment demands an ongoing research program to provide scientific evidence for setting standards for RFR exposure. The UWB study investigated the potential for UWB energy to stimulate excitable tissue. These are the first electrophysiological experiments aimed at characterizing the coupling of UWB RFR energy to electrically excitable tissue and its resulting response.

The blood-brain barrier (BBB) maintains the brain environment, controlling entry of chemicals from the blood, and insulating the brain from rapid changes in the concentration of hormones, ions, peptides, etc. Recent work published in the literature suggest low level RF exposure disrupts the BBB. Veridian employees, working with the AFRL/HED, completed the first stage in an ambitious project aimed at replicating these important findings.

5.1 Dosimetry and Modeling

5.1.1 Description of Work

Veridian scientists and subcontractors (Trinity University) used computer FDTD (Finite-Difference Time Domain) and computational models to predict where RF energy is deposited in the body, and the resulting thermal consequences. Three-dimensional models of common laboratory animals were developed, using magnetic resonance imaging and computer graphics software to assign voxels to particular tissue types. Similar graphics techniques were used to improve greatly the accuracy and resolution of an existing man model. These models were then used with FDTD codes to investigate patterns of RF deposition, and how the results of such FDTD modeling depend on various assignments of tissue

electrical properties. The output of such computer models was also compared to actual measurement of tissue heating.

5.1.2 Funding Sources

AFRL 7757 project funding and JNLWD funding.

5.1.3 Relevance

Determining where RF energy is deposited in the human body is critical to understanding many of the health and safety questions regarding exposed (or potentially exposed) personnel to directed energy NLWs and various DOD radars. Furthermore, the development of accurate computer models of the bodies of humans and various laboratory animals greatly facilitates the experimental work regarding Active Denial System undertaken by the Air Force Research Laboratory. Thermal models of the deposition and distribution in tissues of heat resulting from RF radiation are also helpful in guiding the collection of data important to USAF health and safety issues.

5.1.4 Products

The animal and human models (as well as the Radio frequency Radiation Dosimetry Handbook and other AFRL/HED-sponsored publications) have been made available to researchers world-wide on a website developed by VE personnel (Mason et al., 2000b). Experimental results are described in detail in the publications listed below and attached. VE personnel and their data also contributed to extensive thermal modeling work. Publications and presentations are listed below.

Adair, E.R., **Mason, P.A,** and K.H. Obenshain. On the origin of signals for the initiation of heat loss responses in RF-exposed humans. *Fourth Annual Michaelson Research Conference Abstract*, Canandaigua, NY, 1997.

Cobb, B.L., Jauchem, J.R., Adair, E.R. Radial-arm maze performance of rats following repeated low level microwave radiation. Submitted.

Cook, M.C., Miller, S.A., Murphy, M.R., Merritt, J.H., and Mason, P.A. Genetic susceptibility of three rat strains to a model of post-traumatic stress disorder. *Society for Neuroscience Abstract*, San Diego, CA, November 2001.

D'Andrea, J.A., Ziriax, J.M., Hatcher, D.J., Cox, D.D., Henry, P.J., Kosub, K.R., and **Mason, P.A.** Effects of head resonant radio frequency radiation on time estimation behavior of rhesus monkeys. Presented at 22nd *Annual Bioelectromagnetics Society Meeting*, Munich, Germany, June 2000.

Dick, E.J. Jr., **Kalns, J.E., Ryan, K.L., Mason, P.A.**, Barshay, A., Brown, J.L., Scruggs, J., Gooden, R., and Kiel, J.L. Differential protein nitration in

hypotension resulting from heat stroke or hemorrhage. American College of Veterinary Pathologists meeting, the American College of Veterinary Pathologists Annual Meeting, Amelia Island, Florida, December 3-6, 2000 (*Veterinary Pathology*. 37(5):543, 2000).

Dick, Jr. E., **Mason, P.A., Walters, T.J., DiGiovanni, J., Beason, C.W.,** Jauchem, J.R., Barshay, A., Mahajan, K., Dusch, S.J., Shields, B.A., Merritt, J.H., Adair, E.R., Murphy, M.R., and Ryan, K.L. Lack of effect of 94-GHz radio frequency radiation exposure in an animal model of skin carcinogenesis. *American College of Veterinary Pathologists Abstract*, Salt Lake City, December 2001.

Gajšek, P., Ziriax, J.M., Hurt, W.D., **Walters, T.J.**, and **Mason, P.A.** Parametric dependence of SAR on permittivity values. Presented at *22nd Annual Meeting of the Bioelectromagnetics Society, Munich, Germany, June 2000.*

Gajšek, P., Ziriax, J.M., Hurt, W.D., **Walters, T.J.**, and **Mason, P.A.** Sensitivity of SAR on dielectric properties. Presented at *Seventh Annual Michaelson Research Conference*, Gig Harbor, WA, 2000.

Gajšek, P., Mason, P.A, Ziriax, J.M., Hurt, W.D., and **Walters, T.J.** Parametric dependence of specific absorption rate (SAR) on permittivity of different biological tissues. *3rd International Conference on Bioelectromagnetism Abstract*, Bled, Slovenia, October 2000.

Gajšek, P., Walters, T.J., Hurt, W.D., Ziriax, J.M., **Nelson, D.A.**, and Mason, P.A. Validation of FDTD predictions with empirical data. Presented at *23nd Annual Meeting of the Bioelectromagnetics Society,* St. Paul, Minnesota, June 2001.

Gajšek, P., Ziriax, J.M., Hurt, W.D., and Mason, P.A. Effects of permittivity values on SAR calculations in a man model. Presented at *23nd Annual Meeting of the Bioelectromagnetics Society,* St. Paul, Minnesota, June 2001.

Gajšek, P., Ziriax, J.M., Hurt, W.D., and Mason, P.A. Parametric dependence on specific absorption rate (SAR) on relative dielectric and conductivity of different biological tissues. Presented at *5th International Congress of the European Bioelectromagnetics Association (EBEA),* Helsinki, Finland, September 2001.

Gajšek, P., D'Andrea, J.A., Mason, P.A, Ziriax, J.M., **Walters, T.J.**, and Hurt, W.D. Mathematical modeling of EMF absorption in biological systems. IEEE book chapter: *Biological Effects of Electromagnetic Fields*, submitted.

Gajšek, P., Walters, T.J., Hurt, W.D., Ziriax, J.M., Nelson, D.A., and Mason, P.A. Empirical validation of SAR values predicted by FDTD modeling. *Bioelectromagnetics* 23:37-48, 2002.

Gajšek, P., Hurt, W.D., Ziriax, J.M., and Mason, P.A. Parametric dependence of SAR on permittivity values in a man model. *IEEE Transactions on Microwave Theory and Technique* 48:1169-1177, 2001.

Gajšek, P., Ziriax, J.M., Hurt, W.D., Walters, T.J., and Mason, P.A. Predicted SAR values in Sprague-Dawley rat as a function of permittivity values. *Bioelectromagnetics* 22:384-400, 2001.

Hurt, W.D. and **Mason, P.A**. Dosimetry models used to determine the bioeffects of directed energy exposure. *Proceedings of the NATO Research and Technology Agency Workshop on Models for Aircrew Safety Assessment: Uses, Limitations, and Requirements*. Wright-Patterson AFB, Ohio, October, 1998, RTO-MP-20, Chapter 29, 1999.

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Hurt, W.D., Ziriax, J.M., and **Mason, P.A**. Absorption characteristics and measurement concepts. Presented at *NATO Advanced Research Workshop on Radio Frequency Radiation Dosimetry and its Relationship to the Biological Effects of Electromagnetic Fields*. Gozd Martuljek, Slovenia, 1998.

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5.2 RFR Standards Support

5.2.1 Description of Work

Veridian scientists have been instrumental in supporting the International Committee for Electromagnetic Safety's (ICES) Subcommittee 4 in generating a revision of the C95.1 Safety Standard: "Standard for Safety Levels with Respect to Human Exposure to Radio Frequency Electromagnetic Fields, 3 kHz to 300GHz." Several consultants were hired to review the extensive literature on RFR biological effects – Louis Heynick, Dr. John Osepchuk, and Dr. Robert Adair.

Veridian personnel have contributed to the work of ICES SC4 in two major areas. First, we have developed a database application to facilitate the scientific literature review on which the new standard will be based. Working with the leadership of SC4, Dr. Star Ferdinand wrote a set of database applications that will result in a permanent database encompassing the entire published literature on radio frequency radiation (RFR) bioeffects. The application consists of 12 different stand alone database programs: Literature Surveillance, Risk Assessment, Epidemiology Chair and Reviewer, Engineering Chair and Reviewer, In Vitro Chair and Reviewer, In Vivo Chair and Reviewer, and Statistics Chair and Reviewer. The Literature Surveillance program allows the surveillance chair to produce and update a database containing the bibliographic data on all papers published on RFR bioeffects. The surveillance chair distributes this database, with periodic updates, to each of the other chairs. The other chairs (Epidemiology [EPI], Engineering [ENG], In Vitro [VIT], and In Vivo [VIV]) each have a database consisting of subsets of the master database. The chairs recruit reviewers to assess the scientific quality and relevance to standard setting of papers in their areas. Each paper is sent (along with digital evaluation forms and the reviewers' database program) to 2 independent reviewers. Each paper sent out for review by the biology chairs (EPI, VIT, and VIV) is also sent out for review by the ENG chair, so that quality of each gets 2 kinds of evaluation. When reviewers send back the completed electronic forms to their chairs, the chairs add the evaluations to their databases. Finally they forward the contents of their databases to the Risk Assessment Working Group (RAWG) Chair, which is responsible for determining threshold values for scientifically established adverse health effects. The final database allows the RAWG to select papers that have been judged by reviewers to be of adequate technical quality, as well as having relevance for standard setting, while eliminating from consideration papers of inadequate technical quality.

The second contribution to the standard setting process is the participation of Veridian scientists. During the course of this contract, Dr. Blick, Dr. Brown, Dr. Sherry, and Dr. Mason have regularly attended meetings of

ICES and SC4. In addition, Dr. Blick assumed the position of In Vivo Working Group Chair in 1997. Since then, he has added approximately 900 reviews to the database. Dr. Blick is also a member of the Editorial Working Group, which meets twice a year to work on a draft of the new standard.

5.2.2 Funding

AFRL 7757 project funds.

5.2.3 Relevance

The Air Force is one of the world's largest users of high power electromagnetic devices. In order to maximize the safe use of such devices, while maintaining the health and safety of its personnel, the Air Force needs a science-based safety standard that is protective, without being excessively conservative. Thus, AFRL/HED encouraged its employees and contractors to contribute their expertise to the IEEE/ICES consensus-based standard setting process. Veridian personnel have held and are holding leadership roles in national and international standards setting organizations.

5.2.4 Products

More than 90% of the relevant in vivo papers have been sent out for review, and, except for a few reviewers who have been slow to respond, most of these reviews have been completed and forwarded to the RAWG for final evaluation. Dozens of reviewers scattered around the world have successfully used the Veridian-developed database application to contribute to the literature review. Dr. Blick has attended ICES and SC4 meetings in Bologna, Italy; Munich, Germany; Luxembourg; Victoria, BC, Canada; St. Petersburg, FL; San Antonio; Long Beach, CA; and Minneapolis, MN. Dr. Blick has also attended meetings of the Editorial Working Group in Ft. Lauderdale, FL (twice), Phoenix, AZ, and Washington, DC (twice). The Editorial Working Group will present a draft of the new standard to the entire Subcommittee 4 in June, 2002, at its meeting in Quebec City, Quebec, Canada.

5.3 Effects of Microwave Radiation Combined with Stress on the Integrity of the Blood Brain Barrier

5.3.1 Description of Work

The blood-brain barrier (BBB) maintains the brain environment, controlling entry of chemicals from the blood, insulating the brain from rapid changes in the concentration of hormones, ions, peptides and other items. Its integrity can be altered by disease states (e.g., tumors), physiological insults, (e.g., hyperthermia). Veridian employees (George Lantrip, Kavita Majahan, Patrick Mason, Alexander Salazar, Clarence Theis) nearly completed the first stage in an ambitious project aimed at illuminating the1992 findings of L. Salford, who reported low levels of RFR allow albumin to pass through the BB into the brain and A. Friedman, in 1996 who reported that physical stress allows pyridostigmine (PYR) to enter the brain. Experimental subjects in Phase I of this program experienced stress in the form of 30 min of restraint. This was followed by a subcutaneous injection of 0.177 mg/kg PYR (ED99 dose for 40% serum cholinesterase [ChE] inhibition) and a 30-min exposure to continuous wave 915 MHz RFR at 20 W/kg (or sham exposure). Phase I results failed to indicate any effect of restraint stress or RFR on BBB leakage relative to sham-exposed subjects.

The second phase will attempt to replicate the Salford experiments, examining the effects of continuous wave and modulated 915 MHz RFR on the integrity of the BBB. Post-exposure, subjects will be anesthetized; perfused intracardially, and the brains removed and assayed using an albumin immunohistochemistry assay. To determine the effectiveness of assays in revealing albumin leakage, the results from the immunohistochemistry assay will be compared to those from labeling albumin with Evan's Blue or sodium fluorescein.

