



USER: JOHNSON, SHEVON E (sxj)

FOLDER: K041263 - 290 pages (FOI:08008837)

COMPANY: APPLIED NEUROSCIENCE INC. (APPLNEUR)

PRODUCT: FULL-MONTAGE STANDARD
ELECTROENCEPHALOGRAPH (GWQ)

SUMMARY: Product: NEUROGUIDE ANALYSIS SYSTEM

DATE REQUESTED: Wed Jun 09 24:00:00 2010

DATE PRINTED: Thu Feb 10 11:26:25 2011

Note: Releasable Version

Table of Contents

510K SUMMARY - 8 pages	1
AMENDMENT - 3 pages	9
CORRESPONDENCE - 6 pages	12
ORIGINAL - 212 pages	18
REVIEWER INFORMATION - 20 pages	230
SUPPLEMENT - 39 pages	250

AUG - 3 2004

FDA 510(k) Summary

Section 807.92

(a)(1). **Submitter's Name:** Applied Neuroscience, Inc., 228 176th Terrace Drive, St. Petersburg, FL 33708. Phone: (727) 392-7851; Fax: (727) 319-1027; email: rwthatcher@yahoo.com.

Contact Person: Robert W, Thatcher. Ph.D. Applied Neuroscience, Inc., 228 176th Terrace Drive, St. Petersburg, FL 33708. Phone: (727) 392-7851; Fax: (727) 319-1027; email: rwthatcher@yahoo.com.

Date of preparation: 5/9/2004

(a)(2). **Name of the Device:** NeuroGuide Analysis System (NAS). **Classification name:** EEG Frequency Spectrum Analyzer.

(a)(3). **Predicate/legally marketed devices upon which substantial equivalence is based:** Cordis Brain State Analyzer (no FDA information available); TECA Corporation Neurolab I, II (K844481), Brain Mapper (K890-881), Neuromapper 386 (K894889); Nicolet BEAM I, II (no FDA 510(k) information available); Pathfinder II (K801604); Brain Functional Map (K843598); Cadwell Laboratories, Inc. 8400 (K860801) and Spectrum 32 (K860801 reference); Lexicor Medical Technology Neurosearch-24 (K904269), Neurosearch-4 (K920038); Neuroscience, Inc. Map-10 EEG (K840430), Neuromapper 1620 (K870263); Biologics Systems Corporation. Inc., Modified Brain Atlas III (K854362), Bio-Logic Automatic Event Analysis (K951594); Quantified Signal Imaging, Inc. QSI-9500 (K904294), QSI-9200 (FDA 510(k) information not available); Stellate Systems, Inc. Rhythm Software (K912938); NxLink, Inc. (K974748).

(a)(4). **Device Description:** The NeuroGuide Analysis System (NAS) is a software program for the post-hoc statistical analysis of the human electroencephalogram (EEG). EEG recorded on a separate device (i.e., the host system) is transferred to the NAS for display and user-review. The system requires that the user select reliable samples of artifact-free, eyes-closed or eyes open, resting digital EEG for purposes of analysis. Analysis consists of the Fast-Fourier Transformation (FFT) of the data to extract the spectral power for each of the four primary frequency bands (delta, theta, alpha, and beta), and frequency information from the EEG. The results of this analysis are then subjected to univariate, bivariate, and multivariate statistical analyses and displayed in statistical tables and topographical brain maps of absolute and relative power, power asymmetry, and coherence for 19 monopolar and 171 selected bipolar derivations of the EEG. In all over 1,200 measures are derived for comparison against a carefully constructed and statistically controlled age-regressed, normative database in which the variables have been transformed and confirmed for their Gaussian distribution. Each variable extracted by the analysis is compared to the database using parametric statistical procedures that express the differences between the patient and an appropriate age-matched reference group in the form of Z-scores. Multivariate features are compared to the normative

database using Gaussian Univariate and Multivariate Distance Statistics. The Gaussian multivariate Distance statistic controls for the interrelationship of the measures of brain cortical function in the feature set, and provides an accurate estimate of their difference from normal. The multivariate measures permit an evaluation of regional indices of brain function that reflect the perfusion fields of the brain. Extracted feature sets are further analyzed to determine if the pattern of 'hits' (statistically significant feature score values identified for the patient) are consistent with patterns of 'hits' identified in prior neuroguide evaluations of clinical patients with known disorders. A step-wise discriminate analysis program classifies the patient in terms of their similarity to known neuroguide-defined patterns of abnormality, providing a probability estimate of the patient's profile with the average profile of groups of individuals constituting the normative and clinical database. The discriminant classification program is restricted by confining potential outcomes to specific patient symptoms derived from the patient history profile. Established discriminant functions were evaluated through the use of Receiver Operating Characteristic (ROC) curves for their sensitivity and specificity. The outcome of the statistical analysis is presented in report form that includes (a) patient demographic and history information, (b) selected EEG epochs, (c) statistical tables of monopolar, bipolar, and multivariate extracted feature values, and topographical brain maps. This information is to be read and interpreted within the context of the current clinical assessment of the patient by the attending physician/clinician. The decision to accept or reject the results of the neuroguide analysis, and incorporate these results into their clinical appraisal of the patient, is dependent upon the judgment of the attending physician or clinician.

The NeuroGuide Analysis System is complete on a single CD, which contains a demonstration program with sample NeuroGuide studies, the NAS program, and the print program. The NAS was designed for implementation under Windows, and programmed using C. The user interface was carefully designed and implemented to permit the program to be easy to use, highly reliable in its performance. A variety of control procedures are used to record stops used in program usage, and the conduct of the analysis to insure appropriate function end operation of the software. The NAS can be installed in any appropriately configured IBM-compatible computer system, including systems designed specifically for the recording of digital EEG. The system functions with a wide-range of standard computer platforms and input-output devices, and printers.

(a)(5). Statement of Indications of Use: Indications for the use of the NeuroGuide Analysis System (NAS) are as follows:

Indications of Use

The NeuroGuide Analysis system is to be used by qualified medical and qualified clinical professionals for the post-hoc statistical evaluation of the human electroencephalogram (EEG).

(a)(6). Comparison to Predicate Devices: The NeuroGuide Analysis System uses essentially the same accepted methods of data selection and analysis of predicate devices

to extract the feature measures upon which statistical determination of normal/abnormal are made, and from which derivations of probability estimates of clinical classification are derived. The neuroguide method of EEG selection, analysis, and interpretation have been previously implemented, in whole or in part, in a variety of digital EEG and analysis systems marketed in prior years for the quantitative analysis of the EEG in Man. The NAS database, the same as for predicate devices, was carefully constructed to control for potential sources of Type I and Type II errors in the use of database comparisons in clinical electrophysiological assessment of the human EEG. The purposeful, easy to use, and reliable design of the NAS has been enhanced relative to these earlier systems through the careful consideration of user interactions by optimizing on the speed of modern computer technology to facilitate user feedback and hypothesis testing with mouse clicks.

(b). Non-clinical and Clinical Tests: The NeuroGuide Analysis System's design and implementation was based upon the results of an extensive, 25-year effort to construct a viable normative and clinical database at the Applied Neuroscience Laboratory (ANL) at the University of Maryland. The NAS incorporates the basic methods of data collection, data selection, analysis, and interpretation developed at the ANL during the conduct of numerous government and privately funded normative and clinical database projects

(b)(1). Non-clinical Testing: Non-clinical testing of the NAS included the evaluation of the algorithms and statistical methods used for data analysis. Specifically, control signals, in the form of signal generated waveforms, were analyzed for frequency and power- EEG signals were analyzed for conformity between the host digital EEG system and the NAS. The NAS includes a feature that reproduces sampling frequency in the host digital EEG system, and permits the visualization and evaluation of the EEG waveform for accuracy between the host system and the NAS translation. In addition, data obtained in previous implementations of the NeuroGuide analysis method were evaluated for consistency and accuracy -- the results of the NAS's analysis of stored subject data had to conform to that of the prior analysis (which was conducted using the same method and procedures, algorithms and method of analysis as that implemented on the NAS).

(b)(2). Clinical Testing: The ability of the NAS to accurately translate and present EEGs from clinical patients was confirmed by the non-clinical testing. In order for the NAS to be an effective implementation of the neuroguide method for clinical use, the results of the analysis (both statistical tables and topographical brain maps) had to be in agreement with the results of the analysis conducted on the host system used in the processing of patient information at the Applied Neuroscience Laboratory. In addition, the outcome of the discriminant analysis had to be consistent, not resulting in errors of misclassification (that is, the classification on the NAS had to be consistent with that of the host system used to perform the NeuroGuide analysis at the ANL). These tests confirmed that when eyes-closed resting, and artifact-free EEG was selected for analysis, the results were reproducible within an acceptable degree of variation consistent with reliability estimates identified in the normative studies.

Subjects upon which this device has been tested included individuals which ranged in age

from 2 months to 82 years, and who were either volunteers or clinical patients referred for neuroguide evaluation to the Applied Neuroscience Laboratory by the Department of Psychiatry University of Maryland School of Medicine, and/or Shock Trauma and the Applied Neuroscience Institute at the University of Maryland Eastern Shore. The results of the analysis were conveyed to the referring physician or Ph.D. clinician who was asked to use the information as an adjunct to their clinical interpretation of the patient's traditional EEG. The information was provided in report form (including EEG epochs selected for analysis, statistical tables and topographic brain maps, and the result of the discriminant analysis) to permit the physician or Ph.D. clinician to determine its relevance to their clinical evaluation and diagnosis or treatment of the patient. When the results are used in this manner, the likelihood of introducing error into diagnosis and treatment is substantially reduced. That is, the test is viewed as an adjunct to the evaluation of the patient, and does not serve as a primary basis for the diagnosis.

Potential adverse effects of the use of the device are known if the NeuroGuide Analysis System is used as a stand-alone diagnostic system (a use that is specifically contraindicated by Applied Neuroscience, Inc. and the system's developers) in the absence of other clinical data from more traditional means of patient evaluation. Relying only upon the use of a single index (such as relative power, or the topographical maps alone) without reviewing the traditional EEG, the epochs selected for analysis, or the complete set of statistical summary tables is also contraindicated and a source of potential error. Additional sources of error could arise from the inappropriate selection of EEG (selecting artifacted EEG epochs, or selecting EEG representative of other states, such as drowsiness or eyes-open EEG when comparing to an eyes closed database, or by purposely selecting conditions for testing other than those specified. Additionally, it is possible that errors will occur through the purposeful falsification of symptoms in the patient history, and patient age.

(b)(3) Conclusions Drawn From Non-Clinical and Clinical Testing: The appropriate use of the NeuroGuide Analysis System as an adjunct to the traditional visually-appraised EEG provides the user with the ability to quantify EEG variables and use them to answer questions drawn from their clinical experience with the patient. When used by an experienced, qualified practitioner, or under the proper supervision of a qualified medical professional, the NAS is concluded to be a useful and beneficial addition to the array of clinically accepted medical tests and devices used to evaluate brain structure and function.

The results of non-clinical and clinical resting conducted over the past 25 years demonstrates that the NAS is both safe and effective for the quantitative analysis of the eyes-closed resting EEG in the alert human subject and to be used to help determine if the EEG is normal or abnormal, and if abnormal, to statistically characterize the distribution of selected derived features by their probability of being similarly distributed in specified groups of clinical patients, the NAS provides information that both complements and supplements the outcome of the analysis of a traditional EEG. This information, when properly used in conjunction with other clinical tests as a safe and effective adjunctive aid to diagnosis, treatment planning, and treatment follow-up of the neurologic and psychiatric patient.

Compared to its predicate devices, the NeuroGuide Analysis System's inclusion of specific, appropriate, reliable and effective statistical controls over the method of data selection and analysis, the scientific rigor involved in the construction, refinement, and application of the normative and clinical databases, and the potential for providing practitioner with sensitive and specific quantitative indices of brain structure and function that is both safe and effective and suggests that the NAS is a significant advancement in the use of quantitative technology in neurology, psychiatry, and clinical neuropsychology and is an advancement over predicate EEG analysis systems in terms of speed and ease of use.



Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

AUG - 3 2004

Robert W. Thatcher, Ph.D.
President
Applied Neuroscience, Inc.
228 176th Terrace Drive
Redington Shores, Florida 33708

Re: K041263
Trade/Device Name: NeuroGuide Analysis System (NAS)
Regulation Number: 21 CFR 882.1400, 21 CFR 882.1420
Regulation Name: Electroencephalograph; Electroencephalogram (EEG) signal spectrum analyzer
Regulatory Class: II
Product Code: GWQ, GWS
Dated: July 20, 2004
Received: July 22, 2004

Dear Dr. Thatcher:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to such additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Part 801); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820); and if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

Page 2 - Robert W. Thatcher, Ph.D.

This letter will allow you to begin marketing your device as described in your Section 510(k) premarket notification. The FDA finding of substantial equivalence of your device to a legally marketed predicate device results in a classification for your device and thus, permits your device to proceed to the market.

If you desire specific advice for your device on our labeling regulation (21 CFR Part 801), please contact the Office of Compliance at (301) 594-4659. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21CFR Part 807.97). You may obtain other general information on your responsibilities under the Act from the Division of Small Manufacturers, International and Consumer Assistance at its toll-free number (800) 638-2041 or (301) 443-6597 or at its Internet address <http://www.fda.gov/cdrh/dsma/dsmamain.html>

Sincerely yours,

Miriam C. Provost
for

Celia M. Witten, Ph.D., M.D.

Director

Division of General, Restorative
and Neurological Devices

Office of Device Evaluation

Center for Devices and Radiological Health

Enclosure

Indications for Use

510(k) Number (if known): K041263

Device Name: NeuroGuide Analysis System

Indications For Use: For clinical use the NeuroGuide Analysis system is to be used by qualified medical or clinical professionals for the statistical evaluation of the human electroencephalogram (EEG).

Prescription Use _____
(Part 21 CFR 801 Subpart D)

AND/OR

Over-The-Counter Use X
(21 CFR 801 Subpart C)

(PLEASE DO NOT WRITE BELOW THIS LINE-CONTINUE ON ANOTHER PAGE IF NEEDED)

Concurrence of CDRH, Office of Device Evaluation (ODE)

Miriam C. Provost
(Division Sign-Off)
**Division of General, Restorative,
and Neurological Devices**

Page 1 of _____

510(k) Number K041263

Yung Pak

CM
CLP
ADD TO FILE
08.10.04

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Memorandum

Date: 8/3/04

From: DMC (HFZ-401)

Subject: Premarket Notification Number(s): K041263/A1

To: Division Director: NE/DGRND

The attached information has been received by the 510(k) DMC on the above referenced 510(k) submission(s). Since a final decision has been rendered, this record is officially closed.

Please review the attached document and return it to the DMC, with one of the statements checked below.

Information does not change the status of the 510(k); no other action required by the DMC; please add to image file. (Prepare K-25) THIS DOES NOT APPLY TO TRANSFER OF OWNERSHIP. PLEASE BRING ANY TRANSFER OF OWNERSHIP TO POS.

Additional information requires a new 510(k); however, the information submitted is incomplete; (Notify company to submit a new 510(k); [Prepare the K30 Letter on the LAN]

No response necessary (e.g., hard copy of fax for the truthful and accuracy statement, 510(k) statement, change of address, phone number, or fax number).

hard copy - indications for use statement

OIVD
CIIA

CLIA CATEGORIZATION refers to laboratory test system devices reviewed by the Division of Clinical Laboratory Devices (HFZ-440)

Information requires a **CLIA CATEGORIZATION**; the complexity may remain the same as the original 510(k) or may change as a result of the additional information (Prepare a CAT letter)

Additional information requires a **CLIA CATEGORIZATION**; however, the information submitted is incomplete; (call or fax firm)

No response necessary

This information should be returned to the DMC within 10 working days from the date of this memorandum.

Reviewed by: Yung Pak

Date: 8/10/04

Draft #2 : 9/8/99
Draft #3: 1/3/00
Draft #4: 3/7/03

Handwritten stamp: 8/10/04

Handwritten mark: 1

K041263/A1

Applied Neuroscience, Inc.



228 176th Terrace Drive
Redington Shores, FL 33708
727-392-7851, rwthatcher@yahoo.com

July 29, 2004

Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Boulevard
Rockville, Maryland 20850 USA

Re: 510(k) Number: K041263

Dear Sirs;

Enclosed is an original and two copies of an "Indications for Use Form". Please include this form as part of the Applied Neuroscience, Inc. 510(k) application (K041263).

Sincerely,

A handwritten signature in cursive script that reads "Robert W. Thatcher".

Robert W. Thatcher, Ph.D.
President

FOI/CONFIDENTIAL
JUL 30 2004
A 9:25

Steco
2

Indications for Use

510(k) Number (if known): K041263

Device Name: NeuroGuide Analysis System

Indications For Use: For clinical use the NeuroGuide Analysis system is to be used by qualified medical or clinical professionals for the statistical evaluation of the human electroencephalogram (EEG).

Prescription Use _____
(Part 21 CFR 801 Subpart D)

AND/OR

Over-The-Counter Use X
(21 CFR 801 Subpart C)

(PLEASE DO NOT WRITE BELOW THIS LINE-CONTINUE ON ANOTHER PAGE IF NEEDED)

Concurrence of CDRH, Office of Device Evaluation (ODE)

Page 1 of _____

3



Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

AUG - 3 2004

Robert W. Thatcher, Ph.D.
President
Applied Neuroscience, Inc.
228 176th Terrace Drive
Redington Shores, Florida 33708

Re: K041263
Trade/Device Name: NeuroGuide Analysis System (NAS)
Regulation Number: 21 CFR 882.1400, 21 CFR 882.1420
Regulation Name: Electroencephalograph; Electroencephalogram (EEG) signal spectrum analyzer
Regulatory Class: II
Product Code: GWQ, GWS
Dated: July 20, 2004
Received: July 22, 2004

Dear Dr. Thatcher:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to such additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Part 801); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820); and if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

Page 2 - Robert W. Thatcher, Ph.D.

This letter will allow you to begin marketing your device as described in your Section 510(k) premarket notification. The FDA finding of substantial equivalence of your device to a legally marketed predicate device results in a classification for your device and thus, permits your device to proceed to the market.

If you desire specific advice for your device on our labeling regulation (21 CFR Part 801), please contact the Office of Compliance at (301) 594-4659. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21CFR Part 807.97). You may obtain other general information on your responsibilities under the Act from the Division of Small Manufacturers, International and Consumer Assistance at its toll-free number (800) 638-2041 or (301) 443-6597 or at its Internet address <http://www.fda.gov/cdrh/dsma/dsmamain.html>

Sincerely yours,

for Miriam C. Provost
Celia M. Witten, Ph.D., M.D.
Director
Division of General, Restorative
and Neurological Devices
Office of Device Evaluation
Center for Devices and Radiological Health

Enclosure

→

Indications for Use

510(k) Number (if known): K041263

Device Name: NeuroGuide Analysis System

Indications For Use: For clinical use the NeuroGuide Analysis system is to be used by qualified medical or clinical professionals for the statistical evaluation of the human electroencephalogram (EEG).

Prescription Use _____
(Part 21 CFR 801 Subpart D)

AND/OR

Over-The-Counter Use X
(21 CFR 801 Subpart C)

(PLEASE DO NOT WRITE BELOW THIS LINE-CONTINUE ON ANOTHER PAGE IF NEEDED)

Concurrence of CDRH, Office of Device Evaluation (ODE)

Miriam C. Probst
(Division Sign-Off)
Division of General, Restorative,
and Neurological Devices

Page 1 of _____

510(k) Number K041263

Food and Drug Administration
Center for Devices and
Radiological Health
Office of Device Evaluation
Document Mail Center (HFZ-401)
9200 Corporate Blvd.
Rockville, Maryland 20850

July 14, 2004

APPLIED NEUROSCIENCE INC.
228 176TH TERRACE DRIVE
ST. PETERSBURG, FL 33708
ATTN: ROBERT W. THATCHER

510(k) Number: K041263
Product: NEUROGUIDE
ANALYSIS SYSTEM

We are holding your above-referenced Premarket Notification (510(k)) for 30 days pending receipt of the additional information that was requested by the Office of Device Evaluation. Please remember that all correspondence concerning your submission MUST cite your 510(k) number and be sent in duplicate to the Document Mail Center (HFZ-401) at the above letterhead address. Correspondence sent to any address other than the one above will not be considered as part of your official premarket notification submission. Also, please note the new Blue Book Memorandum regarding Fax and E-mail Policy entitled, "Fax and E-Mail Communication with Industry about Premarket Files Under Review. Please refer to this guidance for information on current fax and e-mail practices at www.fda.gov/cdrh/ode/a02-01.html.

The deficiencies identified represent the issues that we believe need to be resolved before our review of your 510(k) submission can be successfully completed. In developing the deficiencies, we carefully considered the statutory criteria as defined in Section 513(i) of the Federal Food, Drug, and Cosmetic Act for determining substantial equivalence of your device. We also considered the burden that may be incurred in your attempt to respond to the deficiencies. We believe that we have considered the least burdensome approach to resolving these issues. If, however, you believe that information is being requested that is not relevant to the regulatory decision or that there is a less burdensome way to resolve the issues, you should follow the procedures outlined in the "A Suggested Approach to Resolving Least Burdensome Issues" document. It is available on our Center web page at: <http://www.fda.gov/cdrh/modact/leastburdensome.html>

If after 30 days the requested information, or a request for an extension of time, is not received, we will discontinue review of your submission and proceed to delete your file from our review system. Pursuant to 21 CFR 20.29, a copy of your 510(k) submission will remain in the Office of Device Evaluation. If you then wish to resubmit this 510(k) notification, a new number will be assigned and your submission will be considered a new premarket notification submission.

Please remember that the Safe Medical Devices Act of 1990 states that you may not place this device into commercial distribution until you receive a decision letter from FDA allowing you to do so.

If you have procedural or policy questions, please contact the Division of Small Manufacturers International and Consumer Assistance (DSMICA) at (301) 443-6597 or at their toll-free number (800) 638-2041, or contact me at (301) 594-1190.

Sincerely yours,

Marjorie Shulman
Supervisor Consumer Safety Officer
Premarket Notification Section
Office of Device Evaluation
Center for Devices and
Radiological Health

May 12, 2004

Food and Drug Administration
Center for Devices and
Radiological Health
Office of Device Evaluation
Document Mail Center (HFZ-401)
9200 Corporate Blvd.
Rockville, Maryland 20850

APPLIED NEUROSCIENCE INC.
228 176TH TERRACE DRIVE
ST. PETERSBURG, FL 33708
ATTN: ROBERT W. THATCHER

510(k) Number: K041263
Received: 11-MAY-2004
Product: NEUROGUIDE ANALYSIS
SYSTEM

The Food and Drug Administration (FDA), Center for Devices and Radiological Health (CDRH), has received the Premarket Notification you submitted in accordance with Section 510(k) of the Federal Food, Drug, and Cosmetic Act (Act) for the above referenced product. We have assigned your submission a unique 510(k) number that is cited above. Please refer prominently to this 510(k) number in any future correspondence that relates to this submission. We will notify you when the processing of your premarket notification has been completed or if any additional information is required. YOU MAY NOT PLACE THIS DEVICE INTO COMMERCIAL DISTRIBUTION UNTIL YOU RECEIVE A LETTER FROM FDA ALLOWING YOU TO DO SO.

The Act, as amended by the Medical Device User Fee and Modernization Act of 2002 (MDUFMA)(Public Law 107-250), authorizes FDA to collect user fees for premarket notification submissions. (For more information on MDUFMA, you may refer to our website at <http://www.fda.gov/oc/mdufma>).

Please remember that all correspondence concerning your submission MUST be sent to the Document Mail Center (DMC)(HFZ-401) at the above letterhead address. Correspondence sent to any address other than the one above will not be considered as part of your official premarket notification submission. Also, please note the new Blue Book Memorandum regarding Fax and E-mail Policy entitled, "Fax and E-Mail Communication with Industry about Premarket Files Under Review". Please refer to this guidance for information on current fax and e-mail practices at www.fda.gov/cdrh/ode/a02-01.html.

You should be familiar with the manual entitled, "Premarket Notification 510(k) Regulatory Requirements for Medical Devices" available from DSMICA. If you have other procedural or policy questions, or want information on how to check on the status of your submission, please contact DSMICA at (301) 443-6597 or its toll-free number (800) 638-2041, or at their Internet address <http://www.fda.gov/cdrh/dsmamain.html> or me at (301)594-1190.

Sincerely yours,

Marjorie Shulman
Supervisory Consumer Safety Officer
Office of Device Evaluation
Center for Devices and Radiological Health

K041263

Applied Neuroscience, Inc.



