NAV1.950314.005

ATT: LT. FRAMPTON

MEMORANDUM

BY FAX: 11 PAGES INCLUDING COVER

March 1, 1995

To: James Coolbaugh
Head, Personnel Optimization & Biomolecular Science
& Technology Division, Department of the Navy

From: Dr. Haier, UCI, (714) 824-4268 OR (714) 824-3135 (fax)

RE: Human Subject information

Here is the information you requested in your FAX of 2/28/95. I am faxing the original protocol submitted to the UCI Human Subjects Committee (HSC), the consent form with approval stamp (I have no record of any requested changes from the HSC), the signed letter of approval from the HSC Chair, and the signed approval request for one subsequent modification.

Please let me know if I may be of further assistance. I will be out-of-town all next week.

PROTOCOL

Investigators:

Dr. Haier and Dr. Larson

Title:

Mental effort and intelligence studied with positron emission tomography

Purpose:

We have reported statistically significant inverse correlations between overall brain glucose use and performance on a standard test of intelligence (Haier et al., 1988). Subjects who scored best on the test, the Ravens' Advanced Progressive Matrices (RAPM), used about half the glucose than subjects who did the poorest. Since glucose is directly related to neuron firing, one possible interpretation of these data is that good performance on complex tasks like the RAPM is associated with more efficient neural circuits. Haier et al. (1992) showed that brain glucose metabolic rate decreases after learning a complex task, consistent with the brain becoming more efficient. Preliminary data suggests that some cases of mental retardation have higher than normal brain glucose rates.

The purpose of this project is to determine whether the relationship between glucose use in the brain and intelligence is related to mental effort.

Research Plan:

This project will test 20 normal subjects with two PET scans each. The subjects will be preselected on the RAPM so 10 will be average IQ and 10 will be high IQ. Each subject will also undergo evoked potential testing during each PET scan. One MRI scan will also be necessary for each subject. Subjects will be right handed males between 18 and 25 in good physical health. Subjects with significant medical illness, taking psychoactive medication, history of head injury, epilepsy or other interfering neurological illness will be excluded.

For PET, following FDG injection, the subject will perform the task described below for 30-35 minutes, allowing maximal metabolic uptake of the FDG. Then the subject will be transferred to the PET scanner. A standard survey of nine slices will be scanned exactly as in our other current approved protocols.

The subject will return for one additional scan after

approximately 1 week. All procedures will be the same for the second scan except the task will differ as described below.

The task will be digit span backwards. The subject will repeat a string of numbers backwards. The length of the string will be easy or hard (determined in advance for each subject). Each of the two PET scans will be done with a different number of digits to be repeated backwards. This will allow the determination of the relation between glucose used and easy or hard mental effort. Depending on the results from the initial subjects, the task may be altered or another psychophysical task substituted. Other similar simple neuropsychological tasks or behavioral inventories may be administered for a more comprehensive view of individual differences in perceptual and cognitive abilities or personality.

PET scanning

The PET procedure follows our standard PET paradigm. The subjects will be seated in an acoustically attenuated psychophysiological testing room. An intravenous line with a 0.9% saline drip will be inserted into the subject's right arm for radiotracer injection and a second line into the subject's left arm with a plastic cannula for blood sampling. The left arm will be wrapped in a hot pack for arterialization of venous blood (which gives adequate glucose values; see Phelps et al, 1979). Intravenous lines will be started about 60 minutes before FDG injection. The stimuli will be started before the injection so that the initial novelty of the presentation will not be FDG labeled. A black screen surrounds the subject so that only the task screen is visible. The subject's arms protrude through slits in the screen so that the injection of the FDG into IV tubing and blood sampling are not seen by the subject. Up to 5 millicuries of FDG will be injected for each scan.

After about 35 minutes of FDG uptake, the right arm IV will be removed, the subject allowed to void, and then transferred to the adjacent PET scanner room. An individually molded, thermosetting plastic head holder will be used. Approximately nine slices will be scanned for each subject.

MRI

The MRI procedure uses a powerful magnetic field to generate detailed anatomical images. Possible hazards include: movement of metallic prostheses (e.g., surgical clips). Subjects will be screened and excluded for the presence of metallic prostheses. Otherwise, there is no known risk.

Data Analyses:

Regional brain glucose use will be determined and compared for the behavioral conditions.

Costs:

There is no charge to subjects for participation in this study. Each subject will be paid $12 per hour for participation.

Rights:

All data collected will be kept confidential to the extent provided by law. Subjects may end their participation at any time.