5.3.2 Funding

AFRL 7757 project funds.

5.3.3 Relevance

In the early 90s, work by Salford postulated that exposure to very low levels of RFR affected the BBB, allowing albumin to enter the brain. In addition, laboratory results by A. Friedman in 1996. suggested that physical stress allows PYR, a nerve agent prophylactic, to enter the brain. Such findings, if true, could have an impact on the RFR safe exposure standards and for U.S. military personnel exposed to stress and/or RFR.

5.3.4 Products

Miller, S.A., Murphy, M.R., Merritt, J. H., and **Mason, P.A**. Effects of microwave exposure combined with stress on the integrity of the blood-

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5.4 HPM Electrophysiology Program [Ultrawideband (UWB) RFR Studies]

5.4.1 Description of Work

The general programmatic question is " Are there any hazards associated with exposure to ultrawideband (UWB) pulses?" The specific question for this project is can brain or muscle be affected by exposure to UWB pulses? Work began on this project in September 2000 and has continued into the new contract.

For the initial screening study, the classic frog gastrocnemius muscle preparation was selected. This experimentally robust preparation has been used since the time of Galvani and Volta, and it has provided much of the information on how electrically excitable tissues respond to electrical stimulation. Thus the dependent variable is well characterized, and the novelty is in the independent variable.

One classic way of describing the response of electrically excitable tissue to stimulation is the strength-duration (S-D) curve. As the duration of the pulse is decreased, the current (and voltage) required to elicit a response is increased. Plotting the S-D curve for muscle contraction involves determining a series of thresholds for elicitation of a minimal-amplitude contraction at multiple pulse durations, starting with long-duration stimuli of about 100 msec and going as short as the available pulse source can achieve. In the conventional biomedical literature, many S-D curves for muscle or nerve have been described down to 10 usec, and some published data exist at 1 usec. However, the immediate goal of this project is to complete the S-D curve down to 1 nsec, increasing the known domain by a factor of 1,000.

Between September 2000 and October 2001, an electrophysiology laboratory was designed and equipped; a Review Committee was established to set the approach to be used in the first year; and biological and engineering methods were implemented. Four different sources, (1) a conventional Grass stimulator, and pulsers produced by the (2) Avtech, (3) Bournlea and (4) Velonex companies were used; each had its own pulse duration and voltage characteristics. A computerized experimental control and data acquisition system was used, and HP function generators provided control over signal timing. The isotonic contractions of an isolated gastrocnemius muscle were measured by a transducer that converted muscle movement into an electrical signal that could be recorded and measured by an objective mathematical criterion; there were no judges. Over a 10-hour experimental day, more than 300 data points could be acquired.

The project completed the voltage S-D curve down to c. 4 nsec, producing a classically shaped plot. However, when pulse duration got shorter than

about 200 nsec, the signal showed severe ringing and the instrumentation approach could not allow measurement of current or voltage. In November 2001, the Review Committee found the work so promising that they recommended taking the additional time to improve the approach used for signal delivery and measurement and then to reacquire the S-D curve in terms of current, the physiologically most relevant parameter. By the end of February 2002 substantial progress had been made on these tasks. Ringing had been reduced considerably, and an approach allowing current measure had been implemented.

The initial current S-D curve acquired with the new arrangement showed a single UWB pulse of c. 1 nsec and c. 30 A could elicit a contraction. This observation provides an experimentally determined "figure of merit" that could be used to set a safety standard. The Review Committee posed several other questions relating to determining the general mechanism for the observed effect and for establishing that possible artifacts were not responsible for the observed responses. In the next year, the newly implemented methods will be refined, more extensive data will be acquired, and additional questions will be examined.

5.4.2 Funding Source

AFRL 7757 project funding.

5.4.3 Relevance

The USAF is developing sources using UWB pulses.
As part of this effort, safety standards must be developed for these new sources. In the late 21st century, key general questions about safety most frequently have included studies of possible effects on genes and cancer and on reproduction and development. In this case the USAF also is asking about the possibility of effects on electrically excitable tissues, which include muscles and nerves.

5.4.4 Products

To date, four extensive project reports and a major briefing have been completed, and a presentation of the initial work will be made in June 2002, at the 24th Annual Meeting of the Bioelectromagnetics Society.

Rogers W.R., Merritt, J.H., Murphy, M.R., **Barker, T.,** Kuhnel, C., and Johnson, L.H. Extension of the single-pulse, contact-stimulation strength-duration curve down to 5 nanoseconds. To be presented at the *24th Annual Meeting of the Bioelectromagnetics Society*. Quebec City, Quebec, Canada; June 2002.

Rogers, W.R. Testing for Effects of High-Peak, Short-Pulse-Width Electromagnetic Signals on Frog Muscle. Presentation to Review

Committee, November 15 and 16, 2001. Five hours, including lab tour; 101 PowerPoint slides.

Rogers, W.R. Testing for Effects of High-Peak, Short-Pulse-Width Electromagnetic Signals on Frog Muscle. Internal USAF Report submitted November 11, 2001. 99 pp.

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Rogers, W.R. Testing for Effects of High-Peak, Short-Pulse-Width Electromagnetic Signals on Frog Muscle. Internal USAF Report submitted February 15, 21, 2001. 25 pp.

5.5 Genetic Susceptibility of the Laboratory Rat (*Rattus Novigicus*) to a Model of Post-Traumatic Stress Disorder (PTSD)

5.5.1 Description of Work

Brain systems involved in the development of PTSD include those responsible for the response to stress, and also those involved in behavioral processes such as sensitization and fear conditioning. Little research has been directed at the mechanisms underlying the possible genetic susceptibility for this maladaptive stress response. This might be possible by examining stress responsivity in different strains of a given species. We hypothesized that the genetic susceptibility to PTSD lies in those brain systems and regions where the processes of behavioral plasticity (sensitization) and adaptation to stress converge. Beginning in 2000, Veridian and AFRL scientists worked with colleagues at the University of Texas Health Science Center at San Antonio (UTHSCSA) to test this hypothesis by examining genetically diverse strains of rats (Sprague Dawley, Lewis, Wistar, and Wistar Kyoto) in a fear-potentiated startle (FPS) paradigm. (The normal startle is a well-understood reflexive response to mildly noxious stimuli, such as a burst of white noise.) The FPS response involves classically conditioning fear to a previously non-feared stimulus (such as a light) by presenting it in conjunction with mild electric footshock. Later, when the light is presented without the shock, the normal startle response is amplified.

Data from Phases 1 and 2 have all been collected as of November 2001. Data from Phase 1 showed the appearance of FPS for some strains (e.g., Sprague Dawley), but not others (e.g., Wistar Kyoto). Data from Phase 2, in which we tested the effect of a prior stressor (cold stressor task) on FPS in these same rat strains, yielded inconclusive results.

5.5.2 Funding

Veterans Administration

5.5.3 Relevance

Post-traumatic stress disorder may occur in individuals who experience a traumatic event. Although the incidence of PTSD among the general population is quite high (between 1% and 12%), the disorder is particularly prevalent among veterans who have experienced war-related aggression. It is estimated that as many as 35% of Vietnam veterans have developed PTSD at some time during their lives. However, there may be a genetic component to the disorder, since not all individuals subjected to a given trauma go on to develop PTSD.

5.5.4 Products

The results of Phase 1 were presented at the annual Society for Neurosciences meeting, November 10-15, 2001. They will also be

presented at the 3rd Forum of European Neuroscience, July 13-17, 2002, and at *11th Annual Meeting of the International Behavioral Neuroscience Society*, June 19-23, 2002.

5.6 Radial-Arm Maze Performance Of Rats Following Repeated Low Level Microwave Radiation

5.6.1 Description Of Work

This work sought to replicate previous studies that by H. Lai in 1987 who reported a working memory deficit in rats exposed to low-level, 2450-MHz microwave (MW) irradiation when subsequently tested in a 12-arm, radial-arm maze. Lai reported an attenuation of this MW-induced learning deficit in subjects pretreated with either physostigmine or naltrexone hyrdochloride, but not with naloxone methiodide. The present replication utilized the same exposure system (circular polarized waveguides), whole body SAR (0.6 W/kg), pulse regimen, pretreatment drugs, exposure time, and maze configuration used by Lai. Lai employed error rate (viz., re-entry into already-visited maze arms) as their dependent measure; the present study analyzed both error rate and time to criterion. Veridian supplied technician support for this study.

The present study failed to replicate the data of Lai et al. Analyses of the error rate dependent measure showed neither a drug nor an exposure effect, but did reveal a significant effect of time (i.e., performance improvement over consecutive test days). Analyses of the time-to-criterion data showed (a) no effect of exposure; (b) slower acquisition in subjects pretreated with physostigmine or naltrexone hydrochloride (as compared to naltrexone methodide or saline); and (c) an effect of time similar to that found with the error rate data.

5.6.2 Funding

AFRL 7757 project funds

5.6.3 Relevance

The positive results of Lai et al have implications for the adequacy of RFR safe exposure standards. Prior to considering changing exposure standards Lai's results need to be replicated by independent researchers.

5.6.4 Products

N/A

6.0 BIOTECHNOLOGY

This ongoing program used pharmacology, toxicology, and tissue culture expertise for ongoing, national defense-critical research involving bio-agent detection, protection, and neutralization, as well as RFR bio-dosimetry. Veridian scientists evaluated the relative effectiveness of conventional high explosive weapons and conceptual high temperature incendiary weapons against storage and production facilities containing biological agents. They developed the test procedures and the post-test assay to measure the extent of neutralization of the bio-agent simulant. The data provided will aid the Air Force in down-selecting which concept(s) to develop.

Veridian scientists are participated in a research program (in progress) to assess the nature of various simulants with regard to accuracy in representing a particular agent as well as cataloging general characteristics. A spin-off of this program was the development of a new vaccine strain of Bacillus anthracis (Alls/Gifford strain). We anticipate that this strain will result in more sensitive detection sensor technology and better vaccines to protect U.S. troops.

Veridian scientists were also involved in a program to improve sensor technology for bio-agent detection to develop a novel approach to detect and identify a wide variety of bio-agents.

Veridian scientists conducted research into the biomechanisms of the effects of microwave exposure. Researchers have been searching for measurable biomarkers for some time. The team Veridian made what seems to be a breakthrough in biomarker research. Veridian scientists are on the cutting edge of microwave biomarker research and have published several articles in peer-reviewed journals describing this phenomenon.

6.1. Biomarkers of Radio Frequency Radiation (RFR) Exposure

6.1.1 Description of Work

This effort has two objectives. Objective 1 is to find relevant biomarkers of MMW exposure. It was previously observed that levels of nitrated proteins increase during MMW exposure. This suggests that nitrated proteins, their precursors, or metabolites might be relevant endogenous biomarkers to determine MMW exposure in DOD and civilian personnel. Investigation of biomarker compounds in blood was performed following MMW exposure. Objective 2 is to determine how biomarker expression from MMW exposure compares to that from other stressors (environmental and infrared heating and hemorrhage). In developing biomarkers it is essential to know how the levels of expression in response to MMW exposure compare to that produced by other stressors. This will indicate if the biomarker is unique to MMW exposure and can be used to specifically determine occurrence and extent of MMW exposure.

Rats exposed to MMW for tens of minutes experience body temperature increases, circulatory collapse, and death. Since the energy from 35-GHz exposure is absorbed within the first 0.9 mm of the skin, we hypothesized that substances may be released from the skin during prolonged MMW heating that lead to subsequent effects in the internal organs and contribute to death. Investigation by our laboratory showed that prior to vascular collapse, nitrated proteins are increased in both the liver and lung suggesting that substances released from the skin trigger pro-inflammatory events in distant organs. Thus, we focused on determining the feasibility of using nitrated proteins, or their precursors, and inflammatory molecules (cytokines) as potential biomarkers from plasma, liver, lung and skin.

The well-established model of MMW-induced vascular collapse in rats was employed. The results were contrasted to data from experiments using environmental or infrared heating or hemorrhage. Although we anticipated that some of the released substances might be common to all stressors, our goal was to identify those genes, proteins, and nitration pathways that are uniquely associated with MMW exposure. To that end, rats were exposed to sub-lethal levels of the stressors and euthanized at various times following treatment. Organs and blood were collected and assayed for levels of nitrated proteins, nitration precursors and cytokines.

One aspect that was clear from initial results was that the search for mediators produced during exposures could be quite time consuming because most assays are very specific. An alternative strategy that was used is a global screening approach in which large numbers of genes and proteins are surveyed using state-of-the-science genomic and proteomic assays. These results were then used to design more focused, in depth studies of specific targets.

In addition to the above *in vivo* experiments, an *in vitro* MMW exposure system was also developed in order to facilitate the understanding of specific cellular responses evoked by MMW exposure. This includes theoretical and empirical dosimetry that is essential in order to minimize the perturbations produced by the culture flasks on the homogeneous MMW field and ensure consistent sampling.