228 176th Terrace Drive
Redington Shores, Fl 33708
727-392-7851, rwthatcher@yahoo.com

May 10, 2004

RECEIVED

2004 MAY 11 P 1:01

FDA/CDRH/ODE/PMO

Document Mail Center (HFZ401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Boulevard
Rockville, Maryland 20850 USA

Dear Sirs;

Enclosed are two copies of a 510k application for substantial equivalence of software for the spectral analysis of EEG. Applied Neuroscience, Inc. has been designated to qualify as a small business, MDUFMA small business decision number: SBD047091 and a fee has been submitted along with Form FDA 3601. The payment identification number is: 013811-956733.

Sincerely,

Robert W. Thatcher, Ph.D.
President

NE
I

sk 26



DEPARTMENT OF HEALTH & HUMAN SERVICES

Robert W. Thatcher
d/b/a Applied Neuroscience, Inc.
228 176th Terrace Drive
St. Petersburg, FL 33708

Food and Drug Administration
Rockville MD 20857

April 22, 2004

To: Robert W. Thatcher, President
Subject: Request for Qualification as a Small Business

Small Business Decision Number: **SBD047091**
Expires: **September 30, 2004**

This responds to your request for eligibility for Small Business Qualification on Form FDA 3602.

After review of your submission, I am pleased to inform you that your firm does qualify under MDUFMA as a small business for reduced or waived fees for medical device submissions made during the fiscal year 2004.

Please include your Small Business Decision Number (see above) whenever you submit a Medical Device User Fee Coversheet (form FDA 3601). This will allow FDA to quickly confirm that you are entitled to a reduced or waived fee.

Your Small Business status expires at the close of business September 30, 2004. FDA will provide information on how to qualify as a Small Business for FY 2005 in a Federal Register Notice to be published around August 1, 2004. We will also provide this information on our MDUFMA website, at: www.fda.gov/oc/mdufma.

Also, note that reduced fees for 510(k) submissions by small businesses are for fiscal year 2004, effective October 1, 2003.

Cindy Garris
Small Business Decision Reviewer
Division of Small Manufacturers,
International and Consumer Assistance
Office of Health and Industry Programs
Center for Devices and Radiological Health

(727) 244-0240 cell/cv

Form Approved OMB No. 0910-0511 Expiration Date: August 31, 2006. See instructions for OMB Statement.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
 FOOD AND DRUG ADMINISTRATION
 MEDICAL DEVICE USER FEE COVER SHEET

PAYMENT IDENTIFICATION NUMBER: **013811 - 956733**
 Write the Payment Identification Number on your check.

A completed Cover Sheet must accompany each original application or supplement subject to fees. The following actions must be taken to properly submit your application and fee payment:

1. Electronically submit the completed Cover Sheet to the Food and Drug Administration (FDA) before payment is sent.
2. Include a printed copy of this completed Cover Sheet with a check made payable to the Food and Drug Administration. Remember that the Payment Identification Number must be written on the check.
3. Mail Check and Cover Sheet to the US Bank Lock Box, FDA Account, P.O. Box 956733, St. Louis, MO 63195-6733. (Note: In no case should payment be submitted with the application.)
4. If you prefer to send a check by a courier, the courier may deliver the check and Cover Sheet to: US Bank, Attn: Government Lockbox 956733, 1005 Convention Plaza, St. Louis, MO 63101. (Note: This address is for courier delivery only. Contact the US Bank at 314-418-4821 if you have any questions concerning courier delivery.)
5. For Wire Transfer Payment Procedures, please refer to the MDUFMA Fee Payment Instructions at the following URL: <http://www.fda.gov/cdrh/mdufma/faqs.html#3a>. You are responsible for paying all fees associated with wire transfers.
6. Include a copy of the completed Cover Sheet in volume one of the application when submitting to the FDA at either the CBER or CDRH Document Mail Center.

1. COMPANY NAME AND ADDRESS (Include name, street address, city, state, country, and post office code)

APPLIED NEUROSCIENCE, INC.
 228 176TH TERRACE DRIVE
 ST. PETERSBURG, FL 33708

1.1 EMPLOYER IDENTIFICATION NUMBER (EIN)
 593260424

2. CONTACT NAME
 ROBERT THATCHER

2.1 E-MAIL ADDRESS
 rwthatcher@yahoo.com

2.2 TELEPHONE NUMBER (Include Area Code)
 727-392-7851

2.3 FACSIMILE (FAX) NUMBER (Include Area Code)
 727-319-1027

3. TYPE OF PREMARKET APPLICATION (Select one of the following in each column; if you are unsure, please refer to the application descriptions at the following web site: <http://www.fda.gov/oc/mdufma>)

- Select an application type:
- Premarket notification (510(k)); except for third party reviews
 - Biologics License Application (BLA)
 - Premarket Approval Application (PMA)
 - Modular PMA
 - Product Development Protocol (PDP)
 - Premarket Report (PMR)

- 3.1 Select one of the types below:
- Original Application
- Supplement Types:
- Efficacy (BLA)
 - Panel Track (PMA, PMR, PDP)
 - Real-Time (PMA, PMR, PDP)
 - 180-day (PMA, PMR, PDP)

4. ARE YOU A SMALL BUSINESS? (See the instructions for more information on determining this status.)

- YES, I meet the small business criteria and have submitted the required qualifying documents to FDA
- NO, I am not a small business

4.1 If Yes, please enter your Small Business Decision Number:
 SBD047091

5. IS THIS PREMARKET APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCEPTIONS? IF SO, CHECK THE APPLICABLE EXCEPTION.

- This application is the first PMA submitted by a qualified small business, including any affiliates, parents, and partner firms
- This biologics application is submitted under section 351 of the Public Health Service Act for a product licensed for further manufacturing use only
- The sole purpose of the application is to support conditions of use for a pediatric population
- The application is submitted by a state or federal government entity for a device that is not to be distributed commercially

6. IS THIS A SUPPLEMENT TO A PREMARKET APPLICATION FOR WHICH FEES WERE WAIVED DUE TO SOLE USE IN A PEDIATRIC POPULATION THAT NOW PROPOSES CONDITION OF USE FOR ANY ADULT POPULATION? (If so, the application is subject to the fee that applies for an original premarket approval application (PMA).)

- YES
- NO

7. USER FEE PAYMENT AMOUNT SUBMITTED FOR THIS PREMARKET APPLICATION (FOR FISCAL YEAR 2004)

\$2,784.00

Table of Contents

	Page No.
1- Table of Contents	1
2- Cover Sheet	2
3- Cover Letter	7
4- Device Description	8
5- Intended Use of the Device	10
6- Basic Documentation for NeuroGuide OTS Software	11
7- Proposed Labeling	14
8- Predicate/legally marketed devices upon which substantial equivalence is based	16
9- Substantially Equivalent Statement	17
10- Non-Clinical Testing	23
11- Clinical Testing	24
12- Conclusions Drawn From Non-Clinical and Clinical Testing	25
13- 510(k) Summary	26
14- Truthful and Accurate Statement	31
15- 510(k) Checklist	32
 Appendix – A: Labeling and Advertising Documentation	
1- CD Jacket Label	
2- NeuroGuide – Manual	
3- NeuroGuide Introduction Brochure	
 Appendix – B: Calibration Verification and Validation	
1- Verification & Validation using Calibration Signals	
2- Gaussian Distribution Verification & Validation Tests	
3- Example peer reviewed publications	
4- List of peer reviewed publications	

CDRH PREMARKET REVIEW SUBMISSION COVER SHEET

Date of Submission 05/03/2004	User Fee Payment ID Number SBD047091	FDA Submission Document Number (if known)
---	--	---

SECTION A TYPE OF SUBMISSION

PMA <input type="checkbox"/> Original Submission <input type="checkbox"/> Premarket Report <input type="checkbox"/> Modular Submission <input type="checkbox"/> Amendment <input type="checkbox"/> Report <input type="checkbox"/> Report Amendment <input type="checkbox"/> Licensing Agreement	PMA & HDE Supplement <input type="checkbox"/> Regular (120 day) <input type="checkbox"/> Special <input type="checkbox"/> Panel Track (PMA Only) <input type="checkbox"/> 30-day Supplement <input type="checkbox"/> 30-day Notice <input type="checkbox"/> 135-day Supplement <input type="checkbox"/> Real-time Review <input type="checkbox"/> Amendment to PMA & HDE Supplement <input type="checkbox"/> Other	PDP <input type="checkbox"/> Original PDP <input type="checkbox"/> Notice of Completion <input type="checkbox"/> Amendment to PDP	510(k) <input checked="" type="checkbox"/> Original Submission: <input checked="" type="checkbox"/> Traditional <input type="checkbox"/> Special <input type="checkbox"/> Abbreviated (Complete section I, Page 5) <input type="checkbox"/> Additional Information <input type="checkbox"/> Third Party	Meeting <input type="checkbox"/> Pre-510(K) Meeting <input type="checkbox"/> Pre-IDE Meeting <input type="checkbox"/> Pre-PMA Meeting <input type="checkbox"/> Pre-PDP Meeting <input type="checkbox"/> Day 100 Meeting <input type="checkbox"/> Agreement Meeting <input type="checkbox"/> Determination Meeting <input type="checkbox"/> Other (specify):
IDE <input type="checkbox"/> Original Submission <input type="checkbox"/> Amendment <input type="checkbox"/> Supplement	Humanitarian Device Exemption (HDE) <input type="checkbox"/> Original Submission <input type="checkbox"/> Amendment <input type="checkbox"/> Supplement <input type="checkbox"/> Report <input type="checkbox"/> Report Amendment	Class II Exemption Petition <input type="checkbox"/> Original Submission <input type="checkbox"/> Additional Information	Evaluation of Automatic Class III Designation (De Novo) <input type="checkbox"/> Original Submission <input type="checkbox"/> Additional Information	Other Submission <input type="checkbox"/> 513(g) <input type="checkbox"/> Other (describe submission):

Have you used or cited Standards in your submission? Yes No (If Yes, please complete Section I, Page 5)

SECTION B SUBMITTER, APPLICANT OR SPONSOR

Company / Institution Name Applied Neuroscience, Inc.		Establishment Registration Number (if known)	
Division Name (if applicable)		Phone Number (including area code) (727) 392-7851	
Street Address 228 176th Terrace Drive		FAX Number (including area code) (727) 319-1027	
City St. Petersburg	State / Province FL	ZIP/Postal Code 33708	Country USA
Contact Name Robert W. Thatcher			
Contact Title President		Contact E-mail Address rwthatcher@yahoo.com	

SECTION C APPLICATION CORRESPONDENT (e.g., consultant, if different from above)

Company / Institution Name			
Division Name (if applicable)		Phone Number (including area code) ()	
Street Address		FAX Number (including area code) ()	
City	State / Province	ZIP/Postal Code	Country
Contact Name			
Contact Title		Contact E-mail Address	

SECTION D1 REASON FOR APPLICATION - PMA, PDP, OR HDE

<input type="checkbox"/> Withdrawal <input type="checkbox"/> Additional or Expanded Indications <input type="checkbox"/> Request for Extension <input type="checkbox"/> Post-approval Study Protocol <input type="checkbox"/> Request for Applicant Hold <input type="checkbox"/> Request for Removal of Applicant Hold <input type="checkbox"/> Request to Remove or Add Manufacturing Site	<input type="checkbox"/> Change in design, component, or specification: Software / Hardware Color Additive Material Specifications Other (specify below)	<input type="checkbox"/> Location change: Manufacturer Sterilizer Packager
<input type="checkbox"/> Process change: Manufacturing Sterilization Packaging Other (specify below)	<input type="checkbox"/> Labeling change: Indications Instructions Performance Shelf Life Trade Name Other (specify below)	<input type="checkbox"/> Report Submission: Annual or Periodic Post-approval Study Adverse Reaction Device Defect Amendment
<input type="checkbox"/> Response to FDA correspondence:		<input type="checkbox"/> Change in Ownership <input type="checkbox"/> Change in Correspondent <input type="checkbox"/> Change of Applicant Address

Other Reason (specify):

SECTION D2 REASON FOR APPLICATION - IDE

<input type="checkbox"/> New Device <input type="checkbox"/> New Indication <input type="checkbox"/> Addition of Institution <input type="checkbox"/> Expansion / Extension of Study <input type="checkbox"/> IRB Certification <input type="checkbox"/> Termination of Study <input type="checkbox"/> Withdrawal of Application <input type="checkbox"/> Unanticipated Adverse Effect <input type="checkbox"/> Notification of Emergency Use <input type="checkbox"/> Compassionate Use Request <input type="checkbox"/> Treatment IDE <input type="checkbox"/> Continued Access	<input type="checkbox"/> Change in: Correspondent / Applicant Design / Device Informed Consent Manufacturer Manufacturing Process Protocol - Feasibility Protocol - Other Sponsor	<input type="checkbox"/> Repose to FDA Letter Concerning: Conditional Approval Deemed Approved Deficient Final Report Deficient Progress Report Deficient Investigator Report Disapproval Request Extension of Time to Respond to FDA Request Meeting Request Hearing
<input type="checkbox"/> Report submission: Current Investigator Annual Progress Report Site Waiver Report Final		

Other Reason (specify):

SECTION D3 REASON FOR SUBMISSION - 510(k)

<input checked="" type="checkbox"/> New Device	<input type="checkbox"/> Additional or Expanded Indications	<input type="checkbox"/> Change in Technology
<input type="checkbox"/> Other Reason (specify):		

SECTION E ADDITIONAL INFORMATION ON 510(K) SUBMISSIONS

Product codes of devices to which substantial equivalence is claimed

1	K974748	2	K912938	3	K854362	4	K951594
5	K904269	6	K860801	7	K840430	8	K870263

Summary of, or statement concerning, safety and effectiveness information

510 (k) summary attached
 510 (k) statement

Information on devices to which substantial equivalence is claimed (if known)

	510(k) Number		Trade or Proprietary or Model Name		Manufacturer
1	K974748	1	NeuroMetric Analysis System	1	NxLink, Inc.
2	K912938	2	Stellate	2	Persyst Development Corp.
3	K854362	3	Modified Brain Atlas III	3	Biologic Systems Corporation, Inc.
4	K951594	4	Bio-Logic Automatic Event Analysis	4	Biologic Systems Corporation, Inc.
5	K904269	5	Neurosearch-24	5	Lexicor Medical Technology, Inc.
6	K860801	6	Spectrum-32	6	Cadwell Laboratories, Inc.

SECTION F PRODUCT INFORMATION - APPLICATION TO ALL APPLICATIONS

Common or usual name or classification
 EEG Frequency Spectrum Analyzer

	Trade or Proprietary or Model Name for This Device		Model Number
1	NeuroGuide Analysis System	1	
2		2	
3		3	
4		4	
5		5	

FDA document numbers of all prior related submissions (regardless of outcome)

1	2	3	4	5	6
7	8	9	10	11	12

Data Included in Submission

Laboratory Testing Animal Trials Human Trials

SECTION G PRODUCT CLASSIFICATION - APPLICATION TO ALL APPLICATIONS

Product Code GWS	C.F.R. Section (if applicable)	Device Class <input checked="" type="checkbox"/> Class I <input type="checkbox"/> Class II <input type="checkbox"/> Class III <input type="checkbox"/> Unclassified
Classification Panel EEG Frequency Spectrum Analyzer		

Indications (from labeling)
 The NeuroGuide Analysis system is to be used by qualified health practitioners for the post-hoc statistical evaluation of the human electroencephalogram (EEG).

Note: Submission of this information does not affect the need to submit a 2891 or 2891a Device Establishment Registration form.		FDA Document Number (if known)	
SECTION H MANUFACTURING / PACKAGING / STERILIZATION SITES RELATING TO A SUBMISSION			
<input type="checkbox"/> Original <input type="checkbox"/> Add <input type="checkbox"/> Delete	FDA Establishment Registration Number		<input type="checkbox"/> Manufacturer <input type="checkbox"/> Contract Sterilizer <input type="checkbox"/> Contract Manufacturer <input type="checkbox"/> Repackager / Relabeler
Company / Institution Name		Establishment Registration Number	
Division Name (if applicable)		Phone Number (including area code) ()	
Street Address		FAX Number (including area code) ()	
City	State / Province	ZIP Code	Country
Contact Name	Contact Title	Contact E-mail Address	
<input type="checkbox"/> Original <input type="checkbox"/> Add <input type="checkbox"/> Delete	FDA Establishment Registration Number		<input type="checkbox"/> Manufacturer <input type="checkbox"/> Contract Sterilizer <input type="checkbox"/> Contract Manufacturer <input type="checkbox"/> Repackager / Relabeler
Company / Institution Name		Establishment Registration Number	
Division Name (if applicable)		Phone Number (including area code) ()	
Street Address		FAX Number (including area code) ()	
City	State / Province	ZIP Code	Country
Contact Name	Contact Title	Contact E-mail Address	
<input type="checkbox"/> Original <input type="checkbox"/> Add <input type="checkbox"/> Delete	FDA Establishment Registration Number		<input type="checkbox"/> Manufacturer <input type="checkbox"/> Contract Sterilizer <input type="checkbox"/> Contract Manufacturer <input type="checkbox"/> Repackager / Relabeler
Company / Institution Name		Establishment Registration Number	
Division Name (if applicable)		Phone Number (including area code) ()	
Street Address		FAX Number (including area code) ()	
City	State / Province	ZIP Code	Country
Contact Name	Contact Title	Contact E-mail Address	

SECTION I

UTILIZATION OF STANDARDS

Note: Complete this section if your application or submission cites standards or includes a "Declaration of Conformity to a Recognized Standard" statement.

	Standards No.	Standards Organization	Standards Title	Version	Date
1					
2					
3					
4					
5					
6					
7					

Please include any additional standards to be cited on a separate page.

Public reporting burden for this collection of information is estimated to average 0.5 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
 CDRH (HFZ-342)
 9200 Corporate Blvd.
 Rockville, MD 20850

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control

Cover Letter

510(k) Application

Submitter's Name: Applied Neuroscience, Inc.

Submitter's Address: 228 176th Terrace Drive, St. Petersburg, Fl 33708

Submitter's Tel. No.: 727-392-7851

Submitter's Fax No.: 727-319-1027

Contact Name & Title: Robert W. Thatcher, Ph.D.; President

Contact email: rwthatcher@yahoo.com

Date of Preparation: May 10, 2004

Reason for Submission: New Device with Substantial Equivalence (SE)

Name of the Device: NeuroGuide Analysis System (NAS)

Classification Name: EEG Frequency Spectrum Analyzer

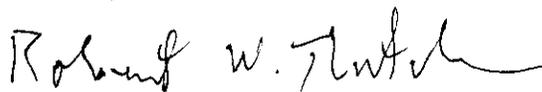
Product Code: GWS

Regulation Number: 882.1420

Device Class: Class I (general controls)

Registration Number: None

Sincerely,



Robert W. Thatcher, Ph.D.
President Applied Neuroscience, Inc.

Device Description - Over the Shelf Software (OTS)

1- Minor level of Concern Medical Device: The NeuroGuide Analysis System (NAS) is over the shelf software (OTS) that analyzes EEG waveforms and represents no threat of direct harm to the patient because there is no direct connection to a patient. The risk of indirect harm from a misdiagnosis relating to medical device malfunction is small since the worst case is an incorrect image or incorrect statistical computation which is considered correct. The NeuroGuide Analysis System software (NAS) is intended to be used to spectrally analyze digital EEG off-line. NAS is not an integral part of EEG systems that acquire and digitize EEG. NAS only accepts digital EEG that has been previously achieved or stored on another device (host system). The OTS Software in this medical device thus represents a Minor Level of Concern and should satisfy BASIC DOCUMENTATION.

2- Device Description: The NeuroGuide Analysis System (NAS) is a software program for the post-hoc statistical analysis of the human electroencephalogram (EEG). EEG recorded on a separate device (i.e., the host system) is transferred to the NAS for display and user-review. The system requires that the user select reliable samples of artifact-free, eyes-closed or eyes open resting EEG from the recording for analysis. Analysis consists of the Fast-Fourier Transformation (FFT) of the data to extract the spectral power for each of the four primary frequency bands (delta, theta, alpha, and beta), and frequency information from the EEG. The results of this analysis are then subjected to univariate, bivariate, and multivariate statistical analyses and displayed in statistical tables and topographical brain maps of absolute and relative power, power asymmetry, and coherence for 19 monopolar and 171 selected bipolar derivations of the EEG. In all over 1,200 measures are derived for comparison against a carefully constructed and statistically controlled age-regressed, normative database in which the variables have been transformed and confirmed for their Gaussian distribution. Each variable extracted by the analysis is compared to the database using parametric statistical procedures that express the differences between the patient and an appropriate age-matched reference group in the form of Z-scores. Multivariate features are compared to the normative database using Gaussian Multivariate Distance Statistics. The Gaussian multivariate Distance statistic controls for the interrelationship of the measures of brain cortical function in the feature set, and provides an accurate estimate of their difference from normal. The multivariate measures permit an evaluation of regional indices of brain function that reflect the perfusion fields of the brain. Extracted feature sets are further analyzed to determine if the pattern of 'hits' (statistically significant feature score values identified for the patient) are consistent with patterns of 'hits' identified in prior neuroguide evaluations of clinical patients with known disorders. A step-wise discriminate analysis program classifies the patient in terms of their similarity to known neuroguide-defined patterns of abnormality, providing a probability estimate of the patient's profile with the average profile of groups of individuals constituting the normative and clinical database. The discriminant classification program is restricted by confining potential outcomes to specific patient symptoms derived from the patient

history profile. Established discriminant functions were evaluated through the use of Receiver Operating Characteristic (ROC) curves for their sensitivity and specificity. The outcome of the statistical analysis is presented in report form that includes (a) patient demographic and history information, (b) selected EEG epochs, (c) statistical tables of monopolar, bipolar, and multivariate extracted feature values, and topographical brain maps. This information is to be read and interpreted within the context of the current clinical assessment of the patient by the attending physician/clinician. The decision to accept or reject the results of the neuroguide analysis, and incorporate these results into their clinical appraisal of the patient, is dependent upon the judgment of the attending physician or clinician. The Windows operating system (Windows 97, 98, ME, 2000, XP and NT) is used to interface the user, the microcomputer hardware platform, the stored or archived digital EEG data, statistical processing programs, data storage, and output devices.

Intended use of the Device

The NeuroGuide Analysis system is to be used by qualified medical and/or qualified clinical professionals (e.g., licensed clinical Ph. D.) for the post-hoc statistical evaluation of the human electroencephalogram (EEG).

Basic Documentation for NeuroGuide OTS Software

1- What is it?

- a- NeuroGuide Analysis Software (NAS) is manufactured by Applied Neuroscience, Inc.
- b- Version Level 2.0, expected release in fall 2004. Documentation for software changes are in the NeuroGuide manual which a user can activate by clicking Help at the menu bar.
- c- OTS Software documentation is a manual and a draft copy is in Appendix A
- d- NAS OTS Software is appropriate for EEG amplifier and EEG acquisition devices and such devices serve as host media by which the EEG is acquired and then off-line copied to a file where the NAS can import the digital EEG wave forms.
- e- The design limitations are proper computation of the spectral analysis which can be evaluated by calibration sign waves using built in programs and the approximation to Gaussian or normal distributions.

2- What are the Computer System Specifications for the OTS Software?

- a- IBM compatible hardware platform (PC), any processor speed, 128 mbyte RAM is recommended, minimum of 100 mbytes of hard disk space, standard display.
- b- Operating system is Windows 97, 98, ME, 2000, XP or NT.

3- How will you assure appropriate actions are taken by the End User?

- a- An installation wizard automatically installs all components of the software.
- b- Once installed the configuration does not change.
- c- Users should be trained in visual or conventional analysis of the EEG, in digital signal processing and in qEEG analysis.
- d- NeuroGuide Analysis Software is a stand-alone software program and non-specified OTS software is prevented from being used or incorporated into the NAS by design.
- e- False positive and false negative errors (i.e., Type I & Type II) are minimized by the use of a range of probabilities from 2 standard deviations ($P < .01$) to 6 standard deviations (i.e., $P < .0000001$). See verification and validation tests of Gaussian distributions in Appendix B.

4- What does the OTS Software do?

- a- The NAS software is intended to compute off-line spectral analyses of EEG waves. The details of the various features and analyses of NeuroGuide are

provided in the NeuroGuide Manual (see Appendix A). Built in error messages are presented if a user performs an illegal operation, e.g., wrong montage, mismatch of host amplifier format (i.e., unable to read file), notification that no age of the subject was specified and thus no Z scores are provided and duplication of electrodes in montage creation. The program will automatically not continue with the user's request for information processing if any error condition occurs. The user has the option to follow the instructions of the error message and then repeat an analysis or to begin a different analysis. The occurrence of an error message indicates an improper procedure and the user can simply repeat the steps using the proper conditions.