Risks/Discomforts:

The amount of radiation exposure during PET equals about 6-10 chest X-rays. The UCI HSC has previously approved FDG use for PET in accordance with FDA guidelines--up to 5 mCi for each of 5 scans within a single calendar year.

Benefits:

No direct benefits to individual subjects are anticipated from this study although the data will be of great importance to the researchers.

UNIVERSITY OF CALIFORNIA, IRVINE

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OFFICE OF THE VICE CHANCELLOR FOR RESEARCH
DEAN OF GRADUATE STUDIES

IRVINE, CALIFORNIA 92717

March 30, 1993

Richard J. Haier, Psychiatry & Human Behavior

RE: HSM# 90*017
CHANGES IN CEREBRAL GLUCOSE METABOLIC RATE FOR DIFFERENT MENTAL WORK LOADS STUDIED WITH POSITRON EMISSION TOMOGRAPHY

The research project referenced above has been approved by the Human Subjects Review Committee (HSRC). Any stipulations of approval imposed by the Committee are recorded below.

Approval of the Human Subjects Review Committee does not, in and of itself, constitute approval for implementation of this project. Other levels of review and approval may be required (e.g. EH&S, Radiation Safety, School Dean). Studies undertaken in conjunction with outside entities, such as drug or device companies, are typically contractual in nature and require an agreement between the University and the company. These agreements must be executed by an ***institutional official*** in the UCI Office of Contract and Grant Administration. The University is not obligated to legally defend and indemnify an employee who individually enters into these agreements and investigators are personally liable for contracts that they sign. *Accordingly, the project should not begin until all required approvals have been obtained.*

No changes are to be made to either the approved protocol nor the approved, stamped consent form without the prior review and approval of the HSRC. The enclosed consent form with the UCI approval stamp must be used for all human subjects entered into this study. In accordance with U.S. Food and Drug Administration regulations and UCI policy, all unanticipated or untoward adverse effects must be reported to the HSRC (via Human Research Administration) within two working days of occurrence.

Unless this research is "exempt," approximately 60 days prior to expiration of this approval, the principal investigator of record should receive an "Application Form for Continuing Review" which must be submitted for HSRC review and approval *prior* to the expiration date noted below. It is the principal investigator's responsibility to assure current approval of his/her projects; therefore, Human Research Administration (856-6068) should be notified if the Application Form for Continuing Review is not received.

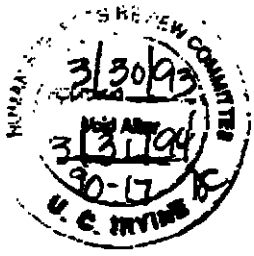
Michael Brodsky M.D.
Chair, Human Subjects Review Committee

Approval Period: 3/30/93 to 3/31/94

UCI has an approved Multiple Project Assurance: # M-1305

____Expedited Review ✓ Full Board Review

THIS APPROVAL EXTENDS TO RESEARCH PERFORMED AT UNIVERSITY OF CALIFORNIA IRVINE FACILITIES ONLY.



University of California, Irvine

Consent to act as a Human Research Subject

TITLE: Changes in cerebral glucose metabolic rate for different mental work loads studied with positron emission tomography

Richard J. Haier, Ph.D. (714 856-4268)
Stephen Lottenberg, M.D. (714 856-4244)

Name of subject:_____

Purpose:

I understand that I have been asked to volunteer for a research project studying how hard the brain works during tests of mental difficulty. This study will involve the use of a technique called Positron Emission Tomography (PET) which measures the rate that sugar (the energy supply for brain activity) is used in the brain.

Procedures:

If I agree to participate in this study, the following will happen:

I will be tested on one or two days (at least one week between each test) while performing a memory task or a math task. This testing will last about 30-40 minutes each day. If I am in the group doing the memory task I will be tested on two days; if I am in the group doing the math task I will tested on one day.

I will undergo a PET scan during each of the testing sessions. For each scan I will be given an intravenous injection of a radioactive experimental drug called 18-Fluorodeoxyglucose (FDG). This is similar to sugar. The FDG allows the researchers to "trace" where in the brain the mental work may be taking place. Two intravenous lines (requiring a needle placed into a vein in each arm) will be put in for each scan. About 45 minutes after I receive the FDG through one of the I.V. lines, I will be asked to empty my bladder and to lie on a bed with my head in a large donut-shaped device, the PET scanner. This device makes pictures of my brain sugar use. Since the scan procedure takes about 1-2 hours, it will be necessary for me to lie quietly during the

entire time. A special plastic mask, custom molded to my face for comfort, will help me hold my head still.