Our original hypothesis was that nitration of proteins may contribute to early death during MMW heating. Under this hypothesis, nitration should increase steadily during heating reaching peak levels at the time of death. This pattern was observed in peripheral leukocytes, but not in other organs including the liver, lung and gut. In fact, the pattern of nitration is tissue specific and transient suggesting that nitration may serve an altogether different function that is unrelated to pathology. These data

indicate that nitrated proteins are not merely the consequence of uncontrolled metabolism or inflammation, but rather that nitration may play a role in protecting organs from injury. This hypothesis will be further tested in subsequent investigations.

We also hypothesized that exposures would cause a systemic up-regulation of inflammatory signaling molecules (e.g., cytokines – TNF α, IL-1, IL-6) leading to injury in distant organs (e.g., lung, liver). Therefore, the levels of several cytokines (TNF-α, IL-1β, IL-6, IFN-γ and soluble phospholipase A-2 (sPLA2 - a rate-limiting enzyme of arachidonic acid pathway) in plasma were measured following exposure to environmental heat and MMW. The only significant change in these cytokines was an increase in the concentration of IL-1β following environmental heating. Thus, the pro-inflammatory cytokines we tested are not appropriate plasma biomarkers for MMW.

Initial data has been collected for the genomic and proteomic surveys. Genomics data from lung tissue revealed changes in expression for 28 genes after MMW treatment. For infrared treatment, expression of 12 genes changed, only three of which overlapped with MMW-induced genes. This indicates somewhat different kinetics or pathways are activated by the two different forms of heating. Most of the changes in gene expression support the hypothesis of a thermal induced immune response for MMW and IR exposures. This is indicated by the up-regulation of the pro-inflammatory mediator IL-1β, as well as other genes involved in inflammation and tissue remodeling. These data demonstrate the utility of this method for studying bioeffects and help lead the way to identifying potential candidate biomarkers for further study.

In proteomics analysis of plasma proteins, as many as 10 proteins were produced in response to prolonged MMW exposure. The data point to an acute phase-like response at 24 and 72 hour post-exposure and demonstrate the promise that proteomics may have for the identification of substances that are uniquely associated with MMW exposure.

6.1.2 Funding source

AFOSR

6.1.3 Relevance

Communication, military radar, weapon detection, and non-lethal weapon technologies are being developed that make use of the millimeter wave (MMW) range (3 - 300 GHz) of the electromagnetic spectrum. Some of these emerging technologies will require increasingly higher power outputs. There is increased possibility of prolonged overexposures, especially of the maintenance technicians or operators, as more of these systems are fielded. The proposed research will: 1) investigate the

biological effects of such exposures and 2) determine which endogenous substances (e.g., proteins, low molecular weight by-products, lipids) produced in response to MMW overexposure could be used as clinical biomarkers. These studies will enable assessment of possible health effects of MMW overexposure.

6.1.4 Products

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6.2 Weapon Performance Measurement for Bio-Agent Defeat

6.2.1 Description of Work

This program (in progress) is a classified project evaluating the relative effectiveness of conventional high explosive weapons and conceptual high temperature incendiary weapons in neutralizing storage and production facilities containing biological agents. John Alls, Veridian, manages the AFRL/HEDB team conducting post-test assays of bio-agent simulants. Three weapon concepts have had initial testing using two different target configurations. The data provided will determine which concept(s) will be developed. Follow on studies will investigate additional neutralization concepts/techniques against additional target configurations.

6.2.2 Funding

AFRL Munitions Directorate, Eglin AFB, FL

6.2.3 Relevance

These are important, timely field tests that will help develop techniques to maximally neutralize an adversary's biological agent production capability. Weapon concepts are being evaluated as significant data points are accumulated. Effective concepts will be pursued further.

6.2.4 Products

Classified reports have been developed for the customer. Data collection and analysis fed into AFRL/MN classified reports

6.3 Bio-Agent Simulant Evaluation and Development

6.3.1 Description of Work

This program (in progress) assesses the nature of various simulants with regard to accuracy in representing a particular agent as well as cataloging general characteristics. A spin-off of this program was the development of a new vaccine strain of Bacillus anthracis (Alls/Gifford strain). A database of simulants used, characteristics, vulnerabilities, and resemblance to actual agents is being compiled and updated. This database includes thermal sensitivity of Bacillus anthracis (Sterne strain), Bacillus thuringiensis, and Bacillus globigii. Additional simulants may be evaluated as well as relating thermal sensitivity to calorimetry data.

6.3.2 Funding

Army/ ECBC

6.3.3 Relevance

Developing simulants of biological agents that possess the same properties of the agents except for their virility is crucial to improving our ability to detect, protect against, and neutralize live agents.

6.3.4 Products

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Kiel, J.L., Gifford, H.D., **Alls, J.L.,** Bacillus Anthracis A/G (Alls/Gifford) As A New Vaccine Strain. U.S. patent pending.

6.4. Bio-Agent Detection and Identification

6.4.1 Description of Work

This program (in progress) is developing a novel approach to detect and identify a wide variety of bio-agents, and has the ability to amplify its sensitivity. It will also be capable of determining viability of agents. Specific aptomers have been produced for anthrax. They are currently being sequenced. Prototype flow cells are being tested. Aptomers will be developed for additional agents.

6.4.2 Funding

AFRL/MN

6.4.3 Relevance

The US military and federal/local agencies have a long-standing requirement to rapidly detect and identify a wide variety of bio-agents. The threat of chemical/biological agents to US troops in Iraq and in Afghanistan and to citizens in the US have underscored the urgency of developing and fielding such a technology. Current methods, although accurate and sensitive, require a dedicated lab and a lengthy assay time (24-48 hours). Development of a methodology that fast and mobile, yet just as accurate and sensitive, allows for quicker isolation and decontamination of infected areas and for more timely treatment of infected individuals. This technology has direct applications to Homeland Defense, Force Protection, and Weapon Neutralization (Neutralization of Weapons of Mass Destruction) efforts of the DoD.

6.4.4 Products

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Presented at *5th Biennial Conference Of The Society For Tropical Veterinary Medicine*, 12-16 June 1999, Key West, Fl.

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6.5 Passive Radio Frequency Radiation Detection Methodology

6.5.1 Description of Work

This program (in progress) has achieved proof of concept in the area of total exposure measurement as well as real time measurement using several frequencies of radio frequency radiation. Detection has occurred at transmission powers of 5 watts or less. Characterization and development of this quantitative photo-detection methodology is currently being pursued.

6.5.2 Funding

AFOSR

6.5.3 Relevance

This effort is aimed at developing an integrating RFR dose dosimeter for use in the field allowing health physicists to track exposures in work areas and radar sites.

6.5.4 Products

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THE NEUROBIOLOGY OF EMOTION
Neural systems, the amygdala, and fear

Is emotion a magic product, or is it a physiologic process which depends on an anatomic mechanism?
-J.W. Papez, 1937

Throughout the day, we experience a variety of *emotions*. For the most part, these emotions are transient in nature. However, when these emotions become intense or are unremitting they can have very dramatic effects on our behavior. The depressive syndrome is an example of a state that is characterized by unrelenting sadness accompanied by a deficit in one's ability to derive pleasure from positive situations. William James proposed one of the first theories of emotion that attempted to relate experience of emotion to physiological functions. He tried to describe the human experience of emotion:

> "Conceive of yourself, if possible, suddenly stripped of all the emotion with which your world now inspires you, and try to imagine as it exists, purely by itself, without your favorable or unfavorable, hopeful or apprehensive comment. It will be almost impossible for you to realize such a condition of negativity and deadness. No one portion of the universe would then have importance beyond another; and the whole collection of its things and series of its events would be without significance, character, expression, perspective. Whatever of value, interest, or meaning our respective worlds may appear imbued with are thus pure gifts of the spectator's mind."

The primary emotions are **anger**, **fear**, **pleasure**, **sadness**, and **disgust**. Emotions can be conceptualized in terms of their *functional or adaptive (help us survive) significance***.** Negative emotions such as anger and fear may promote avoidance or defensive behavior whereas the positive emotion of pleasure may facilitate ingestive, exploratory, sexual, or novel-seeking behavior. Thus, emotions and feelings may serve to achieve homeostasis or to facilitate adaptive behavior and equilibrium.

Emotions can be elicited by external stimuli. However, the stimuli must have relevance or motivational significance in order to guide appropriate, adaptive behavior. Is the stimulus good, bad, or neutral? Does it evoke anger, fear, or pleasure? What are its previous associations, what does it predict, what is an appropriate reaction? This general concept of **stimulus relevance** is important in guiding behavior in many spheres: consummatory, sexual, reproductive, defensive, approach/avoidance and fight/flight.

We typically view emotions as primitive and instinctive responses that are not associated with complex intellectual or cognitive functions. Certainly, key stimulus elements in the environment can trigger instinctive emotional responses (imagine confronting a large, threatening animal). However**,** cognitive-emotional interactions are extremely important in the elicitation of everyday emotions. In primates and humans, the brain has a striking capacity to learn and remember the emotional significance of diverse stimuli and events. Furthermore, our cognitive capacity allows us to assign **emotional valence** to stimuli, and to change the value that was previously assigned to a stimulus. For example, a child may be initially fearful of dogs, but through positive experiences the child may eventually enjoy and approach them. As another example,

imagine the emotions associated with a new relationship. Initially, seeing the person may evoke positive emotions of desire and happiness. However, after a nasty breakup, the same person could easily elicit emotions of anxiety, tension, and anger. This second example illustrates two important points. First, the sensory or perceptual analysis of the person is the same (i.e., this is Bob). The physical expression of emotion may also be the same (i.e., racing heart, flushed sensations, increased breathing rate). Second, the emotional reaction to the stimuli depends on cognitive processing. In other words, the evaluation of the stimulus (the person) in conjunction with past experiences determines the feelings or the conscious experience of joy or anger. Studies of brain functions reveal that neural pathways exist for these important cognitive-emotional interactions.

Brain systems in emotion

The neural basis of emotion has been studied for over a century. Early explorations suggested that specific brain regions are involved in the expression of emotional behavior. Studies in the '30s and '40s showed that electrodes placed in the hypothalamus elicited widespread activation of the sympathetic nervous system as well as coordinated expression of defensive reactions or presumed feelings of pleasure.

In our examination of emotions, emphasis will be placed on the role played by the limbic system and the monoamine systems.

Limbic system

As you know from your earlier lectures, the limbic system (Fig. 1) was originally proposed to consist of interconnected subcortical structures with pathways to the hypothalamus. The limbic system was proposed to modulate the emotional quality of stimuli and support autonomic effector mechanisms associated with emotional states. A key limbic structure that has a critical role in **emotional** expression is the **amygdala**. The amygdala has an important role in evaluating the emotional valence of stimuli. Support for this view arises from extensive work done with lesions of the amygdala. For example, animals with amygdala lesions have difficulty learning associations between environmental stimuli and emotional states. They may fail to learn that a stimulus predicts reward or danger, they may fall in social rank, or show decreased affiliative behavior. Damage to other limbic structures can also produce changes in emotional behavior.

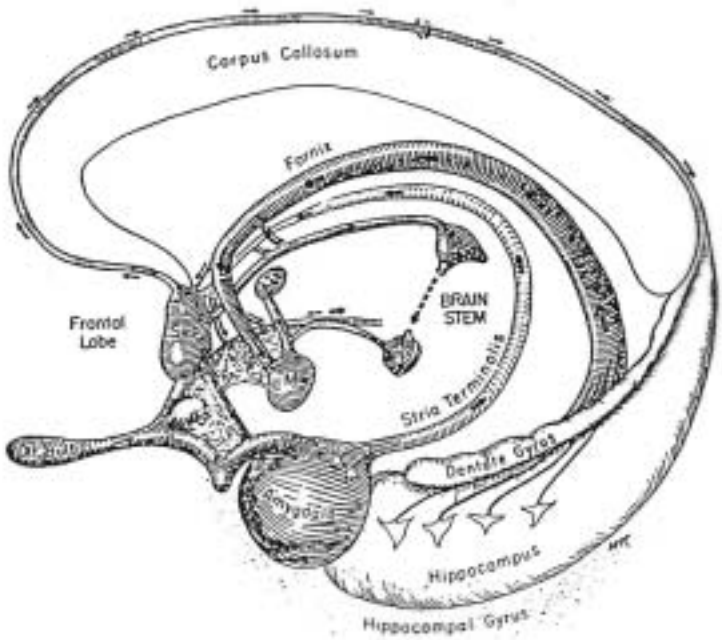


Fig. 1. Schematic drawing of limbic structures and their connections.

It is important to note that an interaction exists between cortical brain regions and the limbic system. There are massive connections between cortical regions, particularly from the frontal and temporal lobes, to subcortical limbic structures (Fig. 2). The implication of these connections is that complex sensory information processing occurring in the cortex can directly influence the limbic system. Conversely, limbic processing can strongly influence higher-level cognitive integration occurring in the cortex. Disconnection in the transmission of information between the cortical and subcortical limbic structures can have dire consequences. For example, patients with frontal lobe lesions show inappropriate emotional and social behavior in the absence of intellectual deficits. These patients might cry or laugh inappropriately, urinate in public, or use profanity.