- b- Links to other software are by saving artifact free selections of digital EEG in ASCII or text format on a disk or in computer memory. ASCII is a universal format in which stand alone software such as Microsoft Word or Excel or EEG inverse solution software such as low resolution electromagnetic tomography (LORETA) or EEG biofeedback or general statistical software which can be used to analyze the digital EEG. Linkage by exporting Z scores and the results of statistical analyses occurs by ASCII export and/or in formats that are valid and accepted by other stand alone software programs for the purposes of verification and validation.

5. How do you know it works? – Based on a Minor Level of Concern

- a- The NAS OTS software is not connected to a patient and it is an off-line analysis that is validated by microvolt calibration sine waves varying in frequency from 0.5 Hz to 30 Hz and in amplitude from 1 microvolt to 100 microvolts. All of the NeuroGuide Analysis system's fast Fourier transform (FFT) algorithms are tested at the same time for all channels using sine waves.
- b- Results of the testing, including verification and validation of testing results is provided in Appendix B and is described as the Signal Generator that the user is recommended to use in order to verify and validate the NAS for themselves.
- c- In the event users find a bug then they can notify Applied Neuroscience, Inc. by email and/or telephone. Updates of the NAS will be posted on the Applied Neuroscience, Inc. website and updates of the software can be downloaded by NAS users.

6. How will you keep track of (control) the OTS Software?

- a- The NAS can be downloaded as a free demo. The NAS is installed as compiled object code which can not be modified.
- b- On start-up a copyright license agreement is displayed and the user is required to accept the terms of the copyright agreement which forbids tampering, adulteration, modification, reverse engineering and other unlawful conduct and provides legal

- safeguards. If user's choose not to accept the terms of the copyright license agreement then NAS automatically terminates.
- c- On start-up NAS software records the serial numbers of the user's computer hard drive and encrypts these values in a 24 element code called Key A. A security Key window displays the Key A and if no Key B is entered then the software automatically launches a demo. The free demo protects NeuroGuide as a product because the Demo does not allow for importation of EEG by the user.
 - d- After purchase the customer's Key A is sent to Applied Neuroscience, Inc. and a 24 element Key B is sent to the user. The Key B is an encrypted version of Key A. On start-up and after accepting the terms of the copyright agreement the NAS software checks the serial numbers of the user's computer and if there is a mismatch to the serial numbers in the user's copyright license Key B then the NAS will only operate in Demo mode. In Demo mode the user is limited to the use of the signal generator and to a sample file of EEG and the user will not be able to import EEG from a host device.
 - e- The NAS software is stored on the user's hard disk. The default location is: c:/program files/NeuroGuide.
 - f- Installation is by a Microsoft installation wizard that automatically installs the software and does allow users an option to modify or change the NAS.
 - g- Maintenance and life cycle support for the NAS OTS Software is provided by Applied Neuroscience, Inc. and updates are posted on the Applied Neuroscience, Inc. website and users are notified of all updates.

Proposed labeling and advertising for the device

1- Labeling on CD Jacket – Appendix A:

“NeuroGuide – EEG Editing and Analysis Software – Featuring a Normative Database, Discriminants and Statistics”

2- Labeling in the NeuroGuide Manual (Page 65 of manual – see Appendix A)

Warning: NeuroGuide does not diagnose and only provides displays of the digital EEG and statistical analyses of selected EEG segments. NeuroGuide requires competent human intervention for its many mathematical tools and NeuroGuide is only considered as an adjunct and/or as a supplement to other measures that may aid in evaluating the status of the EEG by a competent person. Clinical use of NeuroGuide requires a competent medical or clinical professional. NeuroGuide is a standalone software package that uses "look up" table functions to create Z scores which are a reference based on published scientific selection criteria of samples of EEG (Thatcher et al 1987; 1986; 1989; 2003) and the use of these tables is at the discretion of the competent professional. It is advised that reliability measurements and validity tests using different montages and different selections of EEG be conducted as a routine procedure when using NeuroGuide. NeuroGuide was designed to allow for mouse click selections and testings of hypotheses and reliability and validity using digital analyses of the EEG. qEEG is not a substitute for EEG, but an addition to EEG. Some forms of clinically important information are better recognized by eye than by quantification, and the visual inspection of the waveform EEG data is a good way to monitor and control the level of consciousness as well as eye movement and muscle artifacts. A qEEG device will not substitute for lack of EEG training, qEEG is more demanding than classic EEG on both the clinician and technologist. Those performing and reading of qEEG studies must not only have basic EEG skills, but must also have a functional understanding of the numerical and statistical techniques used in qEEG, be specifically trained in qEEG analysis and be aware of the necessity for better control of artifact and subject state. qEEG should always be interpreted by a knowledgeable clinician in the light of all relevant information

Contra indications: EEG artifact can invalidate analyses and improper positioning of electrodes or significant deviations from accepted standards of electroencephalographic recording methodology can invalidate EEG recordings or erroneous storage of data and falsification of data, improper manipulation of data or unlawful uses of NAS including violations of copyright law and other improper uses of NAS are all contra indicated.

3- Labeling in NeuroGuide Introduction Brochure (Page 1 of Manual)

NeuroGuide provides tools as analytical resources and as an EEG reference based on peer reviewed scientific publications. Any clinical use must be by qualified medical

or clinical professionals restricted to the post-hoc statistical evaluation of the human electroencephalogram (EEG). NeuroGuide is to be used only by competent and trained individuals. EEG artifact can invalidate analyses and improper positioning of electrodes or significant deviations from accepted standards of electroencephalographic recording methodology can invalidate EEG recordings or erroneous storage of data and falsification of data, improper manipulation of data or unlawful uses of NeuroGuide including violations of copyright law and other improper uses of NeuroGuide are all contra indicated.

Predicate/legally marketed devices upon which substantial equivalence is based:

Cordis Brain State Analyzer (no FDA information available); TECA Corporation Neurolab I, II (K844481), Brain Mapper (K890-881), Neuromapper 386 (K894889); Nicolet BEAM I, II (no FDA 510(k) information available); Pathfinder II (K801604); Brain Functional Map (K843598); Cadwell Laboratories, Inc. 8400 (K860801) and Spectrum 32 (K860801 reference); Lexicor Medical Technology Neurosearch-24 (K904269), Neurosearch-4 (K920038); Neuroscience, Inc. Map-10 EEG (K840430), Neuromapper 1620 (K870263); Biologics Systems Corporation, Inc., Modified Brain Atlas III (K854362), Bio-Logic Automatic Event Analysis (K951594); Quantified Signal Imaging, Inc. QSI-9500 (K904294), QSI-9200 (FDA 510(k) information not available); Stellate Systems, Inc. Rhythm Software (K912938); NxLink, Inc. (K974748).

Substantially equivalent statement Comparison to Predicate Devices:

The NeuroGuide Analysis System uses substantially the same principles and methods as predicate devices such as NxLink K974748 for data selection and analysis to extract measures upon which statistical determination of normal/abnormal are made, and from which derivations of probability estimates of clinical classification are derived. The NeuroGuide Analysis System uses essentially identical power spectral analysis methods the Fast Fourier Transform (FFT) spectral analysis of the electroencephalogram (EEG) as do all predicate devices: **EEG Frequency Spectrum Analyzer Regulation Number 882.1420**. NAS uses the standard FFT technology which is as safe and effective as the predicate devices and does not raise different issues of safety or efficacy. The Neuroguide (NAS) method of EEG selection, analysis, and interpretation are substantially the same as predicate devices and these methods have been previously implemented, in whole or in part, in a variety of digital EEG and analysis systems marketed in prior years for the quantitative analysis of the EEG in Man. The NAS database was carefully constructed to control for potential sources of Type I and Type II errors in the use of database comparisons in clinical electrophysiological assessment of the human EEG. The NAS database and discriminant functions involve the same statistical methods of Gaussian distributions and multivariate statistics as in predicate devices. The development and cross-validations of the discriminant function and database have been published in peer reviewed scientific journals (see Appendix C). NAS uses the same principles and methods of predicate devices, but adds to these devices, increased efficiency and computer speed thereby improving the user's ability to statistically analyze the EEG.

Table 1. Comparison with Predicate NxLink (K974748)

ELEMENT	NEW DEVICE	PREDICATE - K974748
Intended use	Same as predicate	Same as new device
Inputs host digital EEG	Same as predicate	Same as new device
Frequency range	0.5 – 30 Hz	0.5 – 27 Hz
Spectral Analyses	FFT	FFT
Coherence analysis	Same as predicate	Same as new device
Phase delay analysis	Same as predicate	Same as new device
Amplitude asymmetry	Same as predicate	Same as new device
Ratios of power	Same as predicate	Same as new device
Multivariate statistics	Same as predicate	Same as new device
Topographic color maps	Same as predicate	Same as new device
Normative database	Sample size = 625, age 2 months to 82 years	Sample size = 470, age 6 years to 92 years
Gaussian Distributions	Same as predicate	Same as new device
Z scores	Same as predicate	Same as new device
Discriminant functions	Traumatic brain injury & learning disabilities	Traumatic brain injury, ADD, learning disabilities,

		depression
Reliability statistics	Split/half & test re-test	Test re-test only
Calibration	Sine waves, phase delays, noise simulation	Sine waves
Artifact free editing	Manual & template match	Manual
Save EEG data	ASCII, NeuroGuide & Lexicor format	NxLink format only
Print EEG selections	Same as predicate	Same as new device
Visual Display of EEG	Same as predicate	Same as new device
Neuropsychological correlations	Based on 466 subjects	None provided to user
Peak Frequency Analysis	By visual mouse navigation	By software analysis
Re-montage	Linked ears, Average Reference & Laplacian	Linked ears only
Operating System	Windows	DOS
Demo Software Available	Same as predicate	Same as new device
Safe and effective	Same as predicate	Same as new device
Peer reviewed publications	Yes	Yes
Speed of Computation	Faster than predicate	Slower than new device

1- Intended use – Clinical applications of the NeuroGuide Analysis system is to be used by qualified medical or clinical professionals for the post-hoc statistical evaluation of the human electroencephalogram (EEG). Same as predicate device **K974748**

2- Inputs host digital EEG - The NeuroGuide Analysis System is off-line stand alone software that can be loaded into a IBM PC and used without any physical connection to a patient or to a human subject the same as other predicate devices. EEG digital samples from a host system are used off-line to digitally analyze the EEG samples. The predicate device **K974748** is also OTS and stand alone software and users access stored EEG digital analyses in the same manner as the new device (NAS).

3 – Frequency Range – NAS analyses digital EEG over the frequency range from 0.5 Hz to 30 hz. The predicate device **K974748** analyzes over a similar frequency range but is limited in the high frequency range to 27 hz.

4 – Spectral Analysis Algorithm- Both the NeuroGuide analysis system and the predicate device **K974748** use the Fast Fourier Transform (FFT) algorithm to compute power spectra.

5- Spectral Analysis Measures- Both the NeuroGuide analysis system and the predicate device **K974748** use the same equations to compute absolute power, relative power, ratios of power, coherence, phase delays and amplitude asymmetry.

6- Multivariate Statistics- Both the NeuroGuide analysis system and the predicate device **K974748** use the same multivariate statistical equations (e.g., discriminant

functions, Mahalombis distance, multiple regression).

7- Normative Database - Both the NeuroGuide analysis system and the predicate device K974748 have compiled a reference normative sample of EEG data using accepted and published selection criteria of no history of neurological disorders, performing at grade level and normal range of intelligence and neuropsychological test performance. The NAS normative database (N = 625) spans the age range from 2 months to 82 years while the normative reference database of the predicate device K974748 spans the age range from 6 years to 92 years of age (N = 470).

8- Gaussian Distributions and Z scores- Both the NeuroGuide analysis system and the predicate device K974748 use transforms to approximate a normal or Gaussian distribution before computing any statistics. Both the NAS and the predicate device use accepted tests of Gaussian distributions and both have published the results of these tests. Z scores are computed by NAS and the predicate device K974748 using the same equation.

9- Discriminant Functions- Both the NeuroGuide analysis system and the predicate device K974748 use the same equations to compute discriminant functions. The NAS has only computed discriminant functions for comparative analyses of age matched normal subjects and traumatic brain injured patients as well as learning disabled children. The predicate device K974748 in addition to the above two discriminant functions, uses additional discriminant functions based on other clinical populations. The scientific principles and methods of discriminant analyses are the same independent of the number of sub-groups.

10- Reliability Statistics- Both the NeuroGuide analysis system and the predicate device K974748 use test re-test reliability statistics (i.e., the ratio of variance of the 1st half vs. the second half of the edited selections of EEG). The NAS also uses split-half reliability measures (i.e., the ratio of variance of even vs. odd seconds of edited EEG). NAS provides users with immediate feedback of the split/half and test re-test reliability in a window at the left side margin of the display screen so that the user is immediately provided with the reliability of the EEG selections.

11- Calibration- Both the NeuroGuide analysis system and the predicate device K974748 use sine waves of different amplitudes and different frequencies to calibrate the software. The NAS provides more extensive calibration routines including a general user interface (GUI) in which different phase delays and different ratios of signal to noise can be computed and EEG simulated using mouse clicks. The GUI in NAS facilities tests of the accuracy of the NAS and thus enhances the NAS level of safety and effectiveness in comparison to the predicate device K974748. The principles and mathematical methods are the same, but in comparison NAS takes advantage of the speed of computer processing to make these measures available immediately during the editing process itself.

12- Artifact Free editing- Both the NeuroGuide analysis system and the predicate device K974748 provide an easy to use display window by which users can manually delete

artifact and/or select artifact free segments of EEG. The NAS facilitates the selection of artifact free EEG by allowing users to select a template of artifact free EEG which is then used to match or mismatch the peak-to-peak amplitude of other segments of EEG and thus to select artifact free samples based on the best match to the artifact free template. The artifact selection features of NAS, especially when used with the immediate feedback by reliability statistics further enhances the safety and effectiveness of the NAS over the predicate device. In NAS tutorials the user is encouraged to compare different selections as well as comparing a selection of all of the EEG samples so that the extent of distortion due to artifact can be quickly known.

13- Save EEG data- The predicate device K974748 only exports EEG data in NxLink native format which can only be read by the predicate device and not by other software systems and other predicate devices. The NAS, in addition to exporting in native NeuroGuide format also saves EEG in the universal ASCII or text format which can be read by other software programs and a wide range of stand alone software such as Microsoft windows and Excel.

14- Print EEG selections- Both the NeuroGuide analysis system and the predicate device K974748 allow users to print EEG data for visual analysis.

15- Visual Display of EEG- Both the NeuroGuide analysis system and the predicate device K974748 provide users with a visual display of the digital EEG tracings so that users can scan the EEG data and identify artifact free segments of the EEG. The NeuroGuide analysis system facilitates the visual examination of EEG samples by taking advantage of the windows operating system by which users can use mouse clicks to scan through the EEG display while at the same time viewing the results of the FFT spectral analysis of the edited selections.

16 - Neuropsychological correlations- Both the NeuroGuide analysis system and the predicate device K974748 measured neuropsychological test performance when they acquired their respective normative databases. The predicate device does not provide users with predictive feedback based on the neuropsychological test scores, whereas the NAS does provide users with feedback. This feature is a further enhancement of the effectiveness of the NAS software in comparison to the predicate device.

17- Peak Frequency analysis- Both the NeuroGuide analysis system and the predicate device K974748 provide users with the ability to compute peak frequency for each of the channels of EEG. The users of NAS measure peak frequency by sliding the mouse over the FFT and then reading the values in $\mu\text{V}^2/\text{Hz}$ in 0.5 Hz resolution whereas the predicate device computes peak frequency in a given frequency band and displays these values in a table.

18- Re-Montage- The predicate device K974748 only provides for a single montage of a linked ears. The NAS extends the capability of scrutiny and analysis of the EEG by allowing users to create different montages by a mouse click to Average reference and Laplacian current source density. The average reference and the Laplacian are accepted

measures that enhance the effectiveness of NAS by helping users to eliminate artifact and to identify and select artifact free EEG samples.

19- Operating Systems - The predicate device K974748 uses the older Microsoft DOS operating system whereas the NAS uses the Microsoft Windows operating system. The use of the Windows operating system makes NAS more effective and enhances ease of use by implementing mouse clicks to navigate thru NAS menus and analysis features.

20- Demo Software Available- Both the predicate device K974748 and NAS provide demo software so that users can use stand alone software to learn how to use the respective analysis systems, to educate and to allow users to calibrate the software. The NeuroGuide Analysis System (NAS) includes demo software on a CD that were compiled using a Windows 98, 2000, ME and XP compatible operating systems. The NAS software program can also be downloaded from the internet as a demo software program that is without the ability to open any EEG data file, except the demo file. All of the calibration tests and analytical tests of NAS can be freely evaluated in the Demo. NAS has been thoroughly tested and does not crash or abruptly halt and allows users to save digital data and make back ups using the Window operating system, the same as other predicate devices.

Compared to its predicate devices, the NeuroGuide Analysis System's inclusion of specific, appropriate, reliable and effective statistical controls over the method of data selection and analysis, the scientific rigor involved in the construction, refinement, and application of the normative and clinical databases, and the potential for providing a practitioner with sensitive and specific quantitative indices of brain structure and function that is both safe and effective and suggests that the NAS is a significant advancement in the use of quantitative technology in neurology, psychiatry, and clinical neuropsychology and is an advancement over predicate EEG analysis systems. High speed testing of reliability and statistical measures of EEG is an advancement that NAS offers in comparison to predicate devices.

21- Safe and effective - The software is calibrated and standardized and is safe and effective. There is no direct connection between the software and any device that may be connected to a patient. The NAS OTS and/or stand alone software does not provide diagnoses and is used as an adjunct to other measures and the stand alone software is intended for use by qualified and competent medical or clinical professionals the same as other predicate devices. There is extensive calibration software and reliability measures to enhance effectiveness and to minimize errors.

22- Peer reviewed publications – The NeuroGuide Analysis System utilizes data and procedures that have been published numerous times over the last 25 years in peer reviewed scientific and clinical journals. The software technology of NAS is derived from accepted spectral analysis standards such as the FFT and CD analyses and has been supported by grants from the National Institutes of Health, National Science Foundation, USDA, Department of Defense, Veterans Administration and other government granting agencies. The content and number of peer reviewed publications in support of the

spectral analyses in NAS is substantially similar to the peer reviewed literature in support of other predicate devices. A bibliographic listing of publications and example publications are provided in the appendix.

23- Speed of computation speeds - The NeuroGuide Analysis System optimizes on modern computer hardware and software library calls that substantially improve the speed of computation in comparison to the predicate device.

Non-clinical Testing:

Non-clinical testing of the NAS is essentially equivalent to predicate devices such as NxLink (K974748) which included the evaluation of the algorithms and statistical methods used for data analysis. Specifically, control signals, in the form of signal generated waveforms, were analyzed for frequency and power- EEG signals were analyzed for conformity between the host digital EEG system and the NAS. The NAS includes a feature that reproduces sampling frequency in the host digital EEG system, and permits the visualization and evaluation of the EEG waveform for accuracy between the host system and the NAS translation. In addition, data obtained in previous implementations of the NeuroGuide analysis method were evaluated for consistency and accuracy -- the results of the NAS's analysis of stored subject data had to conform to that of the prior analysis (which was conducted using the same method and procedures, algorithms and method of analysis as that implemented on the NAS). The user of the NAS can verify the accuracy of the EEG spectral analyses by using built in calibration signals. Appendix-B is the manual and documentation for calibration of the NAS.

Clinical Testing:

The ability of the NAS to accurately translate and present EEGs from clinical patients was confirmed by the non-clinical testing. In order for the NAS to be an effective implementation of the neuroguide method for clinical use, the results of the analysis (both statistical tables and topographical brain maps) had to be in agreement with the results of the analysis conducted on the host system used in the processing of patient information at the Applied Neuroscience Laboratory. In addition, the outcome of the discriminant analysis had to be consistent, not resulting in errors of misclassification (that is, the classification on the NAS had to be consistent with that of the host system used to perform the NeuroGuide analysis at the ANL). These tests confirmed that when eyes-closed resting, and artifact-free EEG was selected for analysis, the results were reproducible within an acceptable degree of variation consistent with reliability estimates identified in the normative studies (see Appendix-C).

Subjects upon which this device has been tested included individuals which ranged in age from 2 months to 82 years, and who were either volunteers or clinical patients referred for neuroguide evaluation to the Applied Neuroscience Laboratory by the Department of Psychiatry University of Maryland School of Medicine, and/or Shock Trauma and the Applied Neuroscience Institute at the University of Maryland Eastern Shore. The results of the analysis were conveyed to the referring physician and/or Ph.D. clinician who was asked to use the information as an adjunct to their clinical interpretation of the patient's traditional EEG. The information was provided in report form (including EEG epochs selected for analysis, statistical tables and topographic brain maps, and the result of the discriminant analysis) to permit the physician or Ph.D. clinician to determine its relevance to their clinical evaluation and diagnosis or treatment of the patient. When the results are used in this manner, the likelihood of introducing error into diagnosis and treatment is substantially reduced. That is, the test is viewed as an adjunct to the evaluation of the patient, and does not serve as a primary basis for the diagnosis.

Potential adverse effects of the use of the device are known if the NeuroGuide Analysis System is used as the sole diagnostic system, a use that is specifically contraindicated by NAS in the absence of other clinical data from more traditional means of patient evaluation. Relying only upon the use of a single index (such as relative power, or the topographical maps alone) without reviewing the traditional EEG, the epochs selected for analysis, or the complete set of statistical summary tables is also contraindicated and a source of potential error. Additional sources of error could arise from the inappropriate selection of EEG (selecting artifactual EEG epochs, or selecting EEG representative of other states, such as drowsiness or eyes-open EEG when comparing to an eyes closed database, or by purposely selecting conditions for testing other than those specified. Additionally, it is possible that errors will occur through the purposeful falsification of symptoms in the patient history, and patient age.

Conclusions Drawn From Non-Clinical and Clinical Testing:

The NeuroGuide Analysis System's design and implementation was based upon the results of an extensive, 25-year effort to construct a viable normative and clinical database at the Applied Neuroscience Laboratory (ANL) at the University of Maryland. The NAS incorporates the basic methods of data collection, data selection, analysis, and interpretation developed at the ANL during the conduct of numerous government and privately funded normative and clinical database projects. The results of the use of the NAS to evaluate neurological and psychiatric disorders of the brain is published in numerous peer reviewed papers over this 25 year period.

The appropriate use of the NeuroGuide Analysis System as an adjunct to the traditional visually-appraised EEG provides the user with the ability to quantify EEG variables and use them to answer questions drawn from their clinical experience with the patient. When used by an experienced, qualified practitioner, or under the proper supervision of a qualified medical professional, the NAS is concluded to be a useful and beneficial addition to the array of clinically accepted medical tests and devices used to evaluate brain structure and function.

The results of non-clinical and clinical resting conducted over the past 20 years demonstrates that the NAS is both safe and effective for the quantitative analysis of the eyes-closed resting EEG in the alert human subject. Used to determine if the EEG is normal or abnormal, and if abnormal, to statistically characterize the distribution of selected derived features by their probability of being similarly distributed in specified groups of clinical patients, the NAS provides information that both complements and supplements the outcome of the analysis of a traditional EEG. This information, when properly used in conjunction with other clinical tests as a safe and effective adjunctive aid to diagnosis, treatment planning, and treatment follow-up of the neurologic and psychiatric patient.

FDA 510(k) Summary

Section 807.92

(a)(1). Submitter's Name: Applied Neuroscience, Inc., 228 176th Terrace Drive, St. Petersburg, FL 33708. Phone: (727) 392-7851; Fax: (727) 319-1027; email: rwthatcher@yahoo.com.

Contact Person: Robert W, Thatcher. Ph.D. Applied Neuroscience, Inc., 228 176th Terrace Drive, St. Petersburg, FL 33708. Phone: (727) 392-7851; Fax: (727) 319-1027; email: rwthatcher@yahoo.com.

Date of preparation: 5/9/2004

(a)(2). Name of the Device: NeuroGuide Analysis System (NAS). **Classification name:** EEG Frequency Spectrum Analyzer.

(a)(3). Predicate/legally marketed devices upon which substantial equivalence is based: Cordis Brain State Analyzer (no FDA information available); TECA Corporation Neurolab I, II (K844481), Brain Mapper (K890-881), Neuromapper 386 (K894889); Nicolet BEAM I, II (no FDA 510(k) information available); Pathfinder II (K801604); Brain Functional Map (K843598); Cadwell Laboratories, Inc. 8400 (K860801) and Spectrum 32 (K860801 reference); Lexicor Medical Technology Neurosearch-24 (K904269), Neurosearch-4 (K920038); Neuroscience, Inc. Map-10 EEG (K840430), Neuromapper 1620 (K870263); Biologics Systems Corporation, Inc., Modified Brain Atlas III (K854362), Bio-Logic Automatic Event Analysis (K951594); Quantified Signal Imaging, Inc. QSI-9500 (K904294), QSI-9200 (FDA 510(k) information not available); Stellate Systems, Inc. Rhythm Software (K912938); NxLink, Inc. (K974748).