Blood samples will be withdrawn from one of the two intravenous lines about 16 times (approximately a half teaspoon total) during the scan procedure.

I will have the electrical activity of my brain assessed with the EEC technique of evoked potential, which is the measurement of the small electrical fields generated by normal brain response to the memory task. The evoked potential will be recorded from 16 electrodes attached to my scalp with paste. The whole procedure will last 1 1/2 - 2 hours. The recording of brain electrical activity is not a hazardous procedure.

I will be asked to lie in a Magnetic Resonance Imaging Scanner (MRI) to have pictures of my brain made by a large magnetic field. The MRI scan will take approximately 45 minutes. During this procedure you will receive an injection of gadolinium. This is a commonly used substance that will help make a better picture. Gadolinium is not harmful and is cleared from the body in less than one hour. About 9% of people who receive gadolinium report mild to moderate headaches for a few minutes and 4% of people report nausea for a few minutes. The MRI scanner is at the UCI Medical Center, located in the city of Orange (about 30 minutes from the campus).

I understand that it is important for my own safety and for the scientific validity of the study that the investigators be informed fully about any past medical or psychiatric conditions I may have now or have had in the past. If I have had a PET scan during the past year, I will inform the investigators. In particular, I agree to tell them about any past or present exposure to radiation, history of epilepsy, head injury, liver, bladder, or kidney disease, the use of prescription or nonprescription medications, the use of "recreational" drugs (such as cocaine, amphetamines, marijuana, heroin, LSD, PCP, etc.), use of alcohol, allergies or drug reactions. I may be asked for a urine or blood sample for further testing.

I understand that FDG, the imaging material used in the PET scanning procedure is not burned up nprmally by the body, but in this study only very small doses will be administered- less than one-ten thousandths of the amount required to show any drug behavior or mood effects. It will be passed in my urine within 48 hours after administration and most of it will be eliminated from

my body in the first 72 hours.

Risks:

Cancer occurs normally in one out of four people. To perform the PET scan, a small amount of radioactivity is injected into a vein. Injection of the FDG will expose me to a small dose of radiation, so my risk of developing cancer in the future may be slightly increased. The injection may cause discomfort from the needle and a small bruise.

If I am claustrophobic, the scans may be unbearable and I will be excluded from the study.

MRI Scan

I understand that if I have surgical clips and other metallic prostheses, I should not participate in the study. No short-term ill effects have been reported from MRI scans to date. Longer-term risks, however, are under evaluation at this time. The effects of MRI on pregnant women and children under age two have not yet been fully studied. This is an FDA-approved device for clinical use.

EP Procedure

There are no unusual risks associated with evoked potential testing.

Other Considerations

If at any time I have comments or complaints relating to the conduct of this research, my rights as a research subject, or if I feel I have suffered a research related illness or injury, I should contact the Human Research Administration's Office, 115 Administration Building, UC Irvine, Irvine, CA 92717 (714-856-7114).

The University will provide medical treatment reasonably necessary for any injury or illness which a human subject suffers as a direct result of participation in a University approved research study, or reimburse a subject for such costs except when the injury or illness is a consequence of a medical research procedure which is designed to benefit the subject directly. The University does not provide any other form of compensation, however.

I will not benefit from the PET scan although the data will be of great interest to researchers.

I will be paid $12 per hour for participation. There will be no cost to me for participating in this study.

Participation in this study is entirely voluntary. I may refuse to participate or withdraw at anytime without jeopardy to the medical care I receive at this institution. I understand that any information derived from this research project which personally identifies me will not be voluntarily released or disclosed without my separate consent, except as specifically required by law.

I have read The Experimental Subject's Bill of Rights and have been given a copy of it and this consent form to keep.

I agree to participate.

PART I OF II-see next page

Subject signature	Date
Witness signature	Date
Investigator signature	Date

1. Participation in research is entirely voluntary. You may refuse to participate or withdraw from participation at any time without jeopardy to future medical care, employment, student status or other entitlements. The investigator may withdraw you at his/her professional discretion.

2. If, during the course of the study, significant new information which has been developed becomes available, which may relate to your willingness to continue to participate, this information will be provided to you by the investigator.

3. Any information derived from the research project which personally identifies you will not be voluntarily released or disclosed without your separate consent, except as specifically required by law.