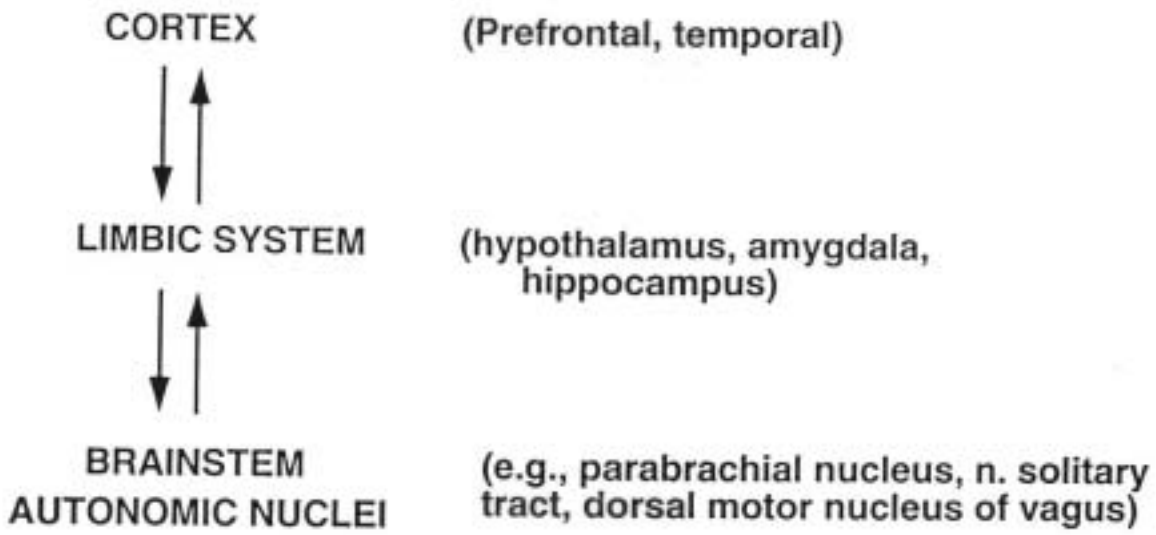


Fig. 2. Schematic diagram emphasizing the interactions between structures in the limbic system and cortical regions of the brain. Reciprocal connections exist between the prefrontal and temporal cortical areas, and both regions project extensively to different limbic structures. Therefore, the cortex has a strong influence on mechanisms governing emotional and autonomic responses. Limbic and brain stem regions may also influence the cortex via pathways through the thalamus (not shown), and via direct connections from the amygdala and hippocampus.

Monoaminergic systems (serotonin, norepinephrine, dopamine)

The neural circuits and brain structures involved in emotions are modulated by a myriad of chemical neurotransmitters. The ascending monoamine systems have received considerable attention over the past several decades. These include the **serotonin, norepinephrine**, and **dopamine** systems. Prior to the discovery of neurotransmitters, researchers believed that a major ascending neural system was responsible for arousal of forebrain (epithalamus, thalamus, subthalamus) and telencephalon (cerebral cortex, basal ganglia and associated structures like the nucleus basilis of Meynert and the nucleus accumbens). This neural system used to be called the **ascending reticular activating system**, before the monoamines were characterized. It is believed that a balance among these systems (as well as other neurotransmitters) is necessary for normal emotional states and arousal. Over the last three decades, the neurochemical basis of this ascending system was described and receptors identified.

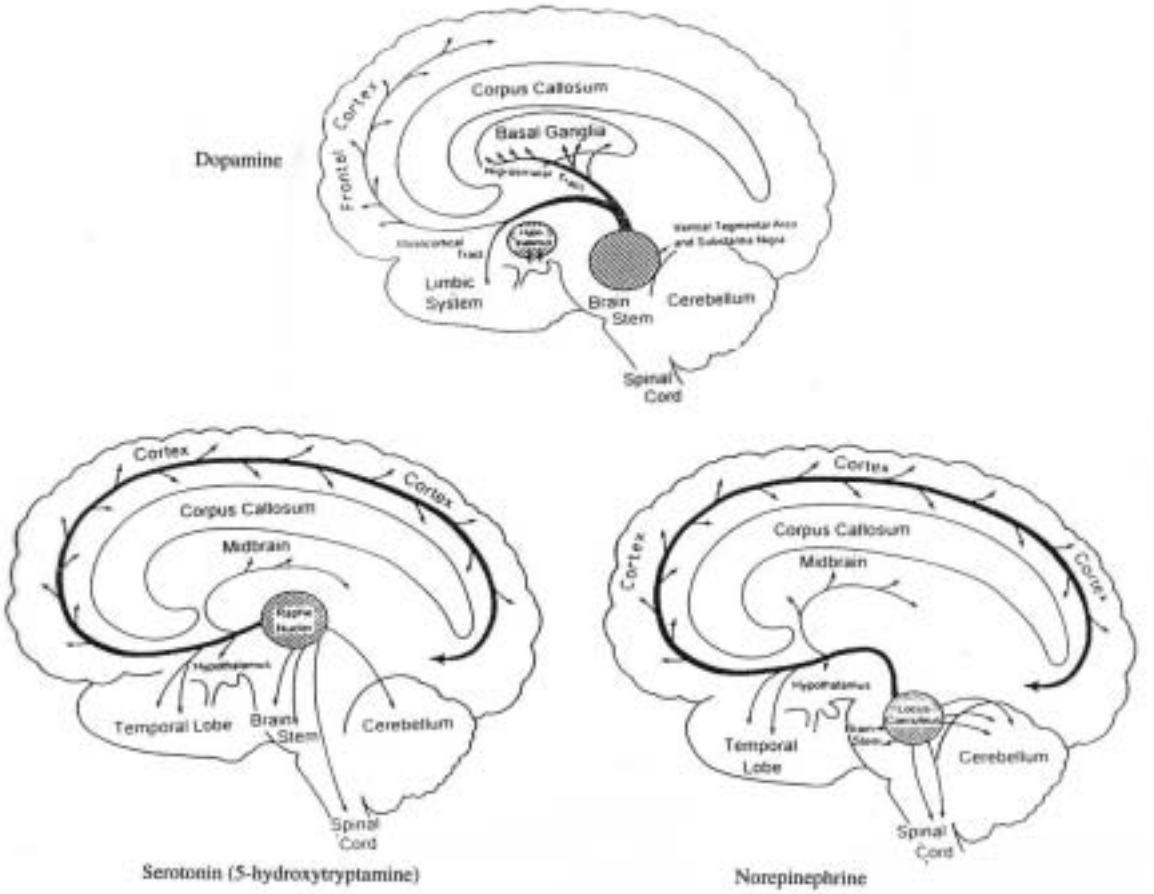


Fig. 3. The brain stem dopamine (DA) system (top), serotonin system (bottom left) and norepinephrine system (bottom right). Cell bodies of the **dopamine** system are located in the ventral tegmental area and substantia nigra and project to regions such as the basal ganglia, limbic system, and **frontal and temporal cortex**. The **raphe nucleus** contains **serotonin** cell bodies that project to **all** areas of the cerebral cortex, temporal lobe structures, (amygdala, hippocampus, hypothalamus), the midbrain as well as the cerebellum and sites in brain stem and spinal cord. **Locus coeruleus** cell bodies contain **norepinephrine** and innervate **all** areas of cortex, cerebellum and spinal cord.

The Neural Substrates of Fear and Anxiety

This class of emotion is elicited by threatening situations and it functions as an internal signal to alert the organism to potential danger. In response to fear, individuals engage in defensive or protective acts that serve to promote survival. These behaviors include **fleeing** or **withdrawing** from a situation, freezing to remain inconspicuous, or fighting.

Nature vs. Nurture

Fear behavior is essential for survival and much of its development appears to be innate. In humans, behavioral responses associated with fear are evident within the first months of life. However, it is not until sometime later that infants display fear reactions that are selectively elicited by unfamiliar situations. For example, most infants go through a period known as stranger anxiety around one year of age. At this time, infants that once smiled indiscriminately now begin to act extremely wary in the presence of strangers.

Developmental studies further indicate that some infants differ in their tendency to exhibit fear. For example, some infants become extremely agitated when confronted with unfamiliar stimuli such as a stranger. These infants display high levels of crying and motor activity, e.g., flexing and extending the arms and legs. In childhood, they often appear behaviorally inhibited. In an unfamiliar context, these children are characterized as very shy, timid, and cautious. In addition, inhibited children have larger increases in heart rate, pupillary dilation, skeletal muscle tension, and a greater HPA response to cognitive stress in comparison to uninhibited children. In adolescence and young adulthood, inhibited individuals may begin to develop problems dealing with anxiety. They may have nightmares and develop phobias. Studies conducted on identical twins and nonhuman primates suggest that a significant part of the tendency to develop extreme behavioral inhibition is inherited. Thus, some individuals appear to have a **genetic predisposition** to express intense fear and stress responses in unfamiliar or changing situations.

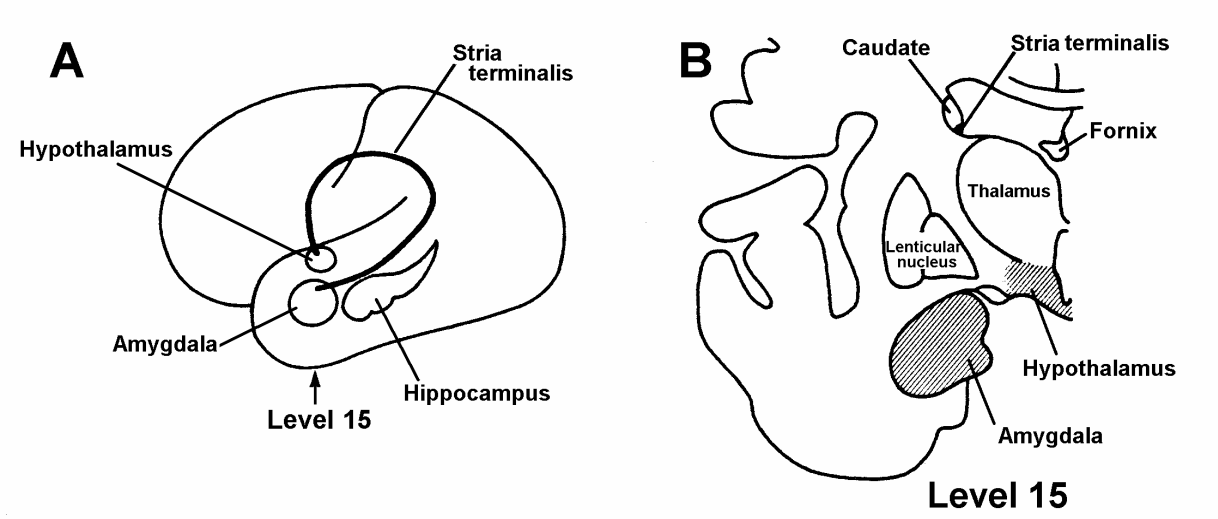
As indicated earlier, certain stimuli are more likely to elicit a fear response than others. However in many cases, a stimulus may acquire properties through learning to elicit a fear response. In addition, we may be **"biologically prepared"** to associate certain stimuli with emotional responses more readily than with other stimuli. Research on the fear of snakes in rhesus monkeys illustrates these important points. For years it was assumed that rhesus monkeys were innately fearful of snakes. Early studies at the Harlow Primate Laboratory demonstrated that when monkeys were exposed to snakes they became upset, grimaced their faces, attempted to run away, and emitted high pitched shrieks. However, it was later noted that these monkeys all shared a common background**:** they were born and reared in the wild. Subsequent studies conducted using laboratory bred monkeys suggested that the fear of snakes appeared to be learned. When lab-bred monkeys were first presented with a snake they showed little signs of any disturbance. However, if these infants were given the opportunity to observe their mothers interacting fearfully with a snake, they became distressed and acquired a long-lasting phobia of snakes. It appears that fear of snakes is not an innate reaction but a response transmitted from mother to infant by observational learning.

Studies further demonstrate that rhesus monkeys appear **biologically prepared** to learn to fear snakes. Infant monkeys were shown videotapes of their mothers displaying fear grimaces in the presence of snakes. As expected, these infants rapidly acquired a fear of snakes. The same monkeys were shown a videotape that was altered by editing a picture of brightly colored flowers in place of the snake. These infant monkeys now saw their mother acting fearful in the presence of flowers. However, the infants failed to acquire a phobia to flowers**.** Thus, young monkeys were biologically prepared to learn to be fearful of snakes but not flowers. Therefore, it is perhaps not by chance that we tend to be fearful of certain objects. Our brains are genetically programmed to associate certain stimuli with emotions such as fear.