(a)(4). Device Description: The NeuroGuide Analysis System (NAS) is a software program for the post-hoc statistical analysis of the human electroencephalogram (EEG). EEG recorded on a separate device (i.e., the host system) is transferred to the NAS for display and user-review. The system requires that the user select reliable samples of artifact-free, eyes-closed or eyes open, resting digital EEG for purposes of analysis. Analysis consists of the Fast-Fourier Transformation (FFT) of the data to extract the spectral power for each of the four primary frequency bands (delta, theta, alpha, and beta), and frequency information from the EEG. The results of this analysis are then subjected to univariate, bivariate, and multivariate statistical analyses and displayed in statistical tables and topographical brain maps of absolute and relative power, power asymmetry, and coherence for 19 monopolar and 171 selected bipolar derivations of the EEG. In all over 1,200 measures are derived for comparison against a carefully constructed and statistically controlled age-regressed, normative database in which the variables have been transformed and confirmed for their Gaussian distribution. Each variable extracted by the analysis is compared to the database using parametric statistical procedures that express the differences between the patient and an appropriate age-matched reference group in the form of Z-scores. Multivariate features are compared to the normative

database using Gaussian Univariate and Multivariate Distance Statistics. The Gaussian multivariate Distance statistic controls for the interrelationship of the measures of brain cortical function in the feature set, and provides an accurate estimate of their difference from normal. The multivariate measures permit an evaluation of regional indices of brain function that reflect the perfusion fields of the brain. Extracted feature sets are further analyzed to determine if the pattern of 'hits' (statistically significant feature score values identified for the patient) are consistent with patterns of 'hits' identified in prior neuroguide evaluations of clinical patients with known disorders. A step-wise discriminate analysis program classifies the patient in terms of their similarity to known neuroguide-defined patterns of abnormality, providing a probability estimate of the patient's profile with the average profile of groups of individuals constituting the normative and clinical database. The discriminant classification program is restricted by confining potential outcomes to specific patient symptoms derived from the patient history profile. Established discriminant functions were evaluated through the use of Receiver Operating Characteristic (ROC) curves for their sensitivity and specificity. The outcome of the statistical analysis is presented in report form that includes (a) patient demographic and history information, (b) selected EEG epochs, (c) statistical tables of monopolar, bipolar, and multivariate extracted feature values, and topographical brain maps. This information is to be read and interpreted within the context of the current clinical assessment of the patient by the attending physician/clinician. The decision to accept or reject the results of the neuroguide analysis, and incorporate these results into their clinical appraisal of the patient, is dependent upon the judgment of the attending physician or clinician.

The NeuroGuide Analysis System is complete on a single CD, which contains a demonstration program with sample NeuroGuide studies, the NAS program, and the print program. The NAS was designed for implementation under Windows, and programmed using C. The user interface was carefully designed and implemented to permit the program to be easy to use, highly reliable in its performance. A variety of control procedures are used to record stops used in program usage, and the conduct of the analysis to insure appropriate function end operation of the software. The NAS can be installed in any appropriately configured IBM-compatible computer system, including systems designed specifically for the recording of digital EEG. The system functions with a wide-range of standard computer platforms and input-output devices, and printers.

(a)(5). Statement of Indications of Use: Indications for the use of the NeuroGuide Analysis System (NAS) are as follows:

Indications of Use

The NeuroGuide Analysis system is to be used by qualified medical and qualified clinical professionals for the post-hoc statistical evaluation of the human electroencephalogram (EEG).

(a)(6). Comparison to Predicate Devices: The NeuroGuide Analysis System uses essentially the same accepted methods of data selection and analysis of predicate devices

to extract the feature measures upon which statistical determination of normal/abnormal are made, and from which derivations of probability estimates of clinical classification are derived. The neuroguide method of EEG selection, analysis, and interpretation have been previously implemented, in whole or in part, in a variety of digital EEG and analysis systems marketed in prior years for the quantitative analysis of the EEG in Man. The NAS database, the same as for predicate devices, was carefully constructed to control for potential sources of Type I and Type II errors in the use of database comparisons in clinical electrophysiological assessment of the human EEG. The purposeful, easy to use, and reliable design of the NAS has been enhanced relative to these earlier systems through the careful consideration of user interactions by optimizing on the speed of modern computer technology to facilitate user feedback and hypothesis testing with mouse clicks.

(b). Non-clinical and Clinical Tests: The NeuroGuide Analysis System's design and implementation was based upon the results of an extensive, 25-year effort to construct a viable normative and clinical database at the Applied Neuroscience Laboratory (ANL) at the University of Maryland. The NAS incorporates the basic methods of data collection, data selection, analysis, and interpretation developed at the ANL during the conduct of numerous government and privately funded normative and clinical database projects

(b)(1). Non-clinical Testing: Non-clinical testing of the NAS included the evaluation of the algorithms and statistical methods used for data analysis. Specifically, control signals, in the form of signal generated waveforms, were analyzed for frequency and power- EEG signals were analyzed for conformity between the host digital EEG system and the NAS. The NAS includes a feature that reproduces sampling frequency in the host digital EEG system, and permits the visualization and evaluation of the EEG waveform for accuracy between the host system and the NAS translation. In addition, data obtained in previous implementations of the NeuroGuide analysis method were evaluated for consistency and accuracy -- the results of the NAS's analysis of stored subject data had to conform to that of the prior analysis (which was conducted using the same method and procedures, algorithms and method of analysis as that implemented on the NAS).

(b)(2). Clinical Testing: The ability of the NAS to accurately translate and present EEGs from clinical patients was confirmed by the non-clinical testing. In order for the NAS to be an effective implementation of the neuroguide method for clinical use, the results of the analysis (both statistical tables and topographical brain maps) had to be in agreement with the results of the analysis conducted on the host system used in the processing of patient information at the Applied Neuroscience Laboratory. In addition, the outcome of the discriminant analysis had to be consistent, not resulting in errors of misclassification (that is, the classification on the NAS had to be consistent with that of the host system used to perform the NeuroGuide analysis at the ANL). These tests confirmed that when eyes-closed resting, and artifact-free EEG was selected for analysis, the results were reproducible within an acceptable degree of variation consistent with reliability estimates identified in the normative studies.

Subjects upon which this device has been tested included individuals which ranged in age

from 2 months to 82 years, and who were either volunteers or clinical patients referred for neuroguide evaluation to the Applied Neuroscience Laboratory by the Department of Psychiatry University of Maryland School of Medicine, and/or Shock Trauma and the Applied Neuroscience Institute at the University of Maryland Eastern Shore. The results of the analysis were conveyed to the referring physician or Ph.D. clinician who was asked to use the information as an adjunct to their clinical interpretation of the patient's traditional EEG. The information was provided in report form (including EEG epochs selected for analysis, statistical tables and topographic brain maps, and the result of the discriminant analysis) to permit the physician or Ph.D. clinician to determine its relevance to their clinical evaluation and diagnosis or treatment of the patient. When the results are used in this manner, the likelihood of introducing error into diagnosis and treatment is substantially reduced. That is, the test is viewed as an adjunct to the evaluation of the patient, and does not serve as a primary basis for the diagnosis.

Potential adverse effects of the use of the device are known if the NeuroGuide Analysis System is used as a stand-alone diagnostic system (a use that is specifically contraindicated by Applied Neuroscience, Inc. and the system's developers) in the absence of other clinical data from more traditional means of patient evaluation. Relying only upon the use of a single index (such as relative power, or the topographical maps alone) without reviewing the traditional EEG, the epochs selected for analysis, or the complete set of statistical summary tables is also contraindicated and a source of potential error. Additional sources of error could arise from the inappropriate selection of EEG (selecting artifacted EEG epochs, or selecting EEG representative of other states, such as drowsiness or eyes-open EEG when comparing to an eyes closed database, or by purposely selecting conditions for testing other than those specified. Additionally, it is possible that errors will occur through the purposeful falsification of symptoms in the patient history, and patient age.

(b)(3) Conclusions Drawn From Non-Clinical and Clinical Testing: The appropriate use of the NeuroGuide Analysis System as an adjunct to the traditional visually-appraised EEG provides the user with the ability to quantify EEG variables and use them to answer questions drawn from their clinical experience with the patient. When used by an experienced, qualified practitioner, or under the proper supervision of a qualified medical professional, the NAS is concluded to be a useful and beneficial addition to the array of clinically accepted medical tests and devices used to evaluate brain structure and function.

The results of non-clinical and clinical resting conducted over the past 25 years demonstrates that the NAS is both safe and effective for the quantitative analysis of the eyes-closed resting EEG in the alert human subject and to be used to help determine if the EEG is normal or abnormal, and if abnormal, to statistically characterize the distribution of selected derived features by their probability of being similarly distributed in specified groups of clinical patients, the NAS provides information that both complements and supplements the outcome of the analysis of a traditional EEG. This information, when properly used in conjunction with other clinical tests as a safe and effective adjunctive aid to diagnosis, treatment planning, and treatment follow-up of the neurologic and psychiatric patient.

Compared to its predicate devices, the NeuroGuide Analysis System's inclusion of specific, appropriate, reliable and effective statistical controls over the method of data selection and analysis, the scientific rigor involved in the construction, refinement, and application of the normative and clinical databases, and the potential for providing practitioner with sensitive and specific quantitative indices of brain structure and function that is both safe and effective and suggests that the NAS is a significant advancement in the use of quantitative technology in neurology, psychiatry, and clinical neuropsychology and is an advancement over predicate EEG analysis systems in terms of speed and ease of use.

PREMARKET NOTIFICATION

TRUTHFUL AND ACCURATE STATEMENT

[As required by 21 CFR 807.87(k)]

I certify that, in my capacity as president of Applied Neuroscience, Inc., I believe to the best of my knowledge, that all data and information submitted in the premarket notification are truthful and accurate and that no material fact has been omitted.

Robert W. Thatcher
(Signature)

Robert W. Thatcher
(Typed Name)

May 10, 2004
(Dated)

(Premarket Notification [510(k)] Number)

510(k) Checklist



CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

FDA Home Page | CDRH Home Page | Search | CDRH A-Z Index | Contact CDRH

SCREENING CHECKLIST FOR ALL PREMARKET NOTIFICATION [510(k)] SUBMISSIONS



510(k) Number: _____

The cover letter clearly identifies the type of 510(k) submission as (Check the appropriate box):

- Special 510(k) - Do Sections 1 and 2
- Abbreviated 510(k) - Do Sections 1, 3 and 4
- Traditional 510(k) or no identification provided - Do Sections 1 and 4

Section 1: Required Elements for All Types of 510(k) submissions:

	Present or Adequate	Missing or Inadequate
Cover letter, containing the elements listed on page 3-2 of the Premarket Notification [510] Manual.		
Table of Contents.		
Truthful and Accurate Statement.		
Device's Trade Name, Device's Classification Name and Establishment Registration Number.		
Device Classification Regulation Number and Regulatory Status (Class I, Class II, Class III or Unclassified).		
Proposed Labeling including the material listed on page 3-4 of the Premarket Notification [510] Manual.		
Statement of Indications for Use that is on a separate page in the premarket submission.		
Substantial Equivalence Comparison, including comparisons of the new device with the predicate in areas that are listed on page 3-4 of the Premarket Notification [510] Manual.		
510(k) Summary or 510(k) Statement.		
Description of the device (or modification of the device) including diagrams, engineering drawings, photographs or service manuals.		
Identification of legally marketed predicate device. *		

Compliance with performance standards. * [See Section 514 of the Act and 21 CFR 807.87 (d).]		
Class III Certification and Summary. **		
Financial Certification or Disclosure Statement for 510(k) notifications with a clinical study. * [See 21 CFR 807.87 (i)]		
510(k) Kit Certification ***		

- * - May not be applicable for Special 510(k)s.
- ** - Required for Class III devices, only.
- *** - See pages 3-12 and 3-13 in the Premarket Notification [510(k)] Manual and the Convenience Kits Interim Regulatory Guidance.

Section 2: Required Elements for a SPECIAL 510(k) submission:

	Present	Inadequate or Missing
Name and 510(k) number of the submitter's own, unmodified predicate device.		
A description of the modified device and a comparison to the sponsor's predicate device.		
A statement that the intended use(s) and indications of the modified device, as described in its labeling are the same as the intended uses and indications for the submitter's unmodified predicate device.		
Reviewer's confirmation that the modification has not altered the fundamental scientific technology of the submitter's predicate device.		
A Design Control Activities Summary that includes the following elements (a-c):		
a. Identification of Risk Analysis method(s) used to assess the impact of the modification on the device and its components, and the results of the analysis.		
b. Based on the Risk Analysis, an identification of the required verification and validation activities, including the methods or tests used and the acceptance criteria to be applied.		
c. A Declaration of Conformity with design controls that includes the following statements:		
A statement that, as required by the risk analysis, all verification and validation activities were performed by the designated individual(s) and the results of the activities demonstrated that the predetermined acceptance criteria were met. This statement is signed by the individual responsible for those particular activities.		
A statement that the manufacturing facility is in conformance with the design control procedure		

requirements as specified in 21 CFR 820.30 and the records are available for review. This statement is signed by the individual responsible for those particular activities.		
--	--	--

Section 3: Required Elements for an ABBREVIATED 510(k)* submission:

	Present	Inadequate or Missing
For a submission, which relies on a guidance document and/or special control(s), a summary report that describes how the guidance and/or special control(s) was used to address the risks associated with the particular device type. (If a manufacturer elects to use an alternate approach to address a particular risk, sufficient detail should be provided to justify that approach.)		
For a submission, which relies on a recognized standard, a declaration of conformity [For a listing of the required elements of a declaration of conformity, SEE Required Elements for a Declaration of Conformity to a Recognized Standard , which is posted with the 510(k) boilers on the H drive.]		
For a submission, which relies on a recognized standard without a declaration of conformity, a statement that the manufacturer intends to conform to a recognized standard and that supporting data will be available before marketing the device.		
For a submission, which relies on a non-recognized standard that has been historically accepted by FDA, a statement that the manufacturer intends to conform to a recognized standard and that supporting data will be available before marketing the device.		
For a submission, which relies on a non-recognized standard that has <u>not</u> been historically accepted by FDA, a statement that the manufacturer intends to conform to a recognized standard and that supporting data will be available before marketing the device <u>and</u> any additional information requested by the reviewer in order to determine substantial equivalence.		
Any additional information, which is not covered by the guidance document, special control, recognized standard and/or non-recognized standard, in order to determine substantial equivalence.		

* - When completing the review of an abbreviated 510(k), please fill out an Abbreviated Standards Data Form (located on the H drive) and list all the guidance documents, special controls, recognized standards and/or non-recognized standards, which were noted by the sponsor.

Section 4: Additional Requirements for ABBREVIATED and TRADITIONAL 510(k) submissions (If Applicable):

	Present	Inadequate or Missing

a) Biocompatibility data for all patient-contacting materials, OR certification of identical material/formulation:		
b) Sterilization and expiration dating information:		
i) sterilization process		
ii) validation method of sterilization process		
iii) SAL		
iv) packaging		
v) specify pyrogen free		
vi) ETO residues		
vii) radiation dose		
viii) Traditional Method or Non-Traditional Method		
c) Software Documentation:		

Items with checks in the "Present or Adequate" column do not require e additional information from the sponsor. Items with checks in the "Missing or Inadequate" column must be submitted before substantive review of the document.

Passed Screening Yes No
 Reviewer: _____
 Concurrence by Review Branch: _____

Date: _____

The deficiencies identified above represent the issues that we believe need to be resolved before our review of your 510(k) submission can be successfully completed. In developing the deficiencies, we carefully considered the statutory criteria as defined in Section 513(i) of the Federal Food, Drug, and Cosmetic Act for determining substantial equivalence of your device. We also considered the burden that may be incurred in your attempt to respond to the deficiencies. We believe that we have considered the least burdensome approach to resolving these issues. If, however, you believe that information is being requested that is not relevant to the regulatory decision or that there is a less burdensome way to resolve the issues, you should follow the procedures outlined in the "A Suggested Approach to Resolving Least Burdensome Issues" document. It is available on our Center web page at: <http://www.fda.gov/cdrh/modact/leastburdensome.html>

Uploaded on March 3, 2004

[CDRH Home Page](#) | [CDRH A-Z Index](#) | [Contact CDRH](#) | [Accessibility](#) | [Disclaimer](#)
[FDA Home Page](#) | [Search FDA Site](#) | [FDA A-Z Index](#) | [Contact FDA](#) | [HHS Home Page](#)

Center for Devices and Radiological Health / CDRH

CD Jacket Label

Appendix - A

Applied NeuroScience, Inc.

NeuroGuide 2.0



Copyright protected.
©2001 Applied NeuroScience, Inc.
All rights reserved.

EEG Editing and Analysis Software

*Featuring a Normative
Database, Discriminants & Statistics*

NeuroGuide – Manual

Appendix - A

NEUROGUIDE

MANUAL AND TUTORIAL

Copyright © 2002 - 2004 Applied Neuroscience, Inc.
(EEG segments were selected for illustrative purposes only)

TABLE OF CONTENTS

INTENDED USE

INSTALLATION INSTRUCTIONS

KEY A and KEY B to ACTIVATE NEUROGUIDE

SUPPORT AND UPGRADES

FORMATS SUPPORTED

Step #1 - Import EEG Demo file(s) and Enter Age of Subject

Step #2 - Scale and re-montage the EEG and visually scan the EEG for artifact, epoch length and the general status of the EEG.

Step #3 - Activate the Dynamic Normative FFT Databases and examine the raw EEG and power spectrum to identify Z scores ≥ 2.0 .

Step #4 - Automatic Artifact procedure to select "Good", "Reliable", artifact free and representative samples of EEG for quantitative analysis.

Step # 5 – Re-Montaging and Use of Average Reference and Laplacian Norms

Step # 6 - Save and Print EEG Selections

Step # 7 – Create And Label Any Montage (1 to 19 channels, Bipolar or Monopolar)

Step # 8 - Annotation Tool to Examine Peak-to-Peak EEG Amplitude

Step # 9 - Digital Filters

Step # 10 – Selecting Report Content

mk:@MSITStore:C:\Program%20Files\RoboHelp%20Office\RoboHTML\NEUROGUIDE\... 5/9/2004

Step # 11 – Screen Capture, Saving, Printing & Bit Map Export

Step # 12 – Import EEG in ASCII Format and/or EDF Format

Step # 13 - Save FFT Power Spectral Analyses in Tab Delimited Format

Step # 14 – Launch LORETA - Frequency Domain

14b - LORETA Raw Values

14e - LORETA Normative Database

Step # 15 – LORETA Export in ASCII Format for the Key Institute Programs

Step # 16 – Import to LORETA-Cross- Spectrum and LORETA Explorer

Appendix – A: Warnings - General

Appendix - B: Warnings about Lexicor EEG Exports

Appendix - C: Workshop EEG Examples

Appendix – D: ASCII Electrode Order and Spherical Coordinates for Use of the NeuroGuide Output Files with the Key Inst. LORETA Explorer

Appendix – E: University of Maryland Amplifier Characteristics

Appendix - F: LORETA Normative Reference Database Z scores

Appendix - G: Spectral Analysis Specifications

Appendix – H: References

Intended Use

For clinical purposes the NeuroGuide Analysis system is to be used by qualified medical or clinical professionals for the post-hoc statistical evaluation of the human electroencephalogram (EEG). For research and education NeuroGuide is intended to be used by competent and ethical students and professionals for the post-hoc statistical evaluation of the human electroencephalogram (EEG).

Installation Instructions

Copy all of the NeuroGuide program files to the same folder. To install NeuroGuide double click the setup.exe file. If you have installed an earlier version then uninstall will run first and one must double click setup.exe a second time to initiate the installation. Click Start > All Programs > NeuroGuide to launch NeuroGuide. We advise that one always use the default directory of c:/program files for the installation directory. If you shift installation to a different directory

mk:@MSITStore:C:\Program%20Files\RoboHelp%20Office\RoboHTML\NEUROGUIDE\... 5/2/2004

after receiving a Key B based on the initial directory then your initial Key B will no longer work. If this happens, please contact us by phone or at qeeg@appliedneuroscience.com.

Key A and Key B to Activate NeuroGuide

The first time that NeuroGuide is launched a copyright agreement appears. Click yes to accept the terms of the agreement, otherwise the program will terminate.

The next window is a NeuroGuide Security Key window that contains a Key A.

Once you pay for NeuroGuide then a Key B will be issued that will unlock the full power of NeuroGuide including the ability to import EEG files. The Key B uses the computer ID numbers that are unique to the single computer and single user license that you register your software. A second but renewable license will be issued to individuals who have a laptop at work and/or a desktop computer at home, etc. It is important to note that a single user's license is all that is allowed and separate licenses must be purchased if users other than the single user intends to use the software (see copyright license agreement which is saved on your computer when you launch NeuroGuide). Demo mode is activated by clicking the CANCEL button. In the Demo mode the user is still bound by the terms of the single user copyright agreement, however, users are limited to using the exemplar files inside of NeuroGuide and demo users will not be able to import their own data.

Support and Upgrades

Support is free for one year and you may contact us via phone or email at qeeg@appliedneuroscience.com. We are constantly updating the program with new features, bug fixes, and new EEG file formats. One year of free upgrades from the date of first purchase is included with each purchase of NeuroGuide. In the future we plan to implement a subscription service which begins at the end of one year and provides service and upgrades beyond the one year period. Your Key B will work with all upgrades of NeuroGuide until we implement the subscription service and maintenance. You will be invited to join the NeuroGuide users group at yahoo.com where open discussion is encouraged and new upgrades are announced. Once you purchase NeuroGuide please join this group and check for the release of new updates of NeuroGuide.

Formats Supported

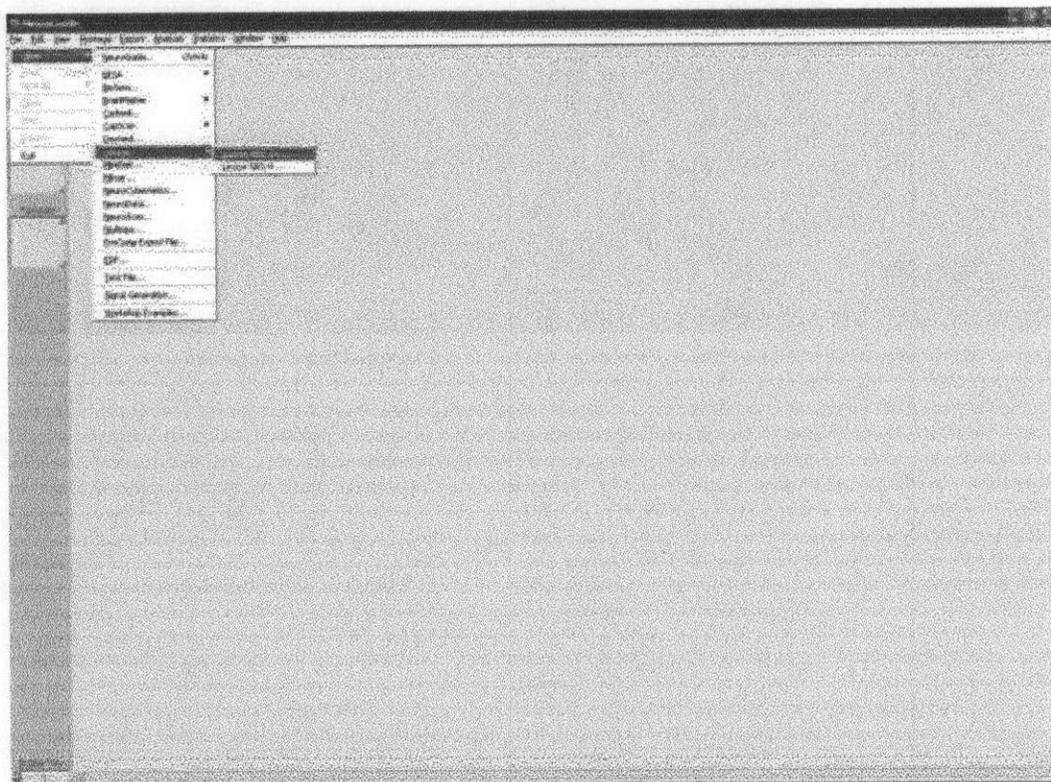
New file formats and features are constantly being added to NeuroGuide. See the [Universal file format hyperlink below](#) and visit our web site at www.appliedneuroscience.com for the most up-to-date list of supported formats.