4. In studies involving investigational drugs and devices, the U.S. Food and Drug Administration may inspect your medical records which relate to your participation in this study. This may include copying of medical records.

5. If at any time you have questions regarding the research or your participation, you should contact the investigator who must answer all questions. A telephone number is provided at the top of Part I of the consent form.

6. If at any time you have comments or complaints relating to the conduct of this research, questions about your rights as a research subject, or if you feel you have suffered a research-related illness or injury, you should contact the UC Irvine Research Committees' Office. The University will provide medical treatment reasonably necessary for any injury or illness which a human subject suffers as a direct result of participation in a University approved research study or reimburse a subject for such costs except when the injury or illness is a consequence of a medical research procedure which is designed to benefit the subject directly. The University does not provide any other form of compensation, however.

For additional information regarding the items above, you should telephone the Research Committees' Office at (714) 856-7114.

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EXPERIMENTAL SUBJECTS' BILL OF RIGHTS

Any person who is asked to consent to participate as a human subject in a medical investigation or who is asked to consent on behalf of another, has the following rights:

1. To be told what the study is trying to find out.

2. To be told what will happen in the study and whether any of the procedures, drugs or devices is different from what would be used in standard medical practice.

3. To be told about the risks, side effects or discomforts which may be expected.

4. To be told if the subject can expect any benefit from participating and if so, what the benefit might be.

5. To be told of other choices available and how they may be better or worse than being in the study.

6. To be allowed to ask any questions concerning the study, both before agreeing to be involved and anytime during the course of the study.

7. To be told of any medical treatment available if complications arise.

8. To refuse to participate at all, either before or after the study has started. This decision will not affect any right to receive standard medical treatment.

9. To receive a signed and dated copy of Parts I and II of the consent form and this Bill of Rights.

10. To be allowed time to decide to consent or not to consent to participate without any pressure being brought by the investigators or others.

Subject's/Parent's/Guardian's Initials _____ Date _____ (Rev. 10/91)

[1] "See attached" is unacceptable. Complete form and continue on reverse side if necessary.

[2] If the study title adequately describes the protocol, # 1 may be left blank.

[3] Note that the

HS # 90-017

HUMAN SUBJECTS REVIEW COMMITTEE

REQUEST FOR MODIFICATION/ADDENDUM TO APPROVED PROTOCOL

THE ENTIRE FORM MUST BE COMPLETED[1] AND TYPED.

PRINCIPAL INVESTIGATOR: Dr. Haier DEPARTMENT: Psychiatry PHONE: X4268

TITLE OF ORIGINAL STUDY Changes in Cerebral Glucose Metabolic Rate for Different Mental Work Loads Studied With Positron Emission Tomography

1. BRIEF DESCRIPTION OF ORIGINAL PROTOCOL[2]:

Normal volunteers receive two PET scans at least 1 week apart.

2. DESCRIBE THE MODIFICATION(S) REQUESTED. ***INCLUDE REASONS FOR THE CHANGE(S).*** *(Continue on reverse side if necessary, and attach any available paperwork from study sponsor).*

Consistent with new IRB guidelines, we wish to drop the 1 week between scans so that now subjects may receive the second scan in less than a week.

3. WILL THE MODIFICATION(S), IN YOUR OPINION, ***INCREASE*** OR ***DECREASE*** THE RISK OF HARM TO THE SUBJECTS? INCREASE____ DECREASE____ NEITHER XX IF RISK WILL BE INCREASED, PROVIDE JUSTIFICATION. (Continue on reverse side if necessary)

4. WILL THE MODIFICATION(S) ALTER THE APPROVED CONSENT FORM? YES XX NO____ IF YES, ATTACH ORIGINAL AND 1 COPY OF A REVISED CONSENT FORM TO THIS FORM FOR REVIEW AND APPROVAL. ***HIGHLIGHT ALL CHANGES ON THE COPY.***

R Haier 9/24/93

SIGNATURE OF PRINCIPAL INVESTIGATOR[3] DATE

[1] "See attached" is unacceptable. Complete form and continue on reverse side if necessary.

[2] If the study title adequately describes the protocol, # 1 may be left blank.

[3] Note that the principal investigator must sign and date the form.

Submit original to Human Research Administration, 115 Administration Building, UCI Campus.
Review and approval will generally take a minimum of one week.

NOTE: No changes are to be implemented prior to HSRC review and approval.

Michael Bradsky M.D. 11/18/93

APPROVED: Human Subjects Review Committee DATE

Rev. 7/93