The amygdala: A key structure mediating fear

Given the complexity of the mammalian brain, is it possible to localize emotional states of fear and anxiety to specific regions of the brain? It turns out that a complex of related cells exists in the limbic system and appears to be involved in fear reactions and the learning of fear. In the 1930's, Kluver and Bucy noted that large lesions of the temporal lobe made monkeys tame in the presence of previously fearful stimuli, such as humans and snakes (you hopefully

remember the **Kluver-Bucy syndrome** from an earlier lecture on the limbic system). The absence of an appropriate behavioral response to fear-eliciting stimuli was termed **"psychic blindness"** because it was presumed that the **cognitive** processing of emotional stimuli was altered. This taming effect could be produced by lesions restricted to the amygdala (Kluver Bucy monkeys had much larger lesions of the temporal lobe). In contrast to the taming effects of amygdala lesions, electrical stimulation of the amygdala elicits defensive and flight reactions in cats and feelings of fear and anxiety in humans. Increased autonomic activity, i.e., heart rate, blood pressure also occurs after electrical stimulation of the amygdala.



Schematic diagram showing the course of the stria terminalis that connects the amygdala to the hypothalamus (A), and the positions of the amygdala, hypothalamus, and stria terminalis (B) in level 15 of the coronal section series. Don't expect to see the stria terminalis on the lab slides (it is lightly myelinated and very difficult to discern).

The amygdala contains four important nuclei: the central nucleus, the lateral nucleus, the basal nucleus and the accessory basal nucleus. All sensory inputs terminate in the lateral nucleus, which then projects to each of the other three nuclei; the basal and accessory basal both feed into the central nucleus. The **central nucleus (CeA)** contains the output cells of the amygdala and connects to many other areas of the brain concerned with emotional responses (fig 5).

Stimuli associated with a highly charged emotional context acquire the emotional qualities of that situation and subsequently have a dramatic effect on the mental life and behavior of the individual. This association can be demonstrated in the laboratory using classical (Pavlovian) conditioning procedures. In classical conditioning (also Pavlovian conditioning), an initially neutral stimulus comes to predict an event. For instance, Pavlov found that a dog would salivate when presented with an auditory or visual stimulus **if** the stimulus came to predict an event that normally caused salivation. Thus, if the experimenter rang a bell just before putting meat powder in the dog's mouth, repeating this sequence a few times would cause the dog to respond to the bell itself by salivation. In this case the sound is called the **conditioned stimulus** (CS) and the meat powder in the mouth the **unconditioned stimulus** (US). The meat powder in the mouth already evokes an **unconditioned response** (UR) and the acquired response to the conditioned response is called the **conditioned response** (CR).

Now, regarding the amygdala. Consider a rat that is exposed to a tone (CS) at the same time as an aversive footshock stimulus (US). Subsequent presentations of the tone CS will elicit fear reactions even in the absence of foot shock. The amygdala plays a key role in conditioned or learned fear. Rats with amygdala lesions show a dramatic reduction in freezing that normally occurs in response to conditioned fear stimului. Moreover, if the lesions are made prior to learning, the animals will not learn the association. It appears, therefore, that the amygdala is involved not only in the cognitive evaluation of emotional stimuli (remember the Kluver Bucy monkeys) but also in the associational learning of stimuli that predict aversive events (classical conditioning experiments).

The amygdala may also be involved in what is termed **"emotional memory."** We seem to be able to better recall events surrounding a strong, negative emotional experience than events not linked to any particular experience. Many people in the U.S. of a certain generation can remember exactly where they were and what they were doing when informed that President Kennedy was shot. Younger people may clearly remember the day the space shuttle Challenger blew up. The amygdala may be involved in this phenomenon, although the precise mechanisms are not known.

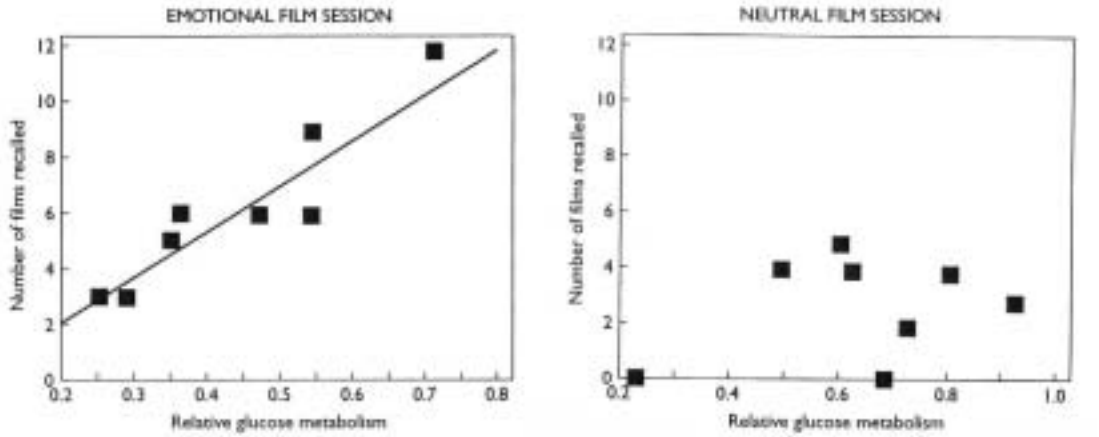


Fig. 4. Eight volunteers viewed emotionally distressing or neutral film clips while their brains were being imaged by positron emission tomography (PET), which measures general metabolic activity. Three weeks later, and without forewarning, a memory test was given to determine how well subjects recalled the film clips. Not surprisingly, recall was better for the arousing film clips. Interestingly, amygdala activity, as demonstrated by relative glucose metabolism (shown on axis), increased with the number of emotionally distressing film clips recalled; thus, the more active the amygdala at the time of learning, the more it has enhanced storage of those memories. (From Cahill et al, 1996).

A human case study illustrates the importance of the amygdala in the recognition of emotional **stimuli.** A patient suffered from **Urbach-Wiethe disease**, a rare genetic disorder, that resulted in bilateral calcification and atrophy of her amygdala. When asked to rate the intensity of various facial expressions, the patient judged faces showing fear expressions to be considerably less intense than ratings made by normal control subjects. Other facial expressions (smiling for instance) were also judged by the patient to be less intense than those reported by controls, but not to the degree made when viewing **fear** expressions. **Bilateral** amygdala damage appears to produce a profound insensitivity to the intensity of fear shown by faces. The patient, however, had no difficulty recognizing people by their faces and could rapidly learn the identity of new faces. These results demonstrate that the human amygdala is involved in the processing of facial

emotions/expressions, especially those related to fear. Damage to the amygdala appears to result in an inability to link visual representations of facial expressions with the emotion of fear.

In summary, the patient, S. M., could learn new facts, had no problems with language or movements and had normal basic intelligence. However, it was as though she were devoid of negative emotions such as fear and anger. She was unable to attribute correctly the emotion of fear in the face of others, or to mimic an expression of fear. If all faces appear trustworthy and approachable, it is hard to appreciate social risks, and this leads to increased vulnerability to environmental dangers.

Below find an interesting article regarding S.M. and the amygdala

The woman who knows no fear

17 Dec 94

A patient who cannot read fear on other people's faces has given researchers a valuable clue to how the human brain processes emotions. Her confusion shows for the first time that the brain processes fear and mixed emotions through a different pathway from those used to process other feelings. The woman, known as S. M., has a rare disease, which has damaged the amygdala region of her brain. She also has problems perceiving other "negative" emotions, such as anger. The amygdala is an almond-shaped structure at a crossroads in the brain's circuitry: it links the cortex, which is responsible for conscious thought, with regions of the brain that control the body's emotional responses. Scientists knew that the amygdala helps regulate reactions associated with strong emotion - such as quickened heart rate and sweating. But what exactly does it do?

Brain researchers determine the function of a part of the brain by studying people whose brains are damaged in that region. But patients with damage to the amygdala alone are very unusual, according to Antonio Damasio of the University of Iowa, who led the team that made the new discovery. S. M. first turned up at a hospital suffering from epilepsy. Later, when her doctors looked for the root of the problem using magnetic resonance imaging, they found that her amygdala was destroyed. This was the result of Urbach-Wiethe disease, which deposits calcium in the amygdala. With S. M.'s consent, the Iowa researchers subjected her to a battery of psychological tests devised by Damasio's colleague Ralph Adolphs, asking her to say what emotions were being expressed by the people pictured in a series of photographs.

S. M. failed what Damasio calls "the Doris Day test". "When we showed her a film clip of Doris Day screaming, she asked, `What is she doing?'," he says. In fact, S. M. was baffled by any picture showing a fearful expression. She also had problems deciphering mixtures of negative emotions, such as anger and surprise. By contrast, she had no difficulty with "positive" emotions such as happiness. She was also perfectly able to recognise familiar faces (Nature, vol 376, p 669).

These results, says Damasio, indicate that the amygdala has a pivotal role in linking frightening signals from the environment with the body's fear responses. Fear is universally important for survival in animals, Damasio notes, so it is reasonable that a special brain system has evolved to deal with it. The amygdala also seems to help us respond correctly to complex mixtures of negative emotions expressed by other people. Because she often fails to recognise criticism or

aggression, S.M. has difficulty interacting socially. Positive emotions seem to be processed in another region of the brain. Just where is a mystery. "We've never seen a patient who can't recognise a happy face," says Adolphs.

JENNIFER ALTMAN From New Scientist magazine, vol 144 issue 1956, 17/12/1994,

The amygdala is well positioned anatomically to play a role in emotional learning. Its lateral sector receives afferent input from sensory nuclei of the thalamus, all sensory cortical regions (visual, auditory, somatosensory) and the hippocampus. Thus, sensory information from all modalities converges on the lateral nucleus of the amygdala. In turn, the amygdala has connections to hypothalamic and brain stem areas via the central nucleus that appear to be involved in many of the features associated with the fear response (Fig 5). The central nucleus projects to the hypothalamus for activation of the sympathetic autonomic nervous system (remember those darn descending fibers from the hypothalamus to the T1-L2 outflow in the spinal cord???) that accompanies fear and anxiety states. Projections also reach the dorsal motor nucleus X, which controls varied autonomic functions (when you are scared you want to inhibit dorsal motor X).

The parabrachial nucleus (part of the solitary complex that you learned in Brain Stem) is involved in respiration (remember, there are descending brain stem pathways to phrenic and intercostal neurons in the spinal cord). The central nucleus projection to the parabrachial nucleus may be involved in the increased respiration during fear. Electrical stimulation of the central nucleus enhances respiration, a major symptom of fear and panic disorder (see the accompanying Panic disorder section).

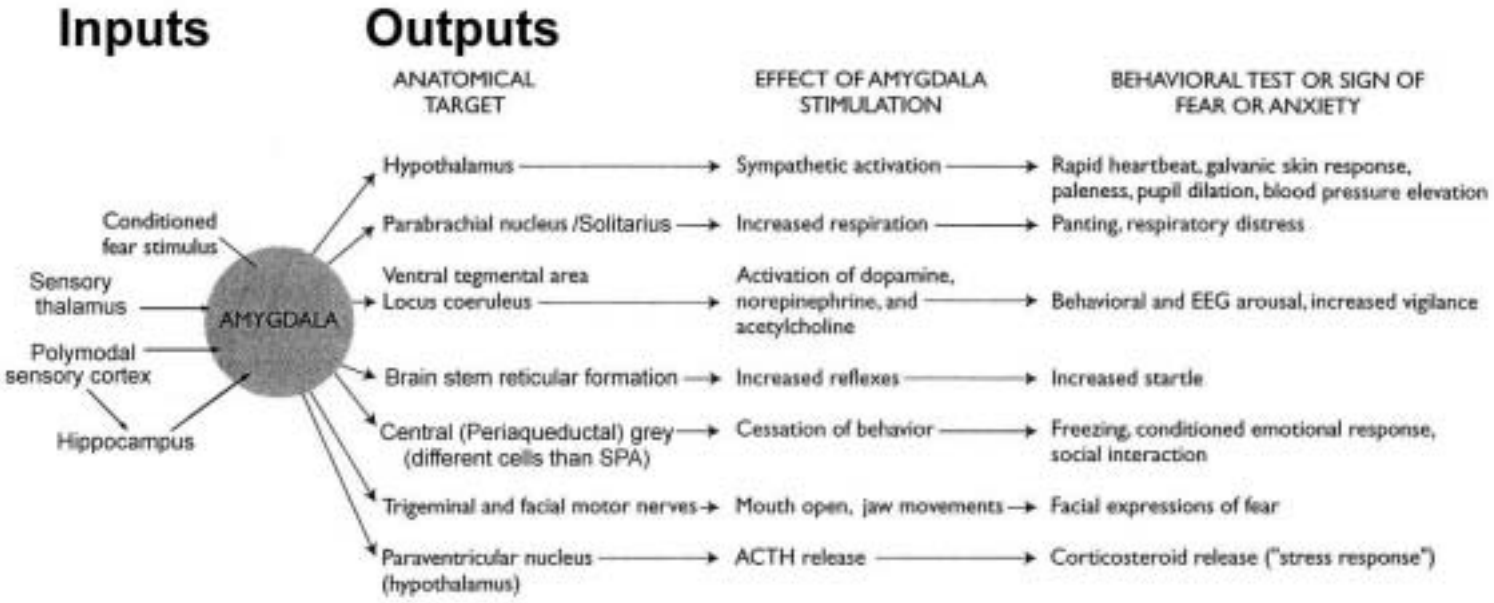


Fig. 5. The amygdala mediates many of the behavioral and autonomic aspects of the reaction **to both** unconditioned (e.g. shock) and conditioned (e.g. light that has been paired with shock) stimuli. It is believed that an associative process takes place in the amygdala, which then projects to hypothalamic and brain stem targets in order to mediate the various symptoms of fear.