To equate the amplifier characteristics of different EEG machines to the amplifier characteristics of the normative reference database mivorvolt calibration sine waves are input into the different EEG machines and equilibrated to the amplifier characteristics of the normative amplifiers. The Universal physics metric of the EEG is then the Volt defined as joules/coulomb.

year old patient with a history of traumatic brain injury.

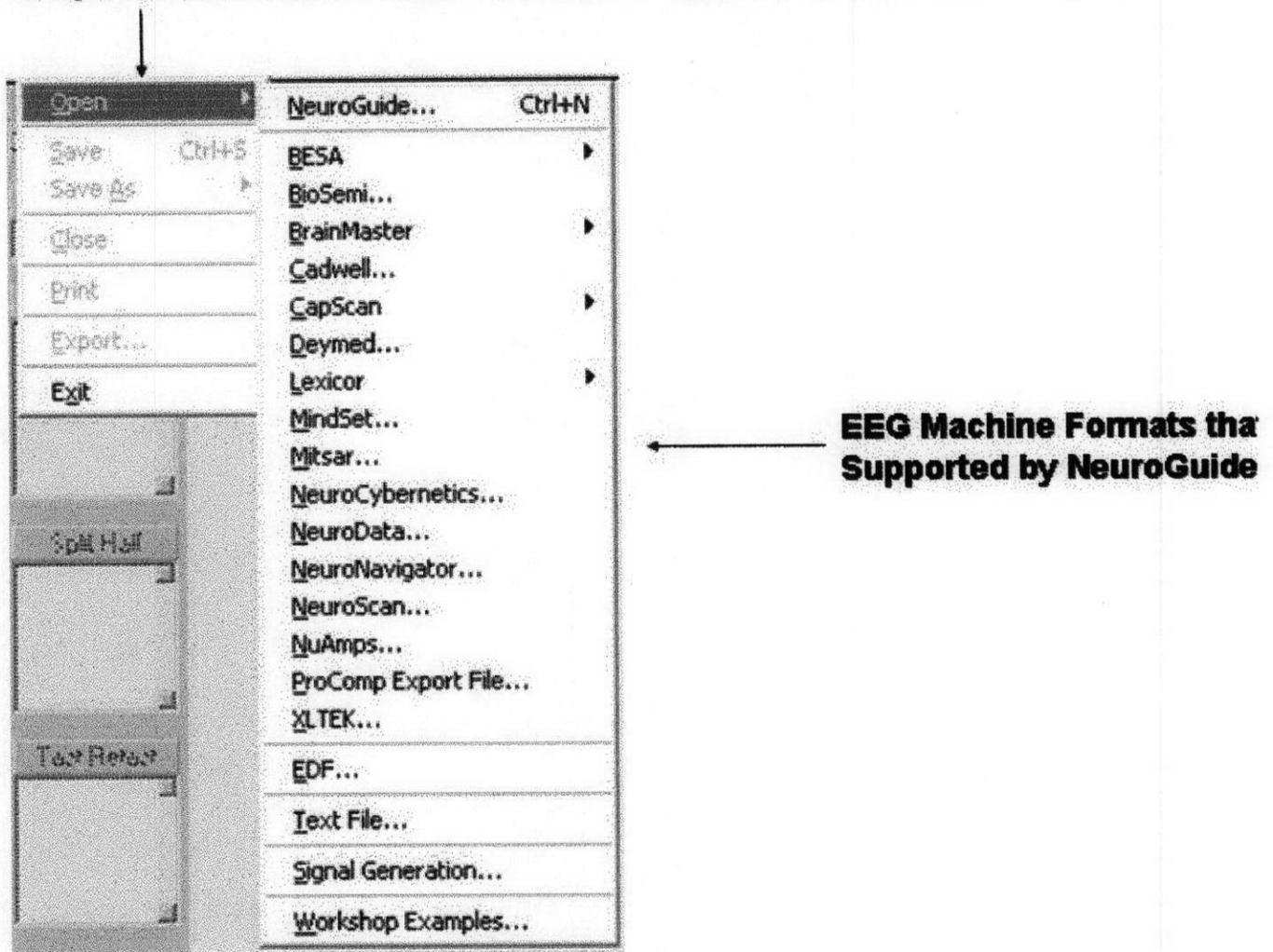
[Return to Top](#)

1a- Click File > Open > Lexicor > Lexicor NRS24 from the Menu bar (Demo example)



Universal file format such as ASCII and EDF and EEG Machine formats (Native Formats) are available in the non-Demo mode

Import Different EEG Formats by clicking File > Open



1b- Access to NeuroGuide age dependent norms requires specifying an age. This can be done by simply typing an age in the Age row or by typing in the date of birth and the date of EEG test. Also, type in full subject information including comments.

Subject Information

Name	Joe TBI
Date of Birth	11/20/1985
Age	18.00
Gender	Male
Handedness	Right

EEG ID	Demo1
Date of Test	11/20/2003
Technician	Mr. Competent

Doctor	Dr. Competent
Medication	None

Comments	Electrode impedences were < 5K, patient was alert and rested. No drowsiness was noted.
----------	--

OK Cancel

1c- For demonstration purposes one can just type in a given age, e.g., 18 years

The screenshot shows a 'Subject Information' dialog box with the following fields and values:

- Name: [Empty]
- Date of Birth: [Empty]
- Age: 18.00
- Gender: [Empty]
- Handedness: [Empty]
- EEG ID: Demo1
- Date of Test: [Empty]
- Technician: [Empty]
- Doctor: [Empty]
- Medication: [Empty]
- Comments: [Large empty text area]

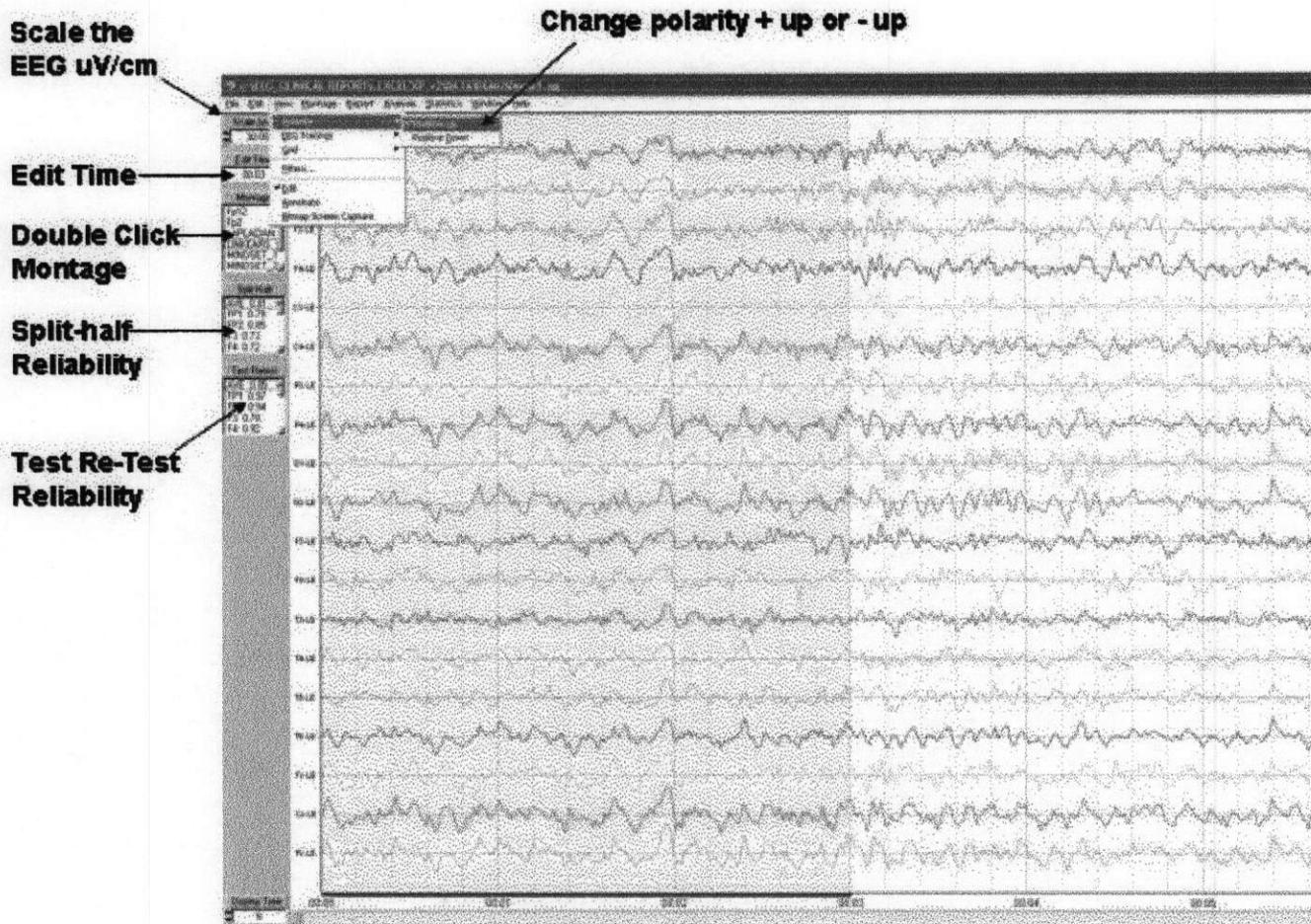
Buttons: OK, Cancel

Step #2 is to Scale and Visually Scan and re-montage the EEG and to further visually scan the EEG for artifact, epoch length and the general status of the EEG.

[Return to Top](#)

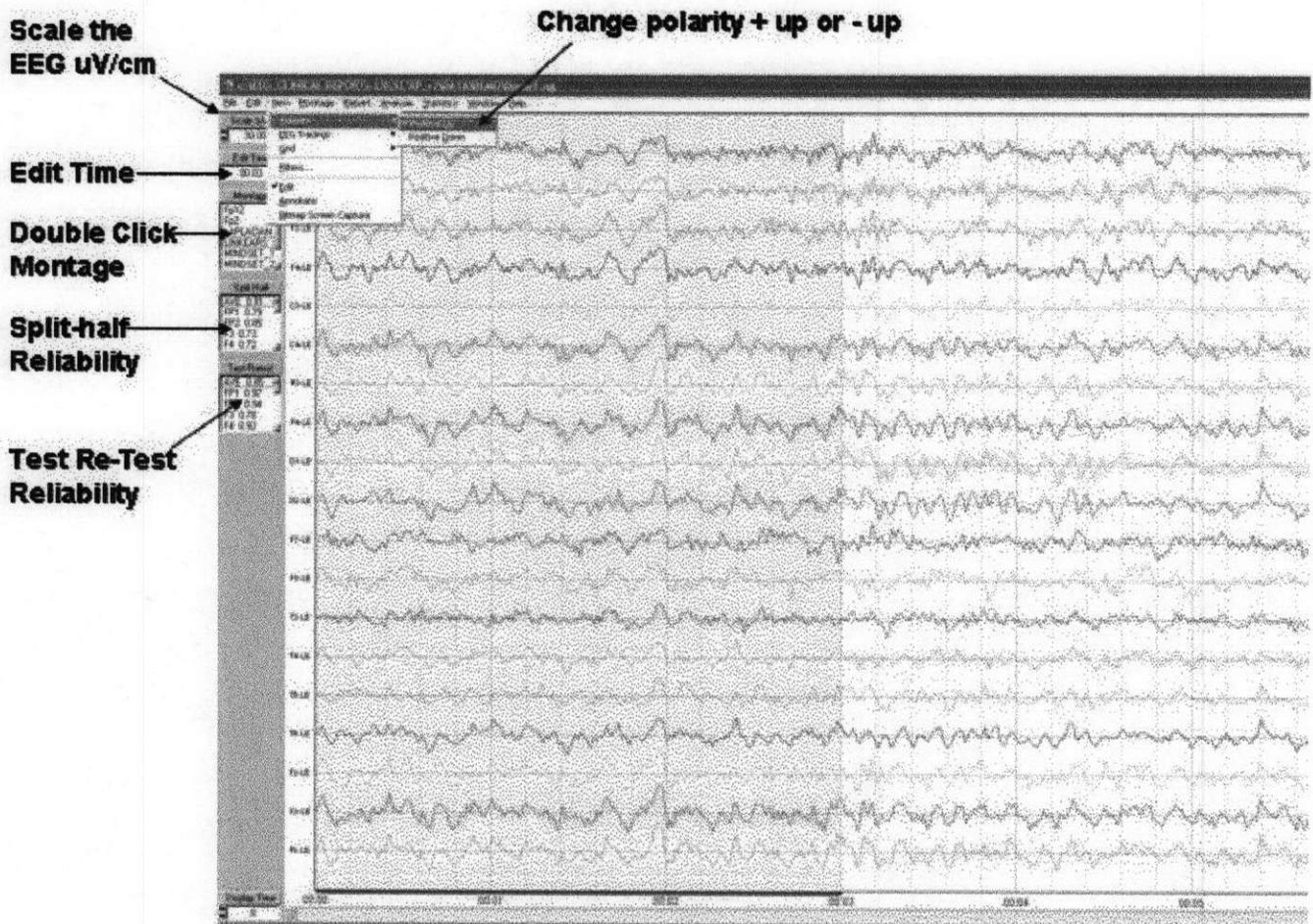
2a – Default Screen Contains Linked Ears Reference Digital EEG and 6/sec vertical grid lines and Polarity = positive up. Click on View and change polarity or eliminate grids.

Scale the EEG tracings in uV/cm and view the length of EEG selections in seconds and view dynamic Reliability measures of the EEG selections

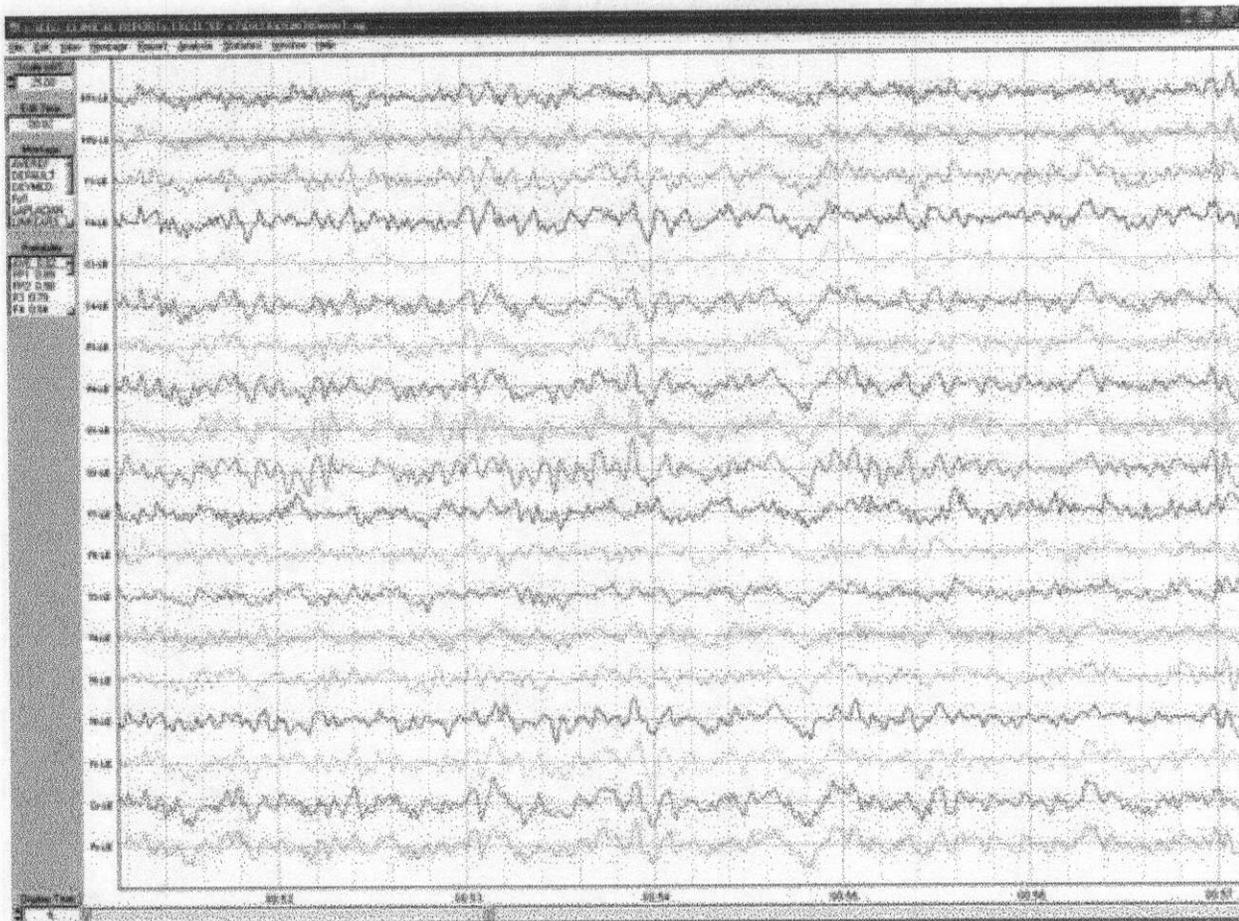


2b – Manual Edit Selection - press left mouse button and drag to select, press right mouse button and drag to erase. As a tutorial Select 1st four seconds of EEG by pressing left mouse button and sliding it. To experiment De-select by pressing the right mouse button and holding over the selected area. Highlight Edit and Select “Clear All”, then re-select 1st 4 seconds.

Scale the EEG tracings in uV/cm and view the length of EEG selections in seconds and view dynamic Reliability measures of the EEG selections

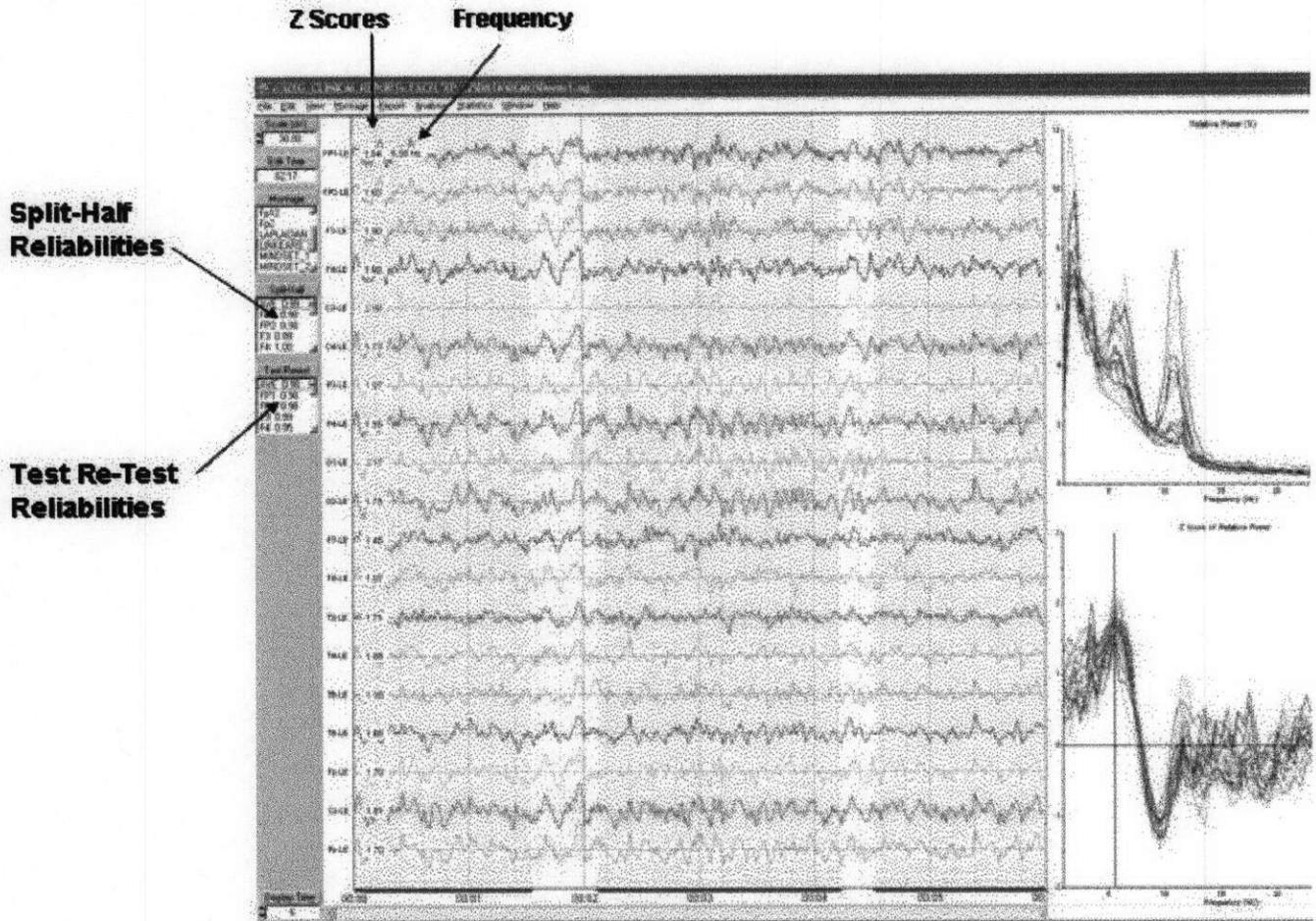


2c- Scan the EEG record by clicking the left mouse button and scanning across the EEG. Move the wiper at the bottom and/or page & arrow keys and home and End Keys. Press Home to move to the beginning and End to move to the end of the of the Digital Record. Experiment using the arrow keys and the page keys and the home and end keys and by dragging the left and right mouse buttons.



2d- Split-Half reliability is the ratio of variance between the even and odd seconds of the time series of selected digital EEG (variance = sum of the square of the deviation of each time point from the mean of the time points). Examine the average reliability and the reliability of each channel as you increase the length of the sample and manually select different segments. Selection of artifact free EEG should have a reliability > 0.95 and a sample length of edited EEG > 60 seconds.

Dynamic Reliability Measures of Edited Selections. Compare Split-Half (even vs. odd 1 sec segments) to Test Re-Test (1st half vs. 2nd half EEG vari...



2e- Test re-test reliability is the ratio of variance between the first half vs. the second half of the selected EEG segments (variance = sum of the square of the deviation of each time point from the mean of the time points). Test re-test reliability > 0.90 and a sample length of edited EEG > 60 seconds is commonly published in the scientific literature. Test re-test reliability is an excellent statistic to compare Brain state changes such as drowsiness as well as the consistency of a measure independent of changes in brain state.

[Return to Top](#)

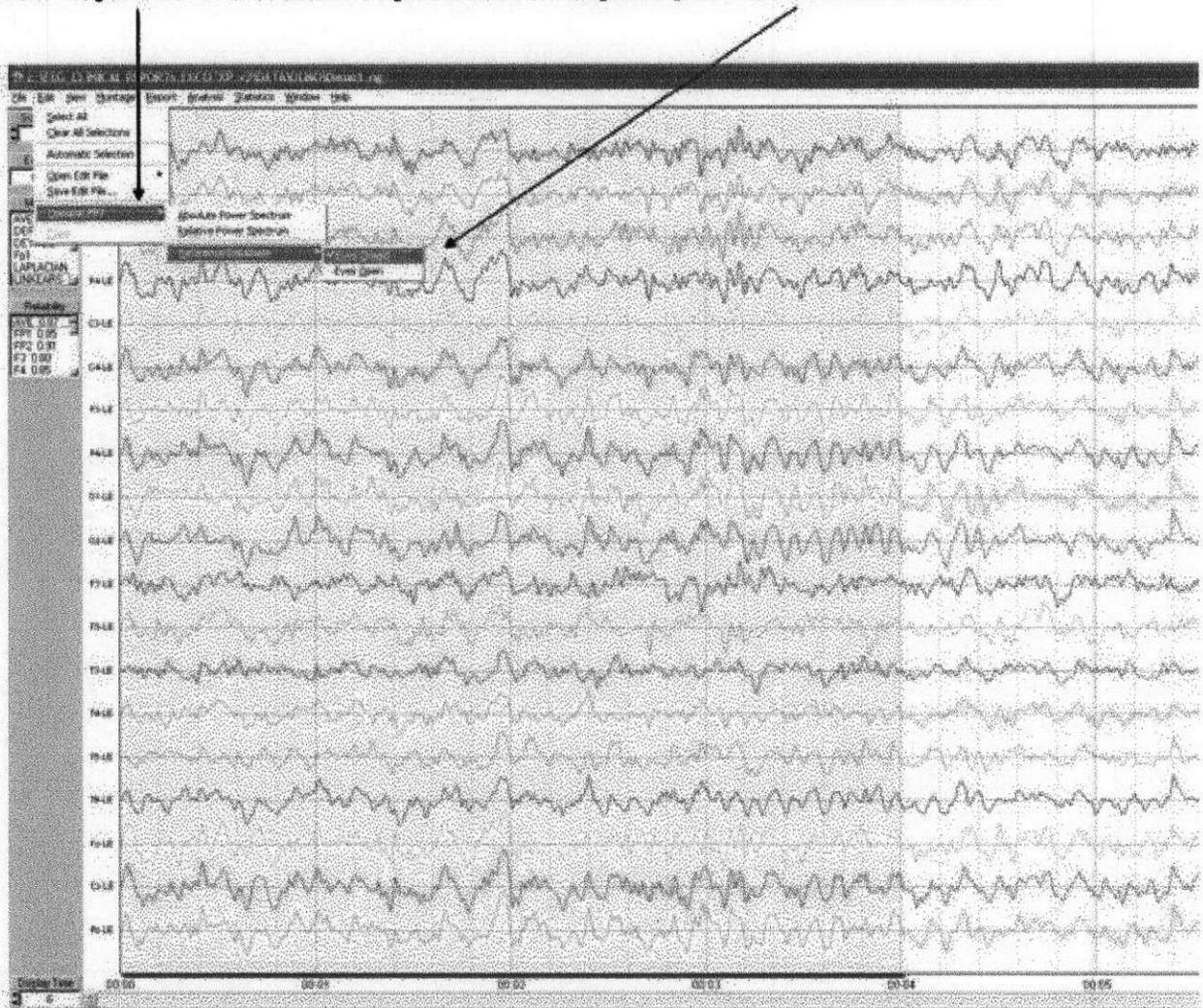
Step # 3 - Activate the Dynamic Normative FFT Databases and examine the raw EEG and normalized power spectrum to identify Z scores ≥ 2.0 and to compare the > 2 SD deviant Z frequencies and EEG channels using the

Average Reference and Laplacian norms and linked ears norms.

Return to Top

3a- Click Edit > Dynamic FFT > Reference Database > Eyes Closed. Release the mouse and repeat the sequence of clicking Edit > Dynamic FFT > Relative Power. This will display the FFT absolute or relative power values in the upper right quadrant and the Z scores in the lower right quadrant. First try relative power eyes closed, then eyes open, then absolute power, etc. Clicks of the mouse allow for quickly repeating multiple mouse clicks for 2 or 3 times for each option and watch the screen change.

Click Edit > Dynamic FFT to Select Eyes Closed or Eyes Open Normative Database

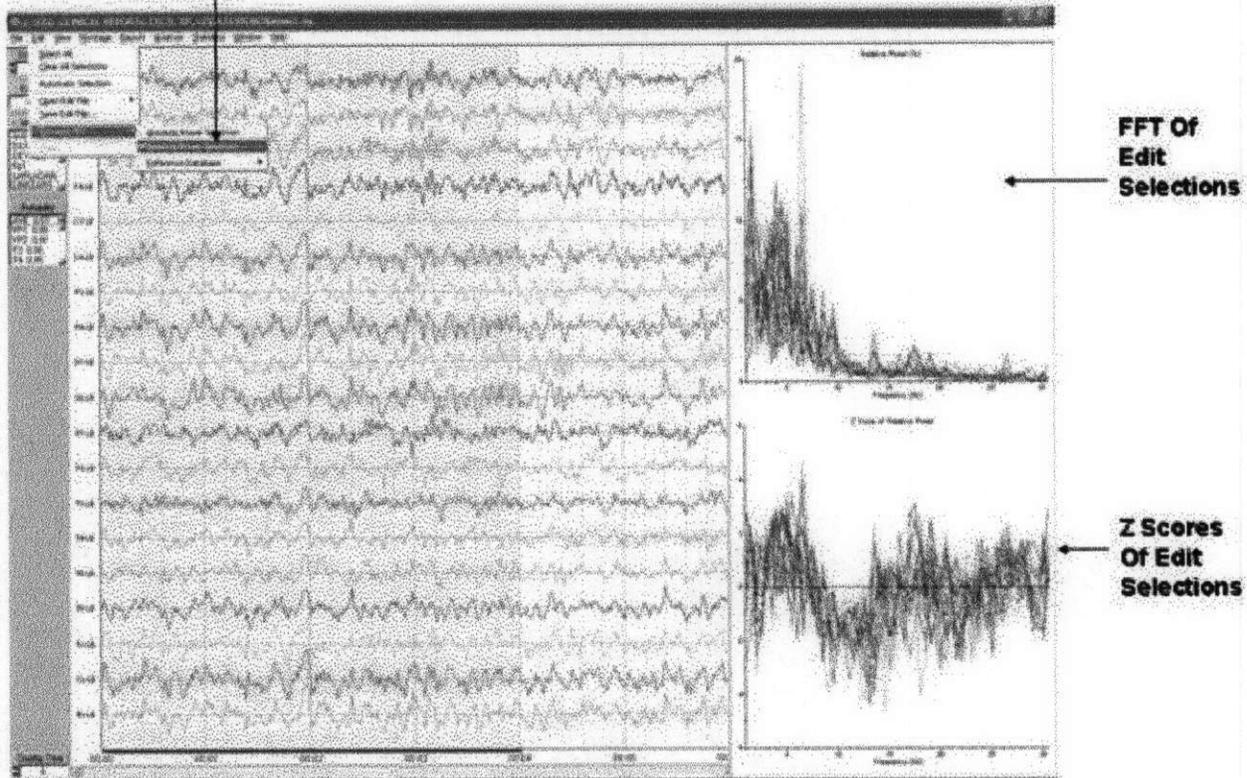


3b – Click Edit > Dynamic FFT > Relative Power and Release Mouse. Average Reliability for all channels is in the Reliability Window on the left margin of the edit screen as well as reliability per channel. Scan through the reliability of different channels. As defined in 2d Split-half reliability is the ratio of the variance of the even 1

mk:@MSITStore:C:\Program%20Files\RoboHelp%20Office\RoboHTML\NEUROGUIDE\... 5/2/2004

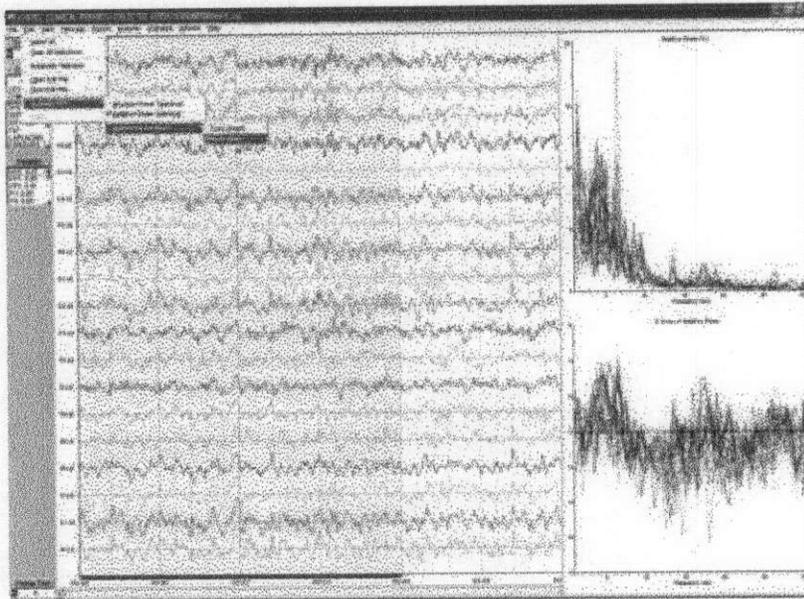
second samples of EEG digital samples divided by the odd 1 second segments of the EEG edited selection. The split-half reliability value 0.86 is low because it represents only 4 seconds of EEG.

Click Edit > Dynamic FFT > Relative Power

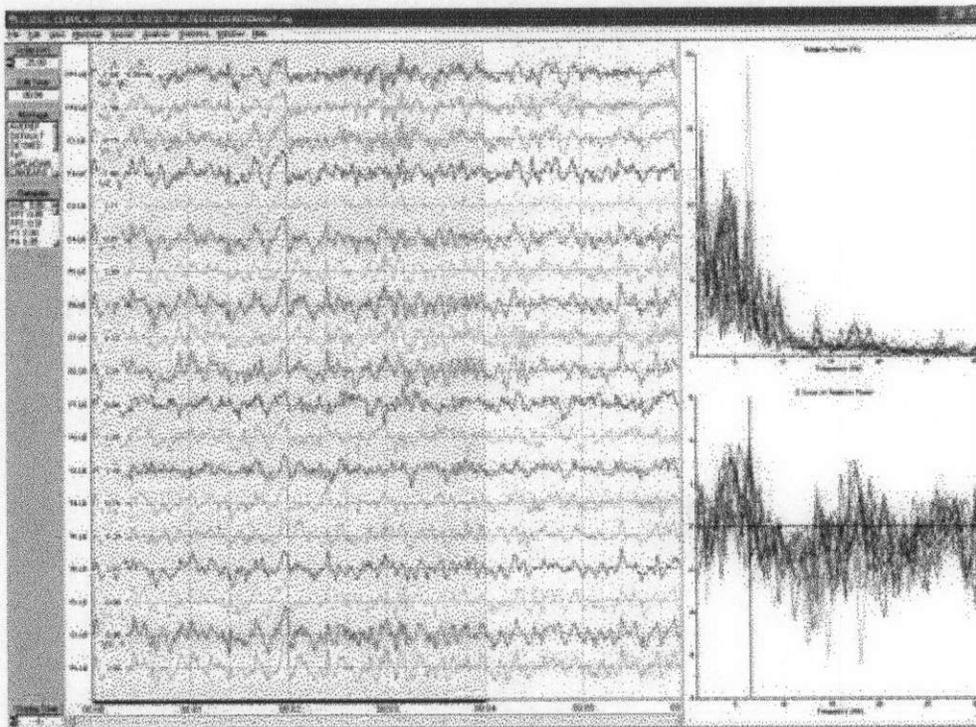


As explained in Step 2e, Higher moment to moment variability is related to a decrease in the split-half reliability and state change variability is more related to a decrease in the test re-test reliability.

3b- Example of how to change normative databases to eyes open



3c- Click & move the left mouse button over the Z Score of Relative Power and read the frequency and Z scores on the left of the EEG display. Note Frequency of 6.59 Hz & the Red Z Scores at P3, O1, Pz & T3.



Step # 4 - Manual Edit select by left mouse button and de-select by right mouse button. Use the Automatic Artifact procedure to

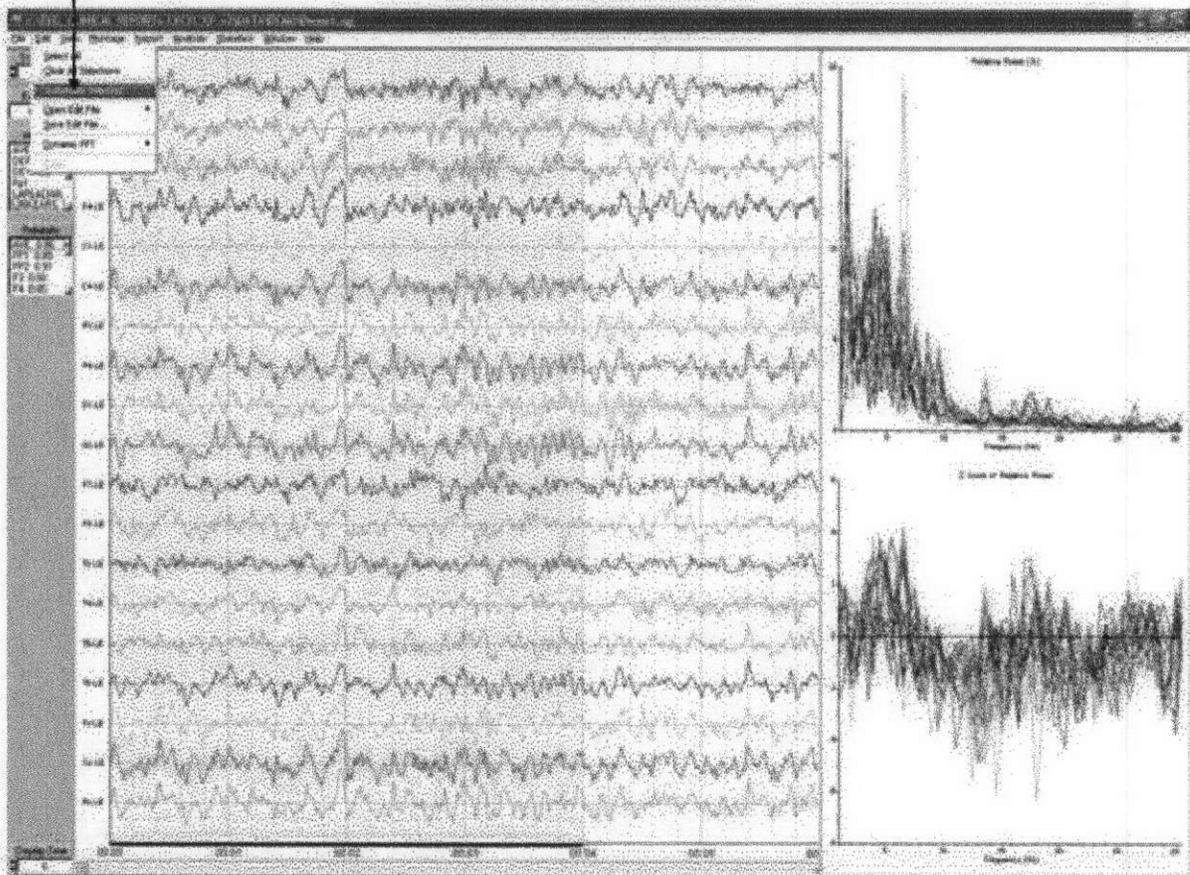
mk:@MSITStore:C:\Program%20Files\RoboHelp%20Office\RoboHTML\NEUROGUIDE\... 5/2/2004

select “Good” & “Reliable” artifact free and representative samples of EEG as a template for quantitative analysis.

[Return to Top](#)

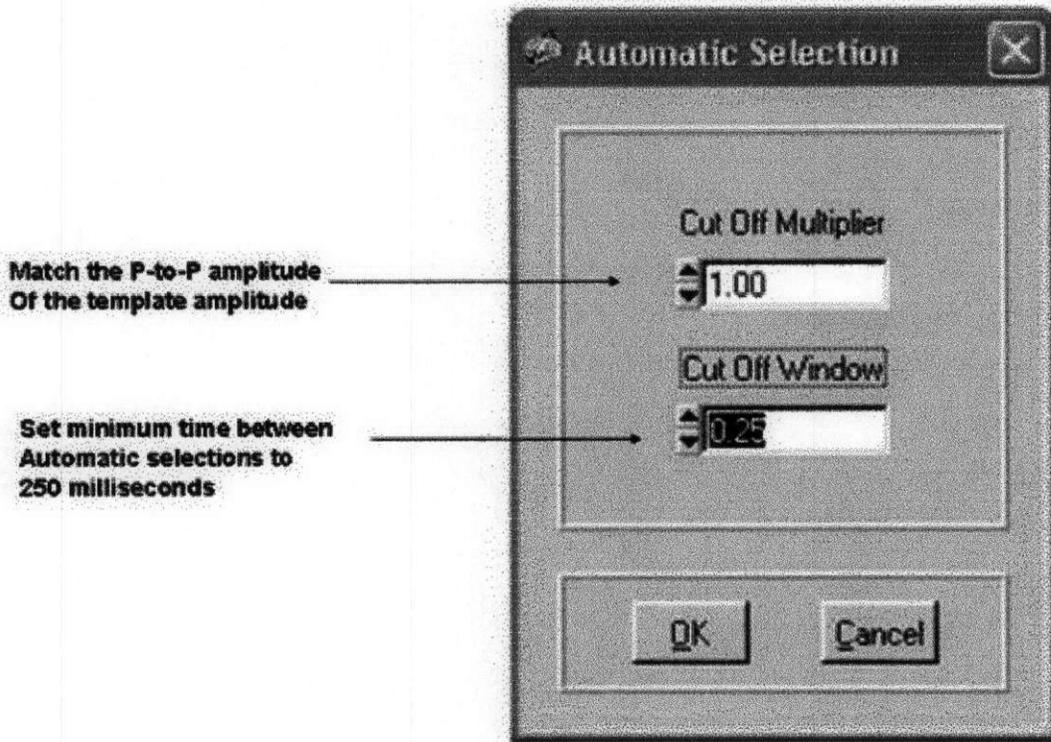
4a- For automatic template selections Click Edit > Automatic Selection. We will use the 1st 2 seconds of selected EEG as a template of “Good” EEG, this is only for illustration and to note that the first 2 seconds is generally not a good period to select from. To test the reliability and validity of your template selections use a different template by clicking Edit > Clear All Selections and then select a different template using the left mouse button and repeat Edit > Automatic Selection. De-select using the right mouse button. A “good” EEG sample is split-half reliability $\geq .95$ and Edit Time ≥ 60 seconds.

Click Edit > Automatic Selection in order to use a Artifact Free Template to Select Additional EEG

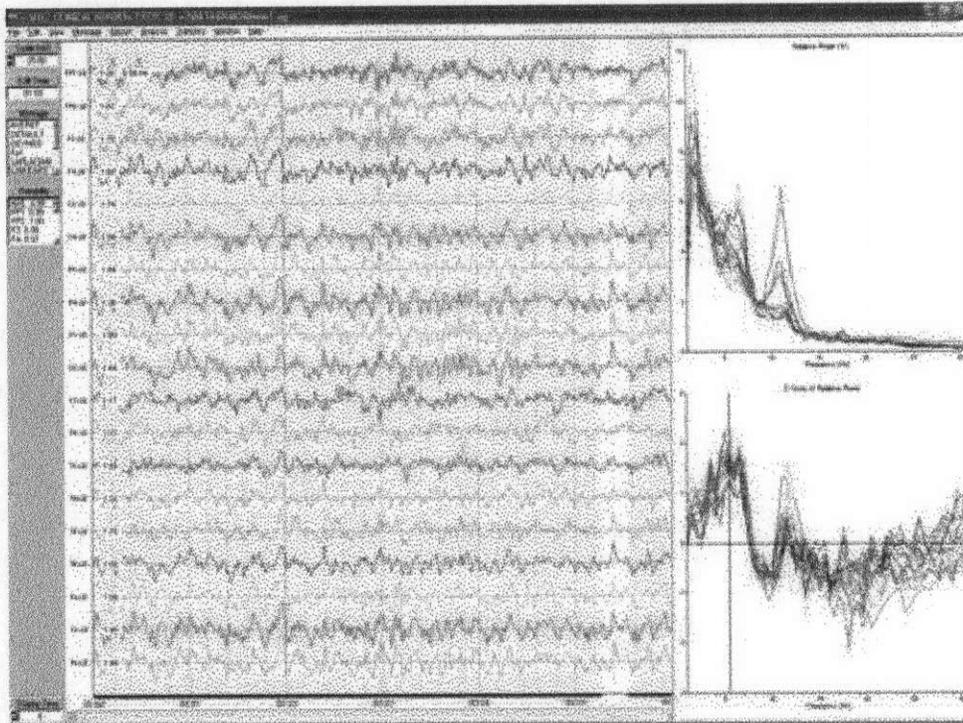


4b- The Default multiplier is 1.0. Click O.K. and the FFT and Z scores of the edited selections will be displayed. Cut Off Multiplier = 1.0 is a RMS amplitude match for each 2 seconds of EEG that are equal to or less than the RMS amplitude of the user selected EEG template.

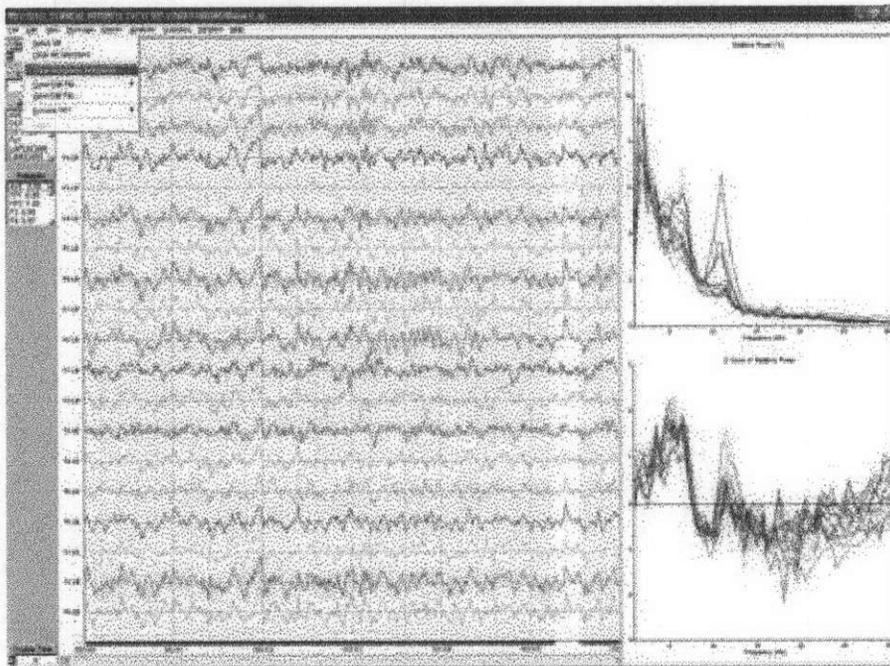
mk:@MSITStore:C:\Program%20Files\RoboHelp%20Office\RoboHTML\NEUROGUIDE\... 5/2/2004

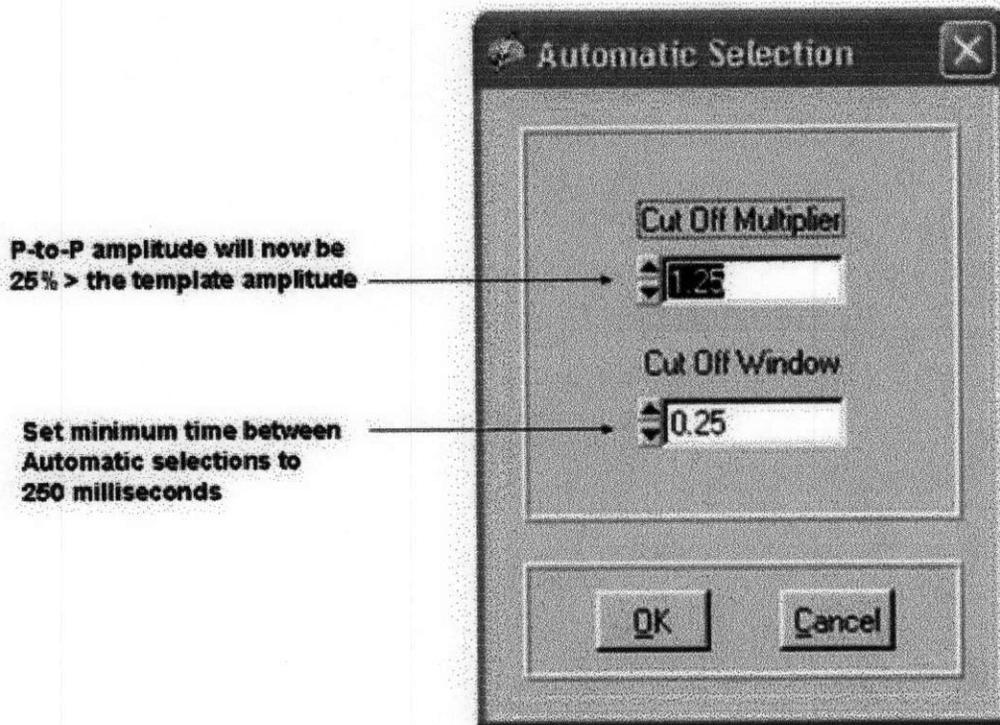


4c - Edit time is now 1 min. & 59 seconds and Reliability is improved. Visually Re-scan the EEG to de-select segments that may have artifact and to select Good and representative EEG segments that may have been omitted.



4d- To change the template selection of “Good” EEG, highlight “Clear Automatic Selections” and then repeat the automatic selection process by clicking Edit > Automatic Selections. To change the Cut-Off highlight “Clear Automatic Selections” and repeat steps 4a and 4b.