The amygdala receives direct, multimodal sensory input from cortex, sensory thalamic areas and the hippocampus; it is via these pathways that conditioned and unconditioned stimuli could reach the amygdala. (Adapted from Davis, 1999)

The central nucleus of the amygdala has direct projections to other brain stem target sites. These include the **ventral tegmental area** (VTA), which contains **dopamine** (DA) cell bodies and the locus coeruleus (LC), whose cell bodies contain norepinephrine (NE). Thus, the central nucleus has the potential to influence a wide array of neurotransmitter systems.

Behavioral fear reactions such as the startle reaction, freezing, facial expressions and reduction of social interactions are also influenced by amygdala projections to brain regions such as the central or periaqueductal grey (to a different part than that concerned with stimulation produced analgesia, SPA) and the trigeminal (motor V) and facial motor (motor VII) nuclei.

The stress-induced endocrine response is modulated in part by central nucleus projections to the paraventricular nucleus of the hypothalamus. Stimulation of the CeA increases plasma concentration of corticosteroids.

Role of corticotropin-releasing hormone (CRH) systems in fear and anxiety

There is increasing evidence to suggest that extrahypothalamic corticotropin-releasing hormone (CRH) systems play an important role in the onset of fear and anxiety. Remember, cells in the central nucleus contain CRH. Axons of central nucleus cells target locus coeruleus neurons (which have CRH receptors and contain NE). In animals, administration of CRH into the cerebral ventricles (so as to eventually reach receptors on amygdala and LC cells) effectively induces anxiety responses, including hypervigilance, enhancement of the freezing posture, and decreased exploration in unfamiliar situations. Furthermore, in anxiety-provoking situations that typically elicit these behavioral responses, administration of a CRH antagonist produces a reduction in the occurrence of these reactions. In rats, infusion of a CRH antagonist into the central nucleus reduces expression of fear behavior (“freezing” in an environment where the animal had been previously shocked) suggesting that blockade of CRH receptors in the central nucleus has an antianxiety effect. In addition, stimulation of the central nucleus with microinfusions of CRH increases the release of norepinephrine and epinephrine) from the adrenal medulla (via the sympathetic outflow). It is hypothesized that dysregulation of CRH systems may underlie or contribute to a state of chronic fear or anxiety by affecting behavioral and autonomic activity.

Clinical correlates: panic attacks and panic disorder

Panic attacks are an example of pathophysiology in the neural systems underlying fear and anxiety. These systems are integral to the original "fight/flight" concepts and appear to be evolutionarily important in protecting the organism from a wide variety of threats, particularly predators. Panic disorder is a prevalent and well-studied psychiatric disorder that consists of multiple disabling panic attacks. Between 2-3 % of people experience an episode of panic disorder in their lifetime and twice as many women as men suffer from the disorder. These panic attacks are characterized by extreme fear and an urge to flee as well as intense autonomic arousal involving a wide variety of symptoms. The symptoms originally occur spontaneously and

unpredictably, and vary in length from several minutes to upwards of 60 min. If they continue for prolonged periods of time, they can be very disabling. Evidence suggests that panic attacks may be due to a hypersensitive autonomic nervous system involving an overly reactive **LC-NE** system.

Agoraphobia is the most common complication of panic disorder. It is defined as a fear of being in places or situations from which escape might be difficult or embarrassing, or in which help might not be available in the event of a panic attack

There are a number of naturalistic observations and research investigations that support the view that panic attacks occur as a result of hypersensitive alarm systems. For example, studies demonstrate that acute panic attacks are generated by abnormal neural activity in the brain stem. Clinical observations indicate that attacks are largely experienced by patients as "storms" of autonomic nervous activity. Patients frequently are fearful of the multiple physical symptoms associated with an attack, including light-headedness, a racing heart, difficulty breathing, chest discomfort, generalized sweating, or weakness.

Research investigations indicate that administration of various doses of pharmacological agents can produce panic attacks in panic-prone, but not in normal individuals. In these studies, the physical symptoms of panic attacks can be reproduced, albeit in varying degrees, by carbon dioxide, yohimbine, and caffeine and epinephrine administration.

Yohimbine (a mild hallucinogen/stimulant extracted from South African tree bark) is an **alpha$_2$-noradrenergic receptor antagonist**. The majority of alpha$_2$ receptors act as **autoreceptors.** Normally, release of endogenous NE from the LC cell will modulate its own release by binding to its autoreceptor; this in turn prevents the release of NE. Thus, alpha$_2$-noradrenergic receptor **agonists** act as a negative feedback signal to **reduce** the release of NE. Antagonists, like yohimbine, that bind to the alpha$_2$ receptor, block this negative feedback signal. Consequently, the LC cell continues to release NE.

In the laboratory, administration of yohimbine to panic-prone patients reproduces many of the symptoms of a panic attack including dizziness, sweating, respiratory distress, lightheadedness, palpitations, and fear. Results of these clinical studies suggest that the NE system may be overly sensitive or hyperactive in individuals predisposed to develop panic disorder. Further evidence to support the involvement of the LC-NE system in panic disorder is obtained from studies showing that administration of clonidine has transient antipanic effects. Clonidine is an alpha$_2$ noradrenergic receptor agonist that effectively reduces the firing of LC neurons. Thus, pharmacological agents that increase LC-NE activity produce panic attack symptoms, whereas agents that reduce LC-NE firing rates appear to reduce panic attacks.

Role of carbon dioxide

Carbon dioxide inhalation is capable of inducing panic symptoms in patients with panic disorder but not in normal subjects. In the clinical laboratory, inhalation of 5% carbon dioxide was found to potentiate a rapid increase in ventilation before the panic (ventilation is mediated by receptors that sense carbon dioxide in the lungs, heart, and brain stem medulla). These results have

suggested that patients with panic disorder may have very sensitive brain stem carbon dioxide receptors, i.e., “suffocation alarm mechanisms.”

Of potential relevance to the NE system, animal studies demonstrate that carbon dioxide produces a dose-dependent increase in LC firing rates. This effect of carbon dioxide on LC discharge rates is probably influenced by medullary (nucleus solitarius-remember, it receives visceral afferent information) projections to the LC.

There continues to be debate on the etiology of panic attacks. However, it appears that some factors are involved in acting centrally upon vulnerable brain stem regions to provoke panic attacks. For example, physiological functions and metabolic demands occurring in the periphery are closely regulated by cells in the brain stem. Information from the cardiovascular and respiratory system reaches the solitary complex and are relayed to, and activate, the LC-NE system. Fearful perceptions and thoughts emanating from the cerebral cortex may also contribute by further lowering the threshold in brain stem systems, and thereby potentiate the production of panic symptoms (one pathway underlying this would be from cortex to amygdala to LC). Some individuals are more likely to experience panic attacks after exposure to stress associated with losses (i.e., death of loved ones, divorce) or certain situations (i.e., exams, near fatal accidents, trapped in a highly confined place). Recently it has been observed that the neuropeptide **cholecystokinin (CCK)** is involved in panic disorders. Some investigators have hypothesized that panic attacks start with an excitation of the CCK neurons in the brain stem (in what is called the reticular formation; those areas that were kind of “left over” in our travels through the brain stem). Such CCK neurons stimulate the noradrenergic neurons of locus coeruleus and the pnic attack begins.

Sadness and negative affect

Negative emotions and sadness are commonly elicited by situations associated with the loss of an important social relationship (death of a spouse) or object (loss of a home due to fire). Sadness is an internal state that signals the need for affiliation and functions to motivate individuals to seek supportive social relationships. As with fear and anxiety, this emotion is present from birth and when expressed early in life alerts the caregiver to meet the infant's needs.

Many years ago, Harry Harlow at the University of Wisconsin observed that when infant monkeys were separated from their mothers, they emitted a high-pitched vocalization (coo call) which alerted the mothers to retrieve the infant. Infant monkeys subjected to prolonged maternal separation frequently succumbed to a state characterized by loss of interest in the environment, a reduction in food intake and huddling in the corner. Harlow drew parallels between this emotional state and that reported in institutionalized human infants undergoing prolonged maternal separation.

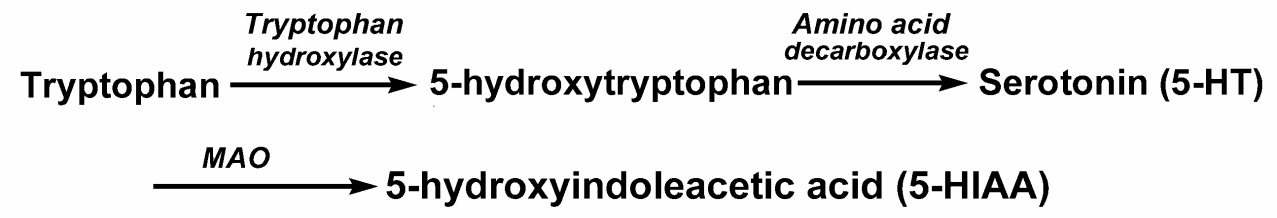
Prolonged disruption of the maternal-infant bond can also have a profound impact on subsequent behavior. Newborn monkeys socially isolated from an early age would not interact with other monkeys. They would not play, fight, or show any sexual interest. Older monkeys subjected to comparable periods of social isolation failed to develop these behavioral alterations. It appears that developmental, environmental, and biological interactions are important factors in determining the individual's emotional patterns of behavior.

Clinical correlates: alterations in brain monoamines are associated with depression

Although sadness is a transient emotional state, **depression** is a mood or syndrome characterized by thoughts of self-worthlessness, excessive guilt, death and/or suicide. Physiological systems are also dramatically altered during depression. Patients with depression may have difficulty concentrating on tasks and may suffer from insomnia, altered appetite, decreased interest in pleasurable activities, and fatigue. Depression is estimated to affect approximately 5% of the adult population at any one time. In addition, approximately 20% of all individuals are likely to experience an episode of depression during their lifetime.

An important clinical observation was made in the 1950's when the antihypertensive agent reserpine was prominently used. Clinicians noted that some individuals became markedly depressed after taking this drug, which produces a long-lasting depletion of monoamines (norepinephrine, serotonin and dopamine). Other work demonstrated that drugs that increased the level of monoamines were effective in the treatment of depression. Together, these observations led to the monoamine hypothesis of depression. According to this hypothesis, depression results from a deficit in brain norepinephrine or serotonin, or both.

Biosynthesis and Metabolism of Serotonin



The amino acid tryptophan is the substrate for the synthesis of serotonin. Tryptophan hydroxylase is the enzyme responsible for the hydroxylation of tryptophan to form 5-hydroxytryptophan. Once synthesized, 5-hydroxytryptophan is rapidly decarboxylated to form serotonin. After release from presynaptic terminals, the deamination of serotonin occurs following reuptake of serotonin and metabolism by monoamine oxidase (MAO) to yield 5 -HIAA.

Additional support for the monoamine hypothesis of depression came from an examination of norepinephrine and serotonin metabolites in depressed patients. In some depressed patients, concentrations of a major metabolite of norepinephrine, 3-methoxy-4-hydroxyphenylglycol, ***MHPG***, were found to be reduced in the cerebrospinal fluid. Similarly, some depressed patients have reduced concentrations of a major serotonin metabolite, 5-hydroxyindoleacetic acid (**5-*HIAA***). Other work demonstrated that rapid dietary depletion of tryptophan, the precursor of serotonin synthesis, produces a rapid return to depression in patients with successful antidepressant treatment. Together, these results suggest that availability of brain monoamines is reduced in depressed patients. Remember, MHPG=norepi while 5-HIAA=serotonin.

Lowered brain serotonin is associated with suicide

Monoamine oxidase inhibitors (MAOI), tricyclic antidepressants, and selective serotonin reuptake inhibitors (SSRIs*)* are effective antidepressants that share the pharmacological property of increasing the level of biogenic amines (DA, NE, epineph serotonin, histamine) but in different ways. **MAOIs** are a class of drugs that block MAO, the major enzyme responsible for the oxidation of monoamines. The tricyclic drugs work by blocking the reuptake (keep it around longer) of NE and serotonin into the presynaptic terminal resulting in a net increase in neurotransmitter availability. Consequently, there is an increase in postsynaptic receptor activity. SSRIs work by selectively blocking the reuptake of serotonin. SSRIs are as effective as the tricycylic compounds but without some of the sedating and cardiovascular side effects of tricyclic antidepressants. As a result, SSRIs (e.g., Prozac, Zoloft) are now used widely and underscore the importance of serotonergic systems in regulating mood.