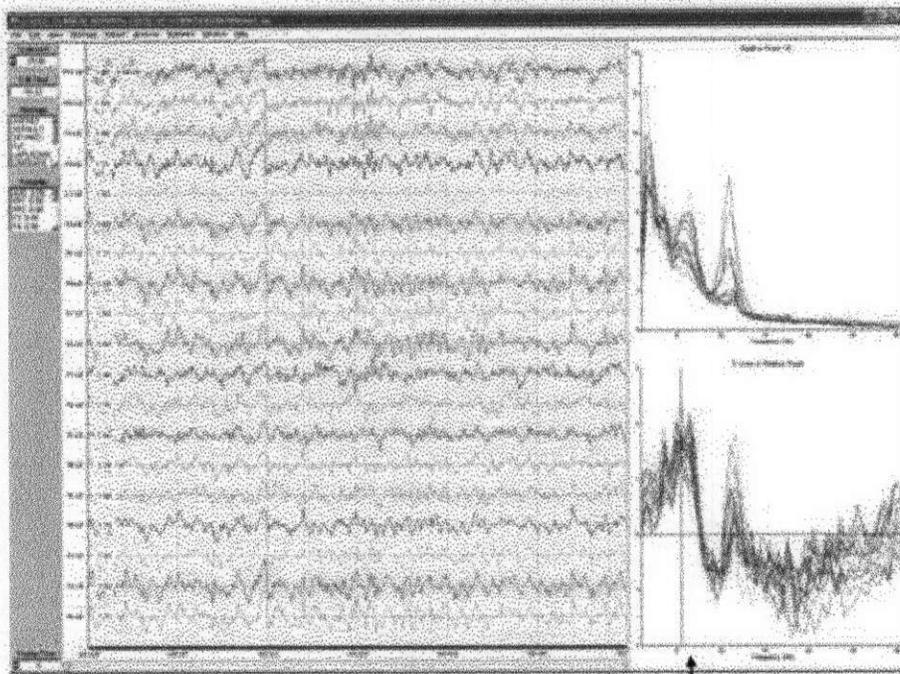




The Cut Off Multiplier determines the amplitude of match to the "Good EEG" template. When the cut off multiplier = 1.25 then the match will be 25% larger peak-to-peak amplitude than the template amplitude, if it is 1.5 then the match will be 50% larger amplitude than the template. The Cut Off Window is the delay between automatic selections. A value of 0.25 = 250 millisecond minimum gap between automatic selections and a value of 0.5 = 500 millisecond minimum gap between automatic selections, etc.

4e- Click O.K. using the 1.25 Multiplier Cut-Off and see a larger sample of EEG of 2:22 minutes and Reliability Increased. Note that the EEG Spectrum and Z Scores did not change much. Scroll through the EEG Selections as an Expert would and look for Epileptic discharges and other possible abnormal features of the EEG that may have been excluded. Change to 1.5, 1.75, etc. to test reliability and then click Edit. Save your selections by clicking Edit > Save Edit File, e.g., Template-nonartifact 30 seconds or Template-nonartifact 2min or Template-All EEG without any artifact rejection.

Compare these three artifact free files to the compare the Z scores and the Dynamic FFT to different selections in order to understand the influence of your selections may or may not have upon the Z scores and FFT. Finally, click Edit > Select All (the worse case scenario in which artifact is not excluded). Conclusion: High Theta (5 Hz – 7 Hz) and Low Beta (15 – 25 Hz) are pervasive and representative of the artifact free EEG.



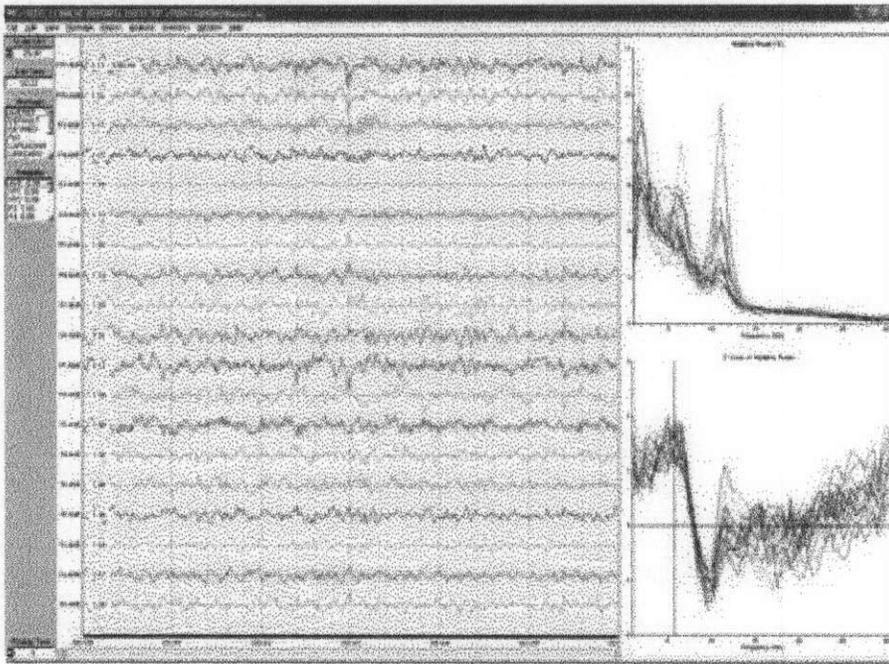
Press left mouse button and Drag
Over Z scores and frequencies

Press the left mouse button and scan the Z scores while observing the Z score values at the left margin of the EEG tracings for the different frequencies of the spectrum

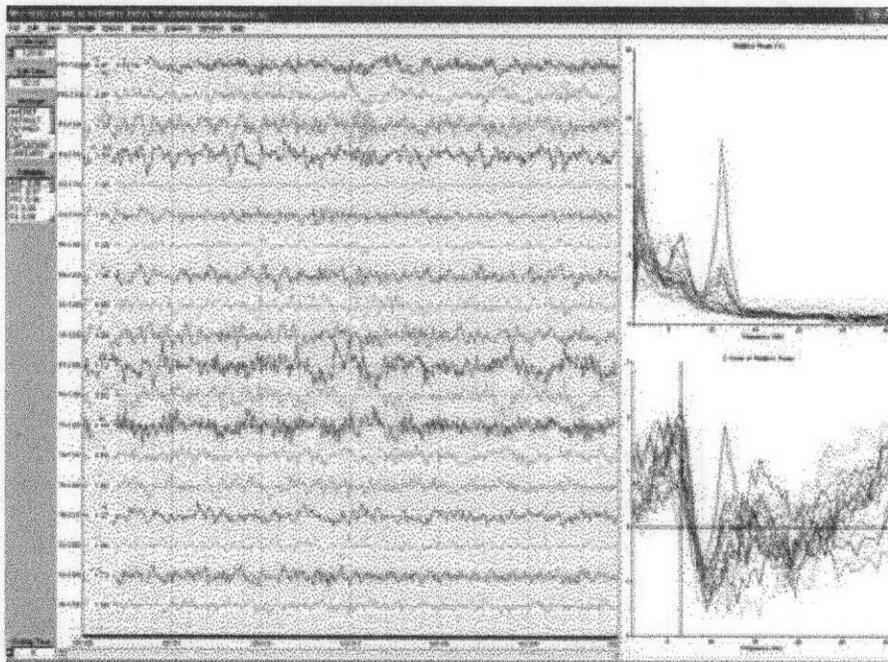
Step # 5 – Re-Montaging and Use of Linked Ears, Average Reference and Laplacian Norms

[Return to Top](#)

5a- Double click on the Average Reference Montage or use the Tab & Arrow keys. The corresponding Z scores will be displayed in the lower right Z Score window. Scan the Z scores and compare to the Linked Ears montage.



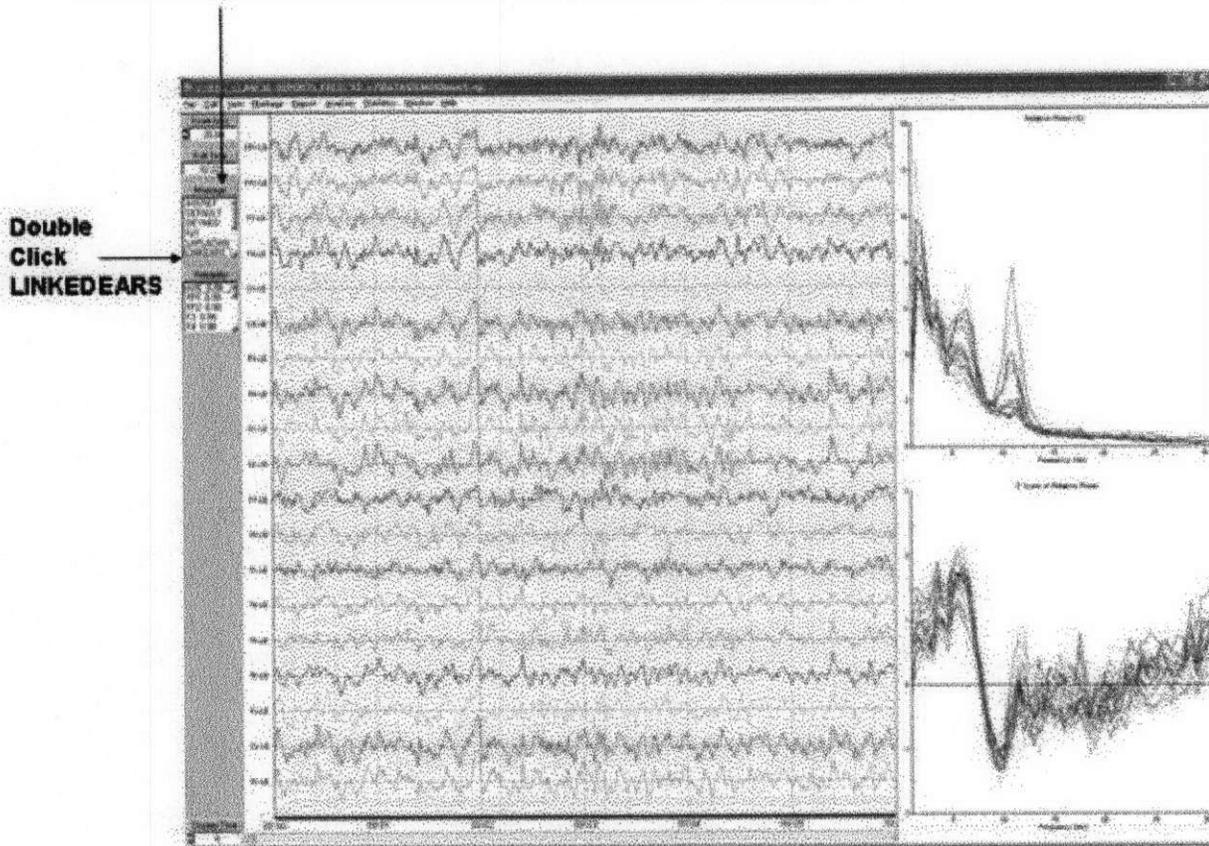
5b - Double click on the Laplacian Reference Montage or use the Tab & Arrow keys. The corresponding Z scores will be displayed in the lower right Z Score window. Hold the left mouse button and scan the Theta peak at 5 Hz to 6.5 Hz and make a written note of the Red Z scores and frequencies in the left margin of the EEG tracings.



Note that the scale is in microamperes because the Laplacian is an estimate of the current flowing at right angles through the skull (Nunez, 1981; 1994; Pasqual-Marqui et al, 1988).

Step # 5c – Linked Ears Reference Montage Revisited - Double click on LINKEARS Montage & Re-Examine Theta and make notes as to which Locations show Red Z scores (i.e., > 1.96 SD). With linked ears reference the significant Z scores are more diffuse.

Double Click in the Montage Window to Change the Montage

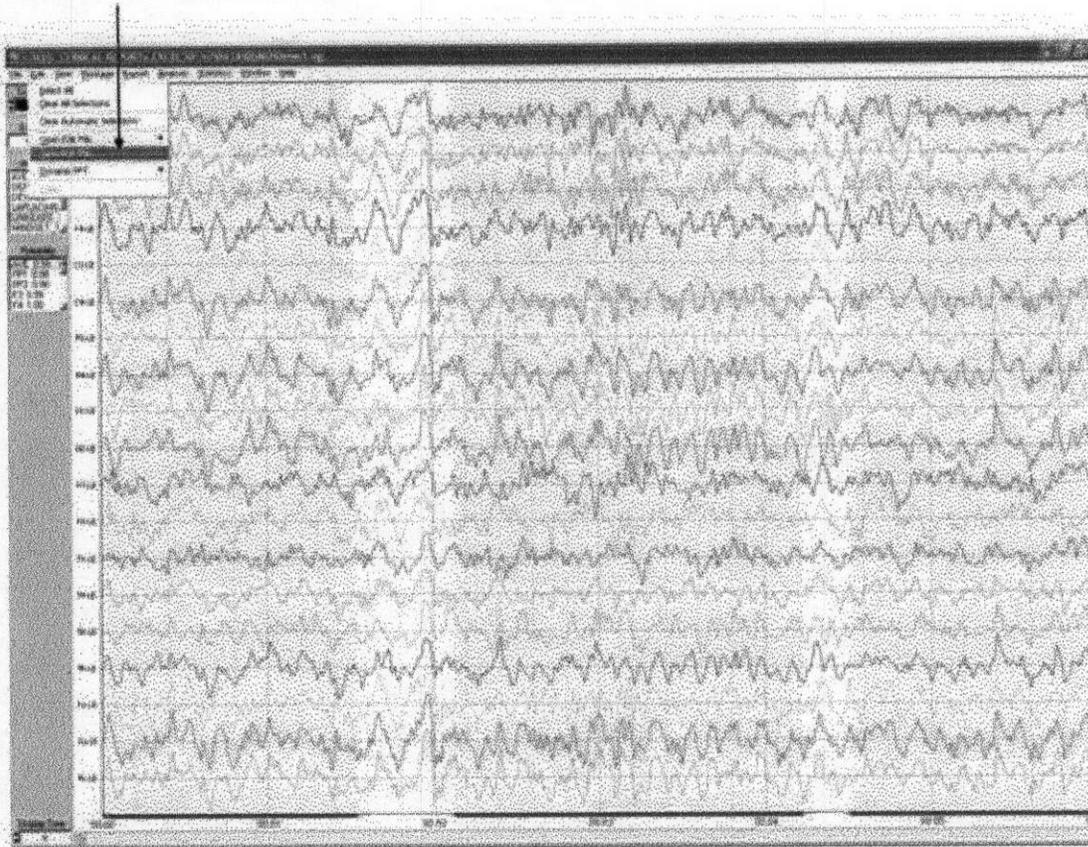


Step # 6 - Save and Print EEG Selections

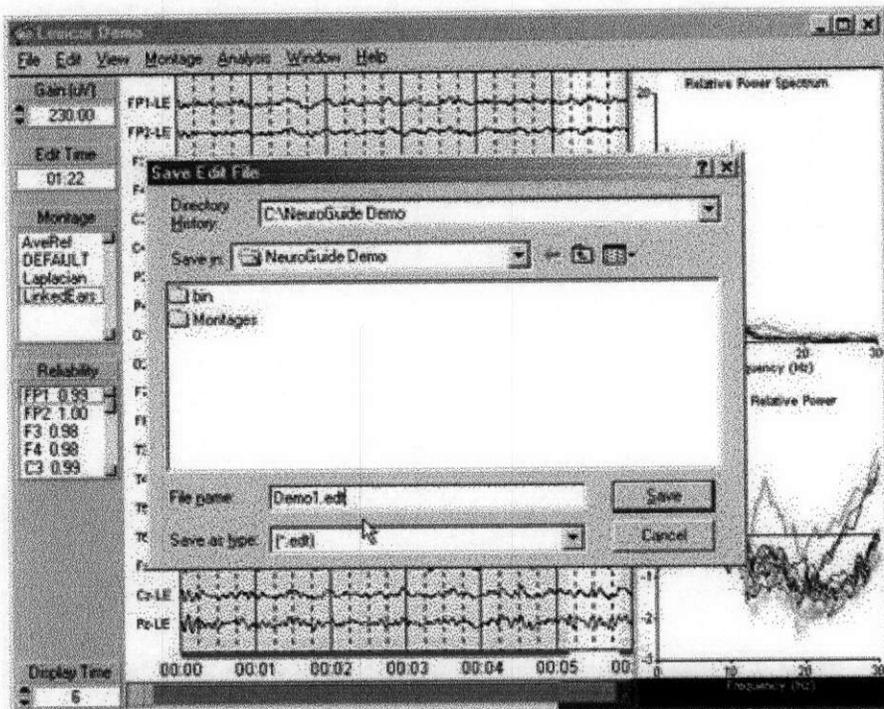
Return to Top

6a - Save the final edit selections that will be used in the QEEG analyses by highlighting "Save. If you want to only print a specific page, save the edits, then clear all selections and select the single page that you want to print.

Click Edit > Save Edit File to Save Only the Edit Selections

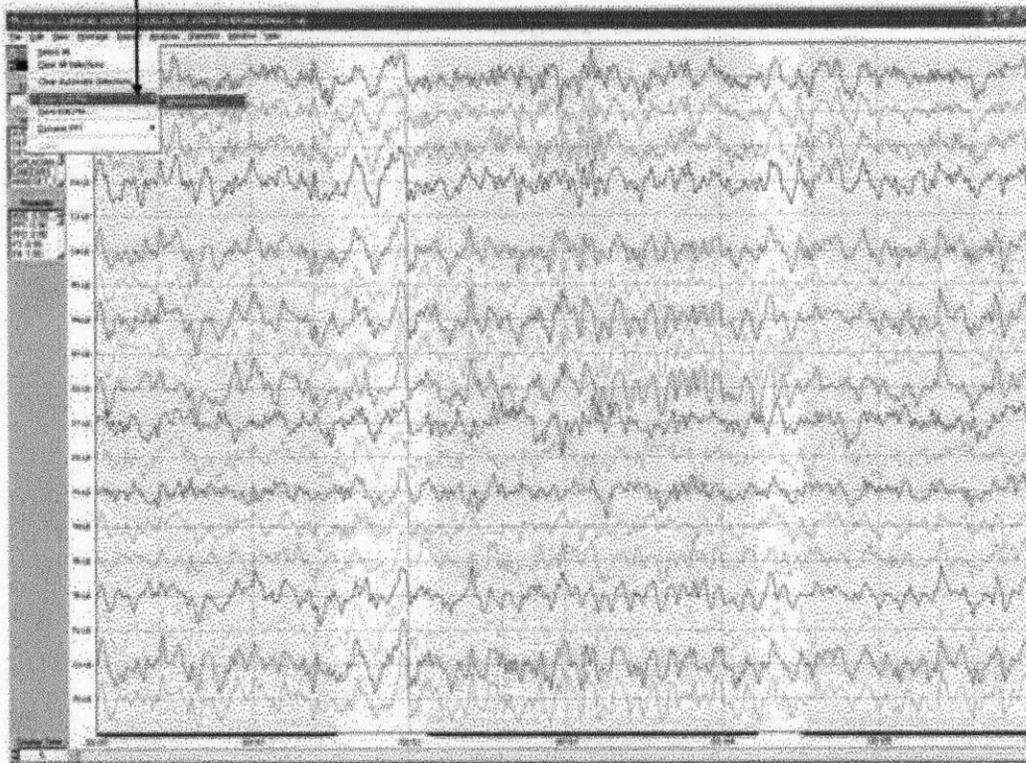


6b – Save in a Directory using the *.edt extension



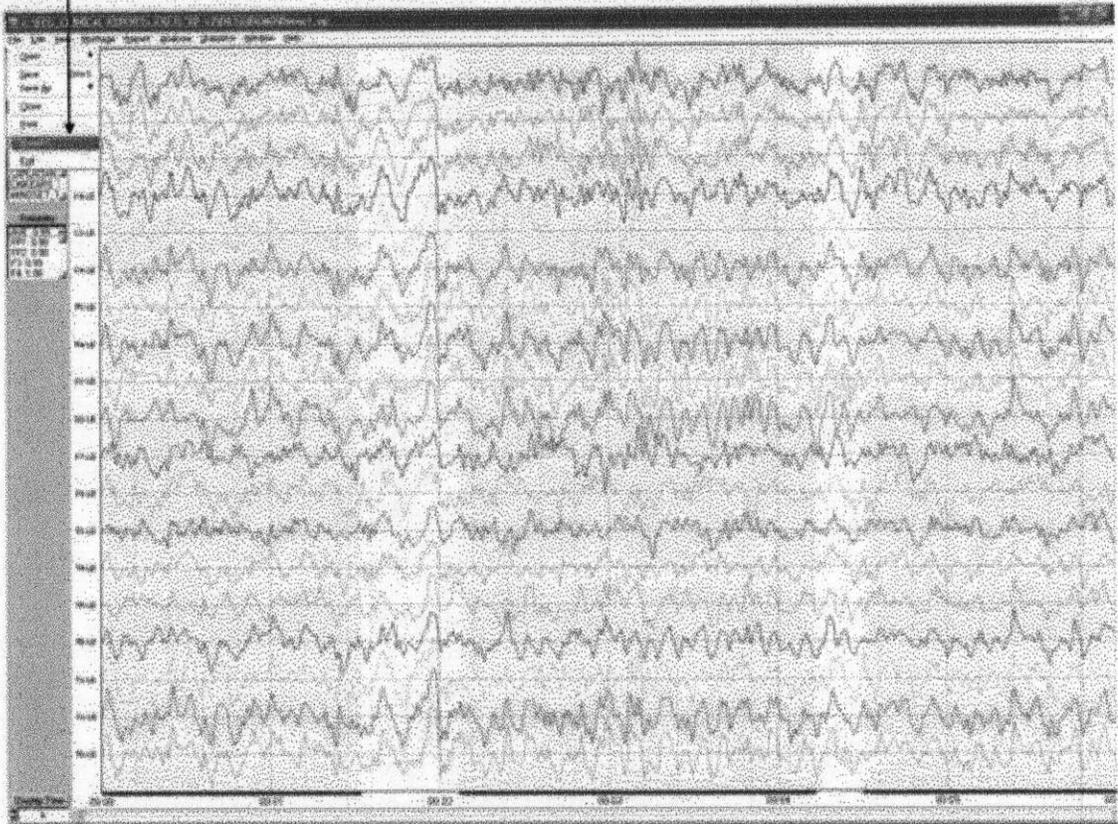
6c – After importing a digital EEG file to open Edit Selections for that file Click Edit > Open Edit File > NeuroGuide and navigate to the location where the edits were saved. This only opens the Edit Selections for a Given EEG data file and an EEG file must be imported first.

Click Edit > Open Edit File > NeuroGuide to Open Edit Selections for a Given EEG Data File



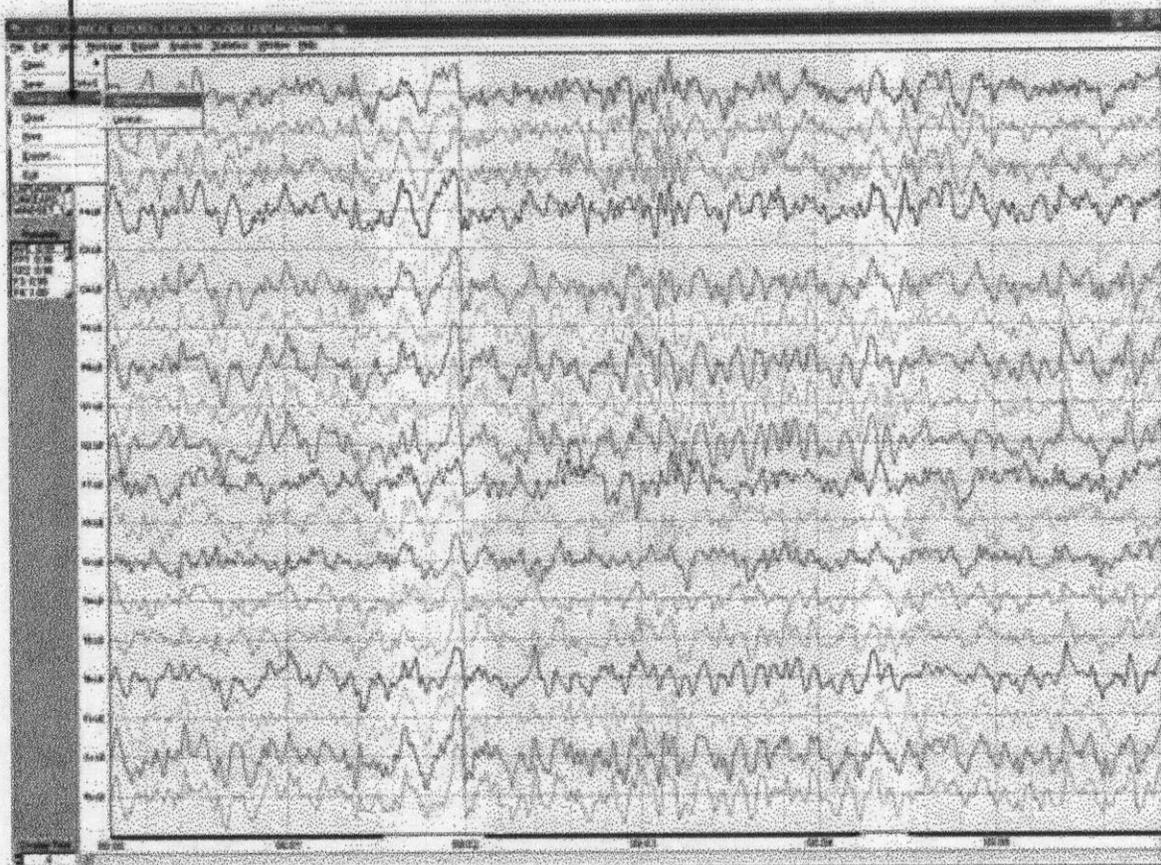
6d – Print or Export the Edited EEG in ASCII format by Highlighting “Print” or “Export” in the File Menu.