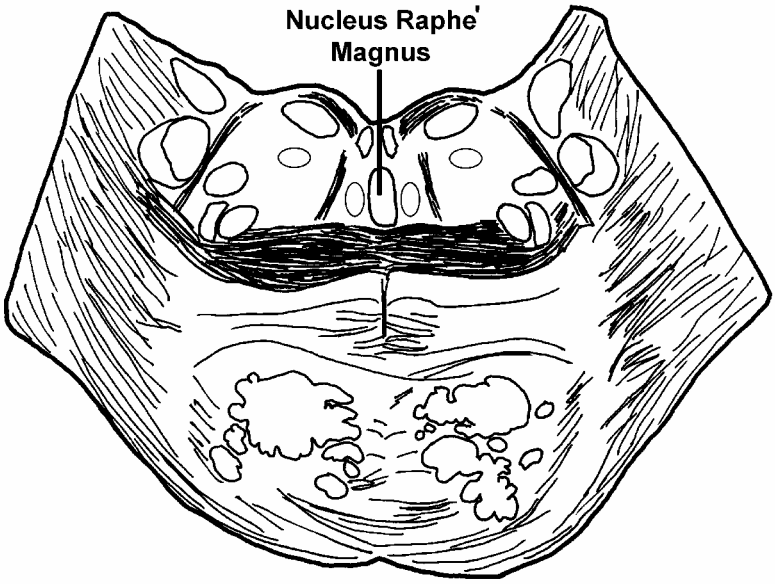
Reboxetine (mesylate), is the first of a novel class of drugs called selective norepinephrine reuptake inhibitors (SNRIs). As the name implies, they specifically boost levels of the neurotransmitter norepinephrine, which is thought to be associated with increased drive. With a unique mechanism of action and a relatively benign side-effect profile, reboxetine promises to give doctors new options for patients who are either treatment-refractory or unable to tolerate other antidepressants. And, although the concept is controversial, some researchers believe that reboxetine's specific effect on norepinephrine will make it particularly useful in the subset of depressed patients with decreased energy.

To summarize, **disruption of brain serotonin (5-HT) and NE concentrations appear to contribute to the depressive syndrome**. The hypothesis that depression is caused entirely by a reduction in monoamines is somewhat simplistic but provides a reasonable account of the pharmacological efficacy of antidepressants.

Suicide is a complex human behavior and remains a significant source of mortality with approximately 30,000 people taking their lives annually. Although suicide is generally thought to be the result of stress or depression, there is little information to distinguish who may successfully take their life by an act of suicide. For example, the majority of patients faced with painful life ending illnesses do not commit suicide. In addition, a number of individuals have taken their own life when it appears that stress was relatively minor, if not absent. Recent research efforts have broadened our understanding of the underlying neurochemistry of suicide.

Postmortem studies done a number of years ago revealed that brain stem levels (raphe nuclei; remember **nucleus raphe magnus** for SPA) of serotonin and its metabolite 5-HIAA are consistently reduced in suicide victims. More recent studies confirm a link between depression and low serotonin activity. These studies have shown that in depressed patients that have attempted or committed suicide, 5-HIAA levels in the CSF are considerably lower than in non-suicidal depressed patients. This association between CSF 5-HIAA levels and suicidal behavior is especially strong in those with violent suicidal attempts. It should be noted that although depression and suicide risk are both linked to disturbances in brain serotonin activity, evidence suggests that serotonin concentrations normalize after mood improvement in depressed patients.

It is presently unclear why reduced brain **serotonin function predisposes individuals to commit suicide. One hypothesis is that low brain 5-HT** values produce an **increase** in impulsive behavior. Impulsivity refers to a propensity to act without considering alternative options in a decision-making process. Although impulsivity is not synonymous with acting rapidly, impulsive individuals tend to act without time for reflection. In people with personality disorders characterized by chronic problems with impulsive behavior, the rate of completed suicide can be as high as 25%. The underlying cause of reduced brain serotonin remains unknown but could be related to heritable factors and/or neurological insults during development.



Summary of the neurobiology of emotion

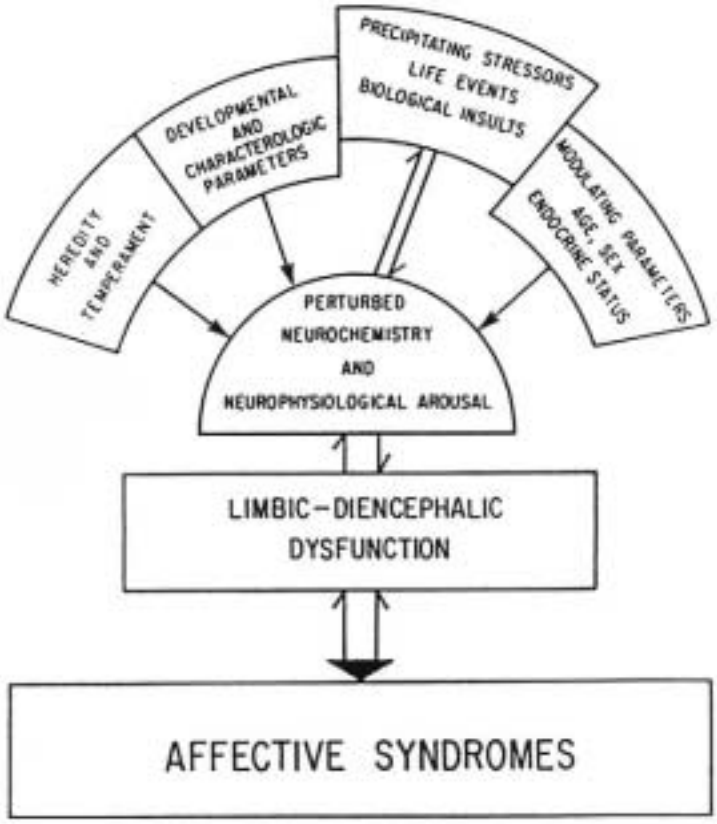


Fig. 6. This figure broadly summarizes how various factors and precipitating variables may interact to eventually induce behavioral disorders or affective illnesses. As we have seen, genetic, developmental, environmental and learning variables can influence neurochemical, limbic and cortical systems which ultimately affect behavior. Alterations in these neurochemical and/or neural structures associated with emotions may underlie or contribute to the emergence of psychiatric illness, particularly depression and anxiety.

Problem Solving

1. Which of the following is **FALSE** regarding lesions of the amygdala?
A. affect emotional memories
B. result in taming effects
C. decrease in autonomic activity
D. decrease in secretion of epinephrine from the adrenal medulla
E. animals “freeze” in response to threats

2. Certain patients that have attempted or successfully committed suicide tend to have:
A. high CSF levels of 5-HIAA
B. high levels of brain NE receptors
C. low CSF levels of 5-HIAA
D. high levels of ACTH
E. high MHPG

3. Serotonin:
A. and NE concentrations are increased in suicide victims
B. reuptake inhibitors (SSRIs) are effective in reducing depression
C. depletion in the central nervous system has little effect on mood
D. cell bodies are located in the substantia nigra
E. cell bodies are located in the LC

4. Activity of LC neurons:
A. is reduced by CRH
B. is reduced by yohimbine, an alpha-2 noradrenergic antagonist
C. is increased by clonidine, an alph 2 noradrenergic antagonist
D. is reduced by clonidine, an alph 2 noradrenergic agonist
E. decreases during stress

5. If the amygdala is damaged:
A. a rat can learn a Pavlovian association between an aversive footshock and a neutral tone
B. a monkey’s responses to previously fearful stimuli will be intensified
C. a person will rate pictures of fearful facial expressions as less intense
D. extrahypothalamic CRH input to the LC will be increased
E. freezing responses will increase

6. Yohimbine:
A. directly binds to and stimulates CRH receptors
B. acts as an agonist at presynaptic autoreceptors
C. elicits enhanced norepinephrine release by blocking alpha-2 noradrenergic receptors
D. is derived from the bark of American oak trees
E. is a drug that prevents panic attack-like symptoms

7. Which of the following statements about depression is **TRUE**?
A. is correlated with normal levels of NE
B. decreased by reserpine
C. drugs which are helpful in depression include SSRIs, tricyclics, MAOIs, and alpha-2 noradrenergic antagonists
D. can result from an increase in NE
E. MHPG and 5-HIAA are increased

8. Which of the following statements about emotion is **TRUE**?
A. negative emotions such as anger or fear promote defensive behaviors but not aggressive behaviors
B. the cognitive processing of an emotionally relevant stimulus does not contribute to emotional experience
C. emotion is primarily processed in limbic regions that are anatomically isolated from the neocortex
D. emotion is processed solely by the prefrontal cortex
E. none of the above are **TRUE**

9. Which of the following statements is **TRUE**?
A. the amygdala receives input from the hippocampus and the sensory thalamus
B. the amygdala projects to the PVN, the dorsal motor X and the LC
C. patients with Urbach-Wiethe have difficulty judging the intensity of fear in a persons face
D. clonidine increases firing of LC neurons
E. three of the above are **TRUE**

10. Which of the following statements is **TRUE**?
A. serotonergic (5-HT)projections arise from the raphe (zipper) nuclei and reach all cortical areas
B. norepinephrine (NE) projections arise from the locus coeruleus and reach all cortical areas
C. dopaminergic (DA) projections arise in the medulla
D. reboxetine is a selective serotonin reuptake inhibitor
E. two of the above are **TRUE**

11. Which of the following statements is **TRUE**?
A. pathways from the nucleus solitarius to the LC play a role in panic attacks
B. carbon dioxide can increase the firing of LC neurons
C. stimulation of the LC results in an increase in the release of NE from the adrenal medulla
D. stimulation of the amygdala results in an increase in the release of NE from the adrenal medulla
E. all of the above statements are **TRUE**

12. Which of the following statements is **TRUE**?
A. when lab-bred monkeys see a snake for the first time they exhibit fear
B. baby monkeys are biologically prepared to learn to be fearful of snakes
C. our brains are genetically programmed to associate certain stimuli with emotions such as fear
D. baby monkeys innately fear roses
E. two of the above are **TRUE**

13. Which of the following statements is **TRUE**?
A. the neuropeptide CCK is thought to be involved in panic attacks
B. someone suffering from agoraphopia might avoid being in crowded places like malls and theaters
C. patients with Urbach-Wiethe disease have difficulty deciphering positive emotions such as happiness
D. patients with Urbach-Wiethe disease are all related to Doris Day
E. two of the above statements are TRUE

PROBLEM SOLVING ANSWERS

1. E
2. C
3. B
4. D
5. C
6. C
7. C
8. E
9. E (A, B, C)
10. E (A, B)
11. E
12. E (B, C)
13. E (A, B)

CHANGING HEARTS AND BRAINS: SOF MUST PREPARE NOW FOR NEUROWARFARE

Articles

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Changing Hearts and Brains: SOF Must Prepare Now for Neurowarfare

By Dr. Shannon Houck, COL John Crisafulli, Lt Col Joshua Gramm, Maj Brian Branagan

The timeworn "changing hearts and minds" idiom may soon take on a more literal meaning as we confront the weaponization of neurotechnology. In December 2016, CIA officers and American and Canadian diplomats stationed in Havana, Cuba reported hearing pulsing sounds, sometimes accompanied by pressure sensations in their heads. Neurological symptoms followed – symptoms like headaches, dizziness, cognitive difficulties, fatigue, and hearing and vision loss.[i] Over 40 U.S. government employees were affected; 24 were diagnosed with brain damage. These were not isolated incidents. Similar reports have emerged from U.S. personnel in China, Russia, Uzbekistan, and CIA officers working in several different countries.[ii] Two separate cases in the Washington D.C. area are currently under investigation after U.S. officials suffered from the same sudden symptoms, one occurring in an Arlington suburb in 2019, and the other in the oval lawn of the White House in 2020.[iii] Most recently, media reports from April 2021 indicate that DoD officials briefed the Armed Service Committee, stating they are "increasingly concerned about the vulnerability of U.S. troops in places such as Syria, Afghanistan, and various countries in South America."[iv]

No official cause has been stated and multiple investigations are ongoing. However, evidence from the Cuba incidents suggest these were targeted attacks. Dr. James Giordano, a neuropathologist and one of the State Department-appointed scientists who investigated the Cuba cases, stated in his 2018 USSOCOM/J5 Donovan Group SOFWERX brief: "this is intentional, this is directed, this seems to be a beta test of some type of a viable neuroweapon.[v]" This conclusion leaves many questions. Who coordinated and executed this beta test? What neuroweapon(s) were used? What state and non-state adversaries have or will soon have advanced neurowarfare capabilities? Are the same actor(s) responsible for the attacks overseas and now domestically? Scholars and practitioners hypothesize different possibilities, including pointing the finger at Russia,[vi] but as of 2021, definitive answers remain unclear. And the most important question looms: *What neurowarfare attacks are coming next that we must prepare for now?*

SOF operators do not currently receive any direct training on neurowarfare (indeed, most are unfamiliar with the concept entirely), and published research is strikingly limited. Of the small number of academic publications on the topic, only a handful directly address neurowarfare. Special Operations Forces (SOF) are uniquely positioned to confront the complex and dynamic threats neurowarfare poses but is currently under-prepared to take up the challenge. Part of the reason is a lack of general awareness. Although US Special Operations Command (USSOCOM) prioritizes neuroscience research and innovation, especially for cognitive enhancement, comparatively less is known about neuroweapons that cause *cognitive degradation*.

In line with USSOCOM's 2020 'Innovation for Future Threats' priority,[vii] the present article aims to fill this gap by providing actionable recommendations: (1) immediately implement training across the SOF enterprise; (2) invest in research on (a) cognitive degradation caused by neuroweapons, and (b) neuroweapons detection, disruption, and targeting; and (3) develop doctrine on neurowarfare. Ultimately, SOCOM needs to take a proactive stance by developing 'neuro SOF professionals' equipped to strategically navigate this new battlespace. To provide the necessary foundation for these recommendations, we first define neurowarfare, briefly discuss its use in defense and security over time, and then detail the critical significance for SOF today.

What is Neurowarfare?

Neurowarfare is the strategic takedown of a competitor[viii] through the use of neuroweapons that remotely "target the brain or central nervous system to affect the targeted person's mental state, mental capacity and ultimately the person's behavior in a specific and predictable way."[ix] Just like cyber warfare, neurowarfare can be waged defensively or offensively. In a defensive capacity, neurowarfare could prevent conflict before it starts, easing tensions by shaping attitudes and perceptions about the potential adversary.[x] In an offensive capacity, neurowarfare could "manipulate the political and social situation in another state," thus destabilizing the adversary, either as a stand-alone tactic or in conjunction with a military strike.[xi] Psychological operations share similar goals but achieve them through communication, typically over the long-term. Neuroweapons physically manipulate the brain and achieve immediate effects.

Neurowarfare: Then and Now

Brain modification in defense and security is not new. Under the guise of Project MKUltra, the CIA conducted human experiments during the 1950s and 60s in the hopes of exploiting mind control through hypnosis and experimental drugs.[xii] Over 80 institutions were involved, ranging from universities, hospitals, prisons, and pharmaceutical companies.[xiii] This program was largely a response to fears of Soviet and Chinese Communist thought-control, or 'brainwashing.' Also consider that during the Vietnam War, some American soldiers took various pharmaceutical agents (e.g., codeine, dexedrine) to heighten alertness and dull feelings of vulnerability.[xiv] Dexedrine/dextroamphetamine – a stimulant drug shown to improve cognition, alertness, and reduce fatigue – is still used today and is indeed an approved cognitive performance mechanism by the U.S. Air Force.[xv]

What makes brain modification new for warfighters today is the rapidly advancing technology in neuroscience. In the 21st century, neuroscience research, development, and innovation, combined with biotechnology, nanotechnology, and artificial intelligence, has paved the way for entirely new industries that will likely lead to commercial development. Most of the research is currently being done in universities and the private sector; however, in 2013 President Obama marshalled the American BRAIN (Brain Research through Advancing Innovative Neurotechnologies) initiative, a National Institute of Health (NIH)-directed plan to further understanding of the human brain by integrating multiple scientific communities, agencies, and organizations.[xvi] As of 2019, over 700 grants totaling $1.3 billion have been allocated, with the initiative continuing at least through 2025.[xvii] As far back as 2013, the neurotechnologies market potential was estimated at more than $150 billion, with projected growth in Asia and South America to surpass the West by 2020.[xviii] The U.S. is not alone in these endeavors, and will need focused attention to stay atop the research and development leaderboard.

The return on investment is evident. USSOCOM is becoming increasingly adept at developing the hyper-enabled operator (HEO) – "a SOF professional empowered by technologies that enhance the operator's cognition at the edge by increasing situational awareness, reducing cognitive load, and accelerating decision making."[xix] Yet these same advancements that add value for cognitive enhancement pose risks when used for cognitive degradation.

Cognitive enhancement versus degradation

Neurotechnological advancements present a double-edged sword, offering opportunities for both cognitive enhancement and cognitive degradation. Both are relevant to SOF readiness and resilience. Enhancement capabilities generally fall into three categories. First, neuropharmacology uses drugs designed to target specific areas of the brain,[xx] potentially even breaching the blood-brain barrier.[xxi] Second, brain stimulation uses electric currents to stimulate specific areas of the brain.[xxii] Third, brain-computer interfaces (BCIs) involve opening up pathways to connect the brain to a computer in order to allow the two-way flow of information, either to program new behaviors or control external machines and devices.[xxiii] Such technologies have the capability to improve warfighter performance by enhancing memory, concentration, motivation, and situational awareness while negating the physiological ills of decreased sleep, stress, pain, and traumatic memories.[xxiv] According to a 2020 RAND report, "In general, BCI could theoretically be applied to help future warfighters make more informed decisions within a shorter timetable or to more effectively engage with more robotic systems than their current counterparts."[xxv] In the future, military commanders may not only be able to *monitor* but also *control* the mental performance of troops under their command by increasing performance without sleep, modulating emotions under stress, and thinking through emerging threats. The U.S. Army is even pursuing 'synthetic telepathy,' a technology designed to allow military members to communicate using only their brains.[xxvi] But in the hands of an adversary, all enhancement technologies can also be used for degradation.

Neuroweapons cognitively degrade a target using different modalities. First, similar to neuropharmacology on the enhancement front, biochemical agents can incapacitate or influence the actions and emotions of enemies and noncombatants alike.[xxvii] Second, directed energy weapons include a broad class of devices that use intense energy to achieve a desired effect, be it lasers, electro-magnetic pulse (EMP), or radio-frequency/acoustic weapons that impair brain function causing temporary incapacitation and/or death.[xxviii] Some form of directed energy weapon was likely responsible for the attacks against U.S. personnel in Cuba and China.[xxix] Finally, information- and software-based weapons can manipulate the brain, either tangibly with implants or at a distance by manipulating brain responses.

The Department of Defense has rightly recognized the benefits that neurotechnology can have on individual soldiers, and so the focus, at least from what is publicly available, is overwhelmingly on cognitive enhancement. The same level of effort is now needed to understand cognitive degradation and forecast what is on the horizon in the neurowarfare domain, especially given the stated priorities of U.S. adversaries. For example, China is seeking to dominate the field of neuroscience; their Grand Strategy calls to be a world leader by 2030.[xxx] China's aggressive research into this field makes it likely China will find ways to effectively militarize this emerging technology in future years.[xxxi] In spite of the DoD's acute focus on Great Power Competition, relatively little attention is granted to neurowarfare. SOF needs to strategize how to combat this threat now and forecast accelerating developments in this domain in the coming years.

What does this mean for SOF?

Great Power Competition is about access and influence; so is SOF. Similar to the ideological battles of the Cold War, the competition space between an American-led world order and a Chinese or Russian-led one is likely to play out on the periphery more than direct confrontation. These are the very places SOF lives and excels. Serving as human sensors and being attuned to the changing global dynamics requires innovative, adaptable, and highly specialized warfighters that SOF brings every day. SOF should position themselves in a leading role in the domain of neurowarfare for several reasons.

First, SOF is small, specialized, and thrives under uncertain and dynamic conditions that require constant adaptation; neurowarfare will also continue to develop under a veil of uncertainty, complexity, and secrecy that will require an attuned ethos. Second, SOF has a large global footprint, operating in as many as 141 countries as recently as 2019.[xxxii]This means they are both uniquely engaged and uniquely exposed to new forms of warfare. Due to the longer training cycles and specialized skills, SOF would be considered high-value targets for potential adversaries. Similar to high-value cyber targets, emphasis should be placed on hardening SOF against neuroweapon threats. Third, the past two decades of counterterrorism operations has enabled SOF to develop strong interagency partnerships that can be leveraged in neurowarfare. Finally, SOF has experience being at the forefront of technological developments and is already heavily invested in cognitive enhancement research and development. Much as they do today in many areas, USSOCOM can be a pathfinder organization, serving as an incubation laboratory that builds expertise and capability, which can subsequently be exported to the rest of the force at reduced costs.

Recommendations for USSOCOM

1. **Training and education across the SOF enterprise.**

Awareness of current and emerging threats is critical for force readiness. In the short-term, formalized training should be developed and implemented now. All USSOCOM components would benefit from a general awareness training on neurowarfare that covers basic information -- what it is, why it matters, effects on the brain, and warning signs to be aware of. But more in-depth, specialized training is merited for information practitioners working in intelligence, psychological operations, and cyberwarfare. Such training would ideally detail the neuroscience of influence, defensive and offensive cognitive enhancement and degradation applications, current and near-future neuroweapons capabilities, and an analysis of neuroweapons attacks case studies.

Longer-term, it will be critical to develop 'Neuro SOF' professionals who remain at the cutting edge of the neuroscience of war. Naval Postgraduate School, for example, is perfectly positioned to serve as the critical nexus between the strategic and operational challenges of neurowarfare. Similar to the cyber domain, competing with our adversaries in neurowarfare requires technical experts who can think through the terrain and develop innovative solutions. In the longer-term, primary military education (PME) institutions should staff credentialed neuroscientists who can fill current curricular gaps to rising military leaders. In the meantime, PME's may be able to leverage currently employed cognitive scientists or scholars in the private sector to contribute to this educational need. Moreover, strengthening education and training requires ongoing, rigorous research.

2. **Investigating neuroweapons: Cognitive degradation research**

To compete in this space, USSOCOM must place the same level of investment and momentum on research specific to cognitive degradation as it does cognitive enhancement. This means making cognitive degradation research a documented priority and putting resources behind it. These simultaneous lines of effort are mutually beneficial. Considering operator well-being and performance holistically means building up enhancement capabilities such that operators are "hyper-enabled" *and* hyper-protected. Right now, the force is vulnerable to neuroweapons attacks, in part because we do not have answers to basic questions. How do we detect and disrupt neuroweapons? What is needed to overcome the challenges with discerning attribution of neuroweapons attacks? What type operators should be developed into 'neuro SOF professionals' and what skills should they have? Under what conditions should SOF employ neuroweapons against adversaries, if at all?

Similar to SOF's "Hyper-enabled operator," USSOCOM's acquisition arm, SOF Acquisition, Technology, and Logistics (SOF AT&L), is flexible and responsive enough to stay engaged with private sector advancements and transmit information rapidly to the force. The possibilities and potential use-cases for neurowarfare are almost endless and will depend on the technologies created, thus a tight relationship is essential. This uncertainty in the face of rapid neurotechnological acceleration underscores the importance that SOF is guided by doctrine to help shape the way forward.

3. **Develop doctrine**

As in all areas of conflict and competition, USSOCOM's actions in the neurowarfare domain should be guided by doctrine. Currently, there are no national laws or international agreements that restrict the weaponization of the human brain. While U.N. treaties against biological and chemical weapons send a signal to be wary that future bans may be coming, neuroweapons fall into a legal and regulatory gap. Similar to nuclear development, science often forges ahead of political and ethical matters of use, a term called "the Collingridge dilemma." As neuroweapons likely expand in the future, the legal and ethical challenges that need to be address will become paramount. SOF has developed expertise in precise, narrowly tailored effects on the battlefield that likely have similar spillover properties for neurowarfare.

Additional Considerations

While we've focused on the unique role SOF and USSOCOM can and should play when it comes to neurowarfare, the fact is that this new form of warfare will ultimately require the United States to take a whole-of-government approach, requiring attention and resources not only from the DoD, but also the interagency and the National Security Council. The most difficult—and likely to be the most contentious—are the serious moral and ethical concerns of whether the United States should consider pursuing offensive neuroweapons. Should the United States pursue an offensive capability, even if only discovered accidentally through private sector research? If so, what sort of weapons would be morally acceptable to use and how should they be employed? Should these weapons be reserved for high-priority targets or will we get to a point where neuroweapons are routinely employed in conjunction with more traditional forms of warfare? It is beyond the scope of this article to enter into that debate, but we acknowledge the seriousness and gravity with which academics and policy makers will need to approach this topic.

Conclusion

The weaponization of neurotechnology poses unique challenges in a strategic environment that emphasizes competition between major powers. As powers compete for influence against one another, neuroweapons that directly target the brain to sway an adversaries' actions are likely to be employed with increasing frequency. USSOCOM must adopt a proactive stance. Too often, reactionary measures leave U.S. Forces playing catch up, as we are currently doing in the information environment. No longer should we conceptualize the human mind as a target for psychological influence through communication operations over long periods of time; neurotechnology paves the way for influence via physical brain modification to achieve almost immediate psychological shifts. SOF needs to decide now how to operate in this domain.

Disclaimer: *The views expressed in this article are the views of the authors alone. They do not reflect the official position of the Naval Postgraduate School, the U.S. Navy, the Department of Defense, or any other entity within the U.S. Government.*

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