Click File > Export to Save EEG Selections in ASCII format



6e – Save the Edited EEG Selections in NeuroGuide Format (*.ng) or in Lexicor Format (*.dat).

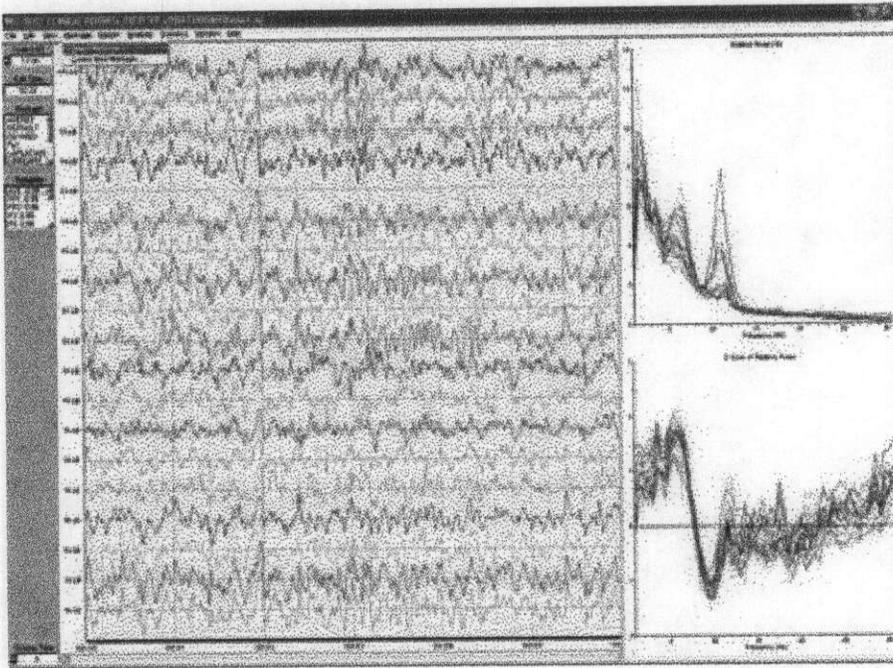
Click File > Save As > NeuroGuide to Save EEG Entire EEG File + Selections + Patient Information



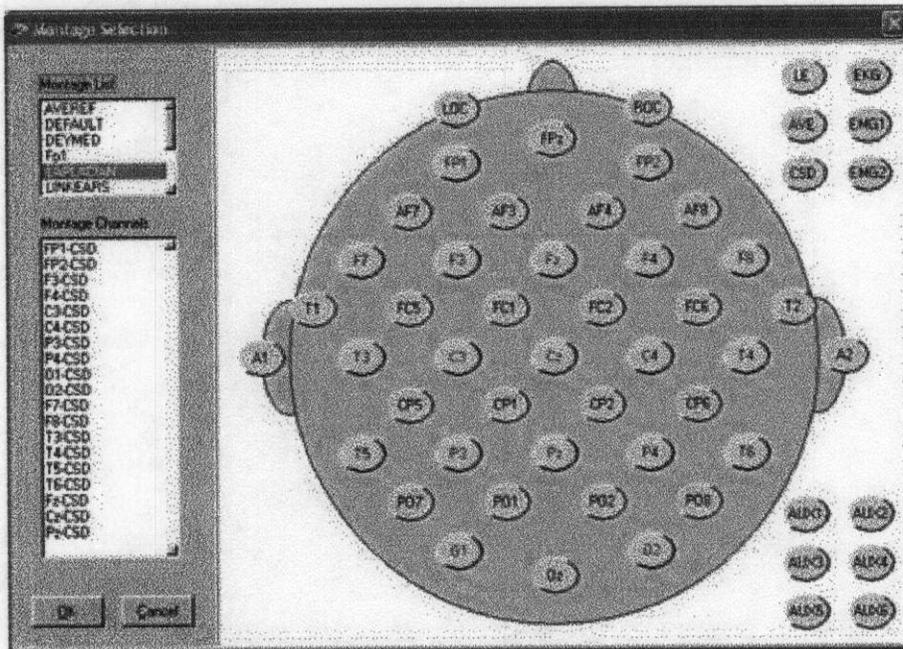
Step # 7 – Create and Label Montages (1 to 19 channels, Bipolar or Monopolar)

[Return to Top](#)

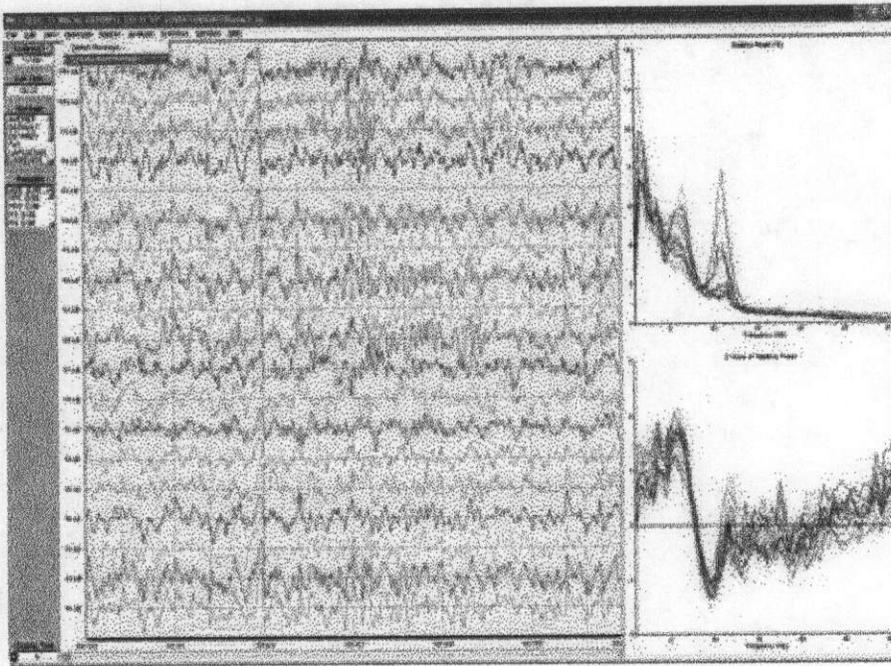
7a – Click Montage > Select Montage in the Montage Menu



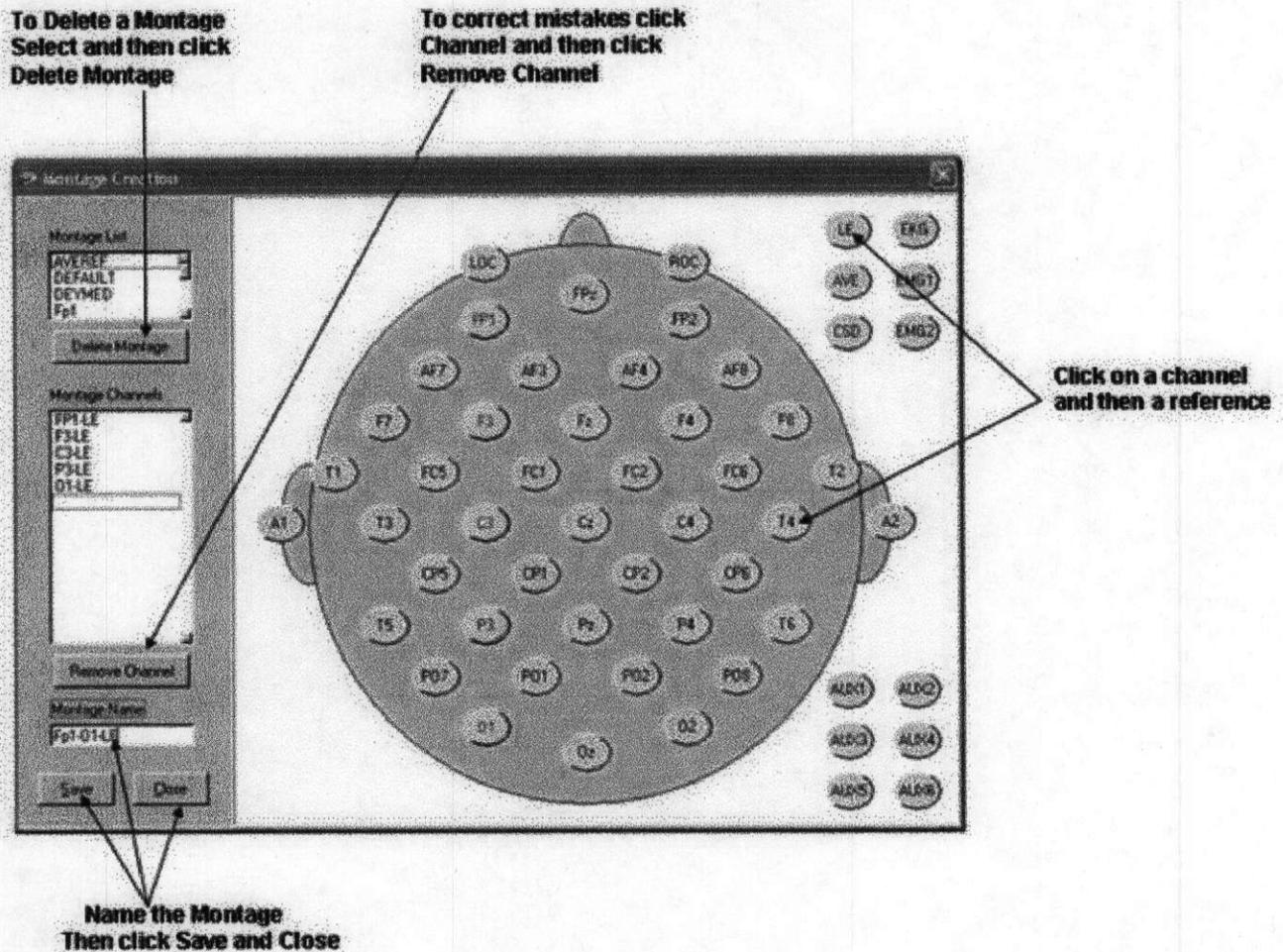
7b – Click a Montage in the Montage List to view the electrode order and references that are present in the left column of the EEG View screen



7c – Click Montage > Create New Montage” in the Montage Menu



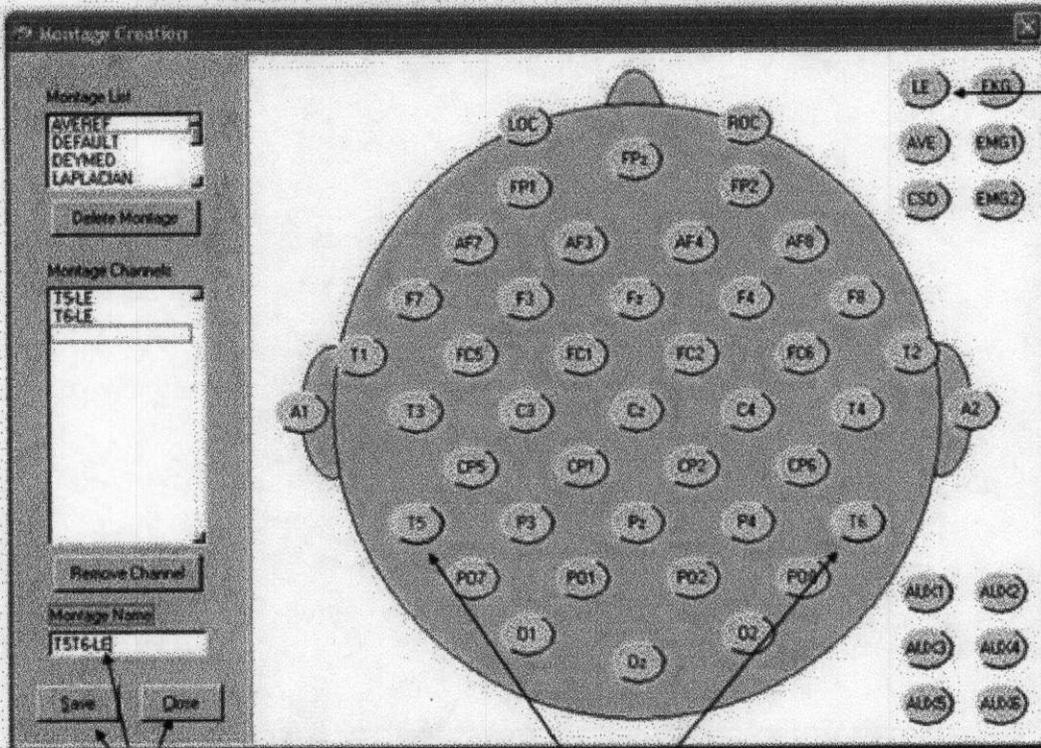
7d – Click on Electrode Locations and a Reference (e.g., Linked Ears, then Name the Montage then click Save and then click close.



7e - If You Make a Mistake or Want to Remove an Electrode Selection, Double Click on the Electrode and then Click Remove Channel. To Delete a Previously Created and Saved Montage, Click on the Montage and then Click Delete Montage. Click Close to Return to the EEG Display or Create and Save A New Montage.

7f - Example of a Two Channel Display with Dynamic FFTs Designed To Evaluate T5 and T6 Theta Activity. First create a T5-linked ears and a T6 linked ears Montage then click Close

Example of Creating a T5 and T6 Linked Ears Montage

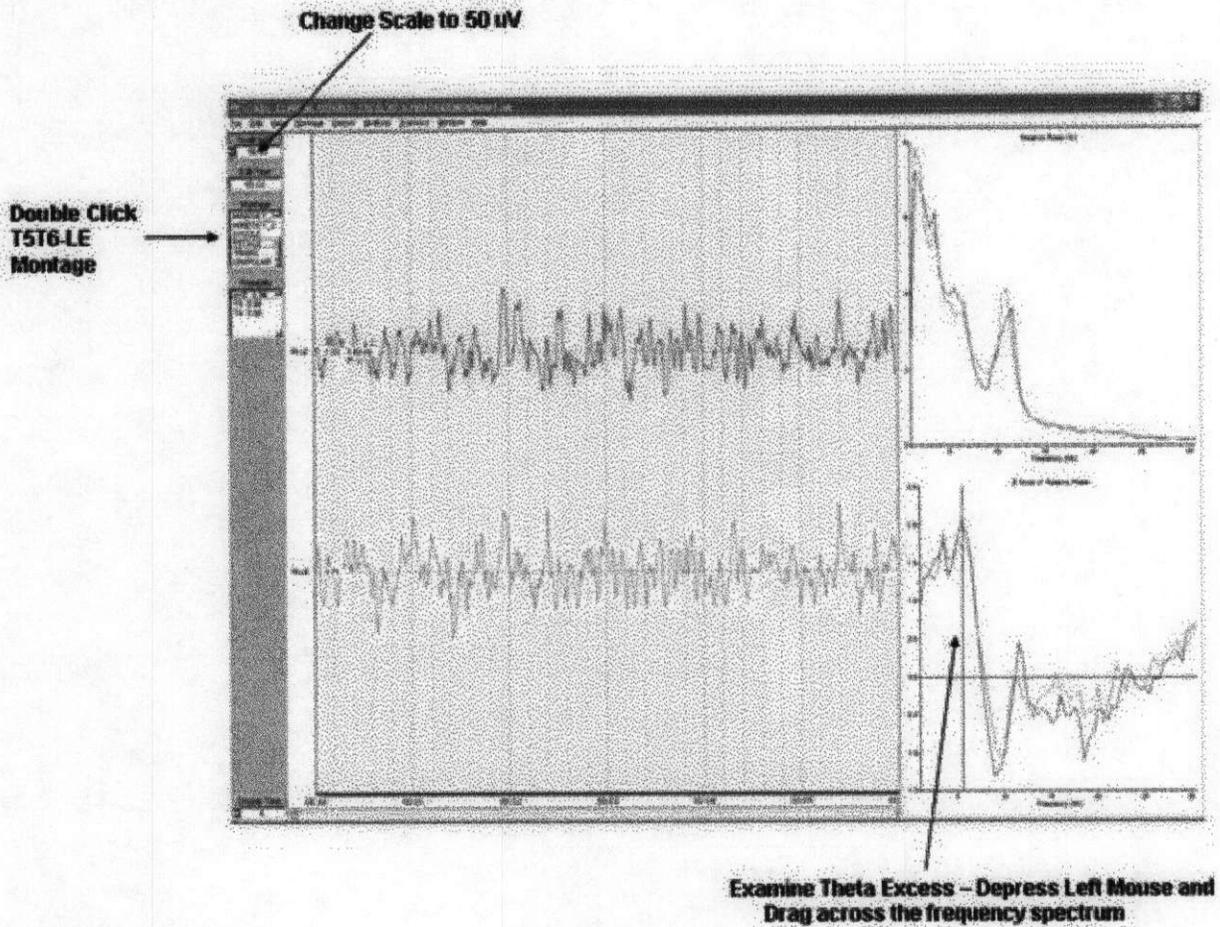


Reference is Linked Eras

Name Montage
T5T6-LE, click Save
Then click Close

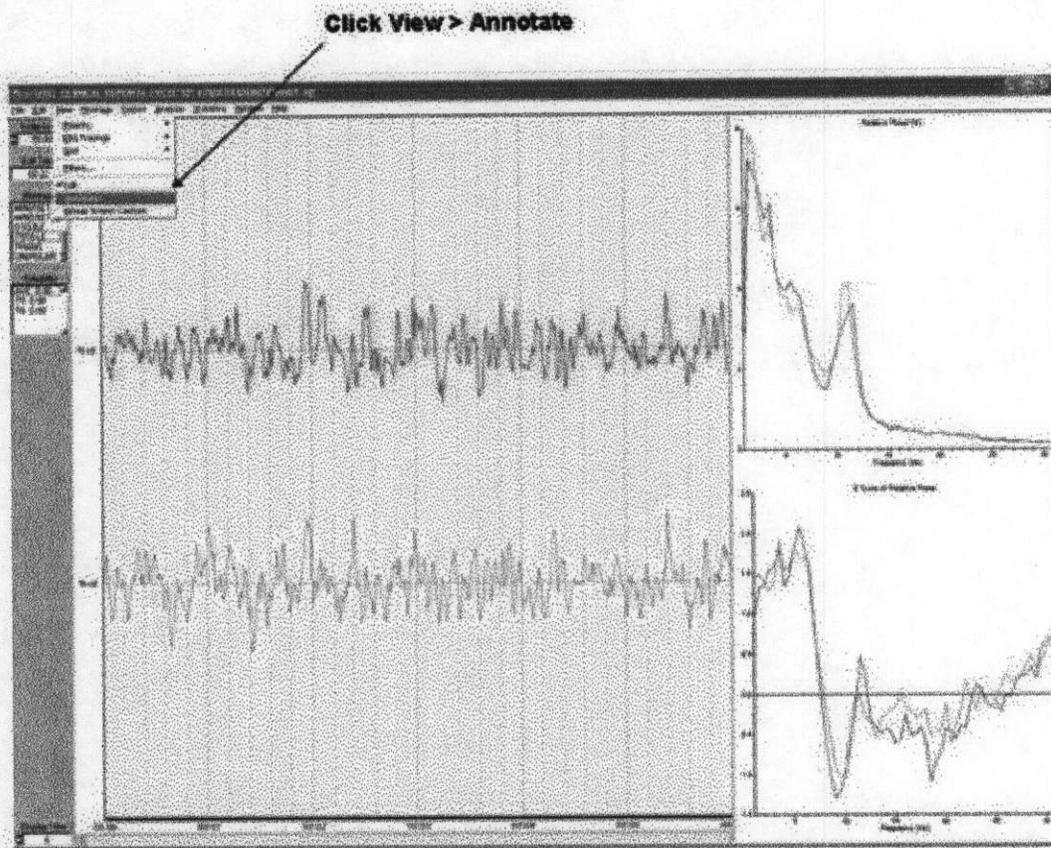
Click T5 then LE, click T6 then LE

7g - Display the T5 and T6 Linked Ears Montage in the NeuroGuide Viewer

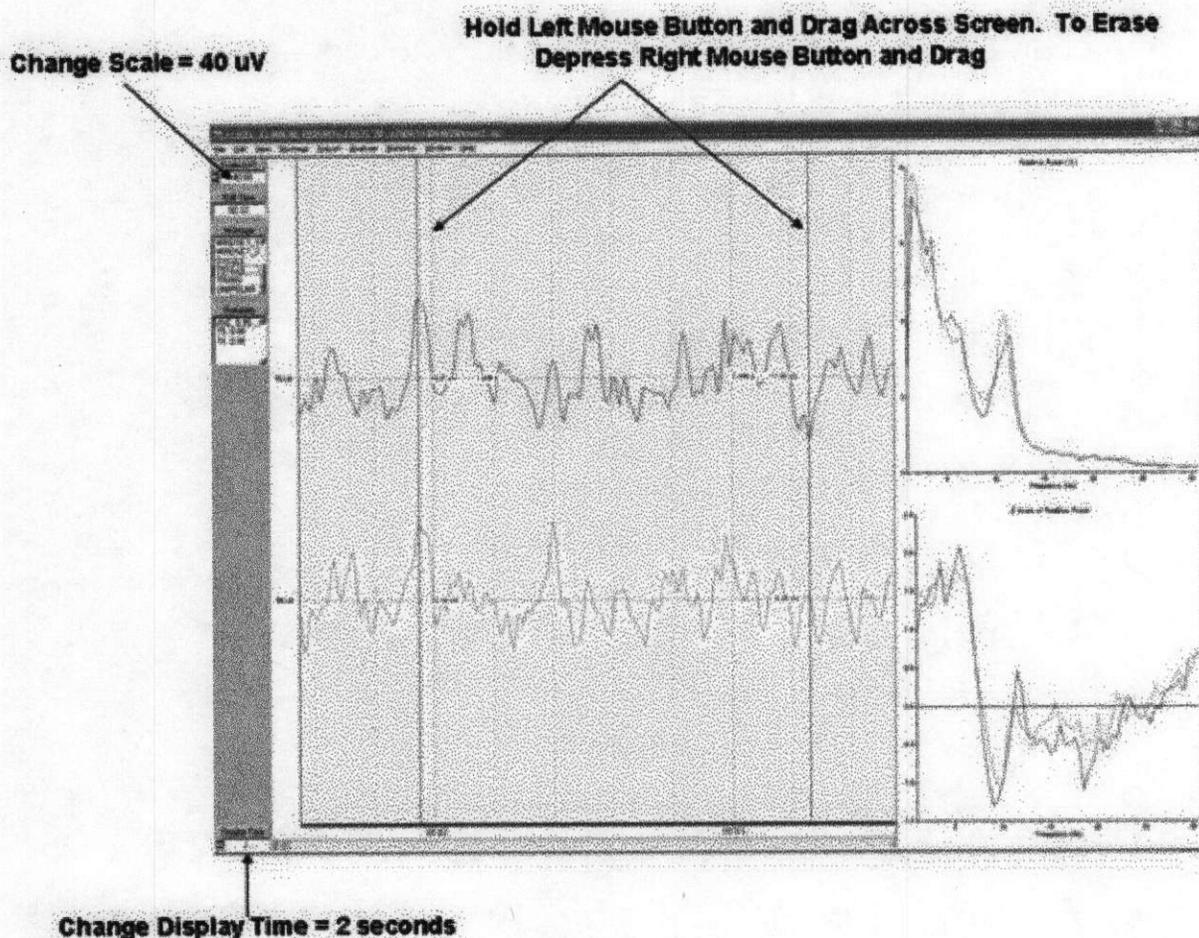


8 – Use Annotate Tool to Examine peak-to-peak features of the EEG

[Return to Top](#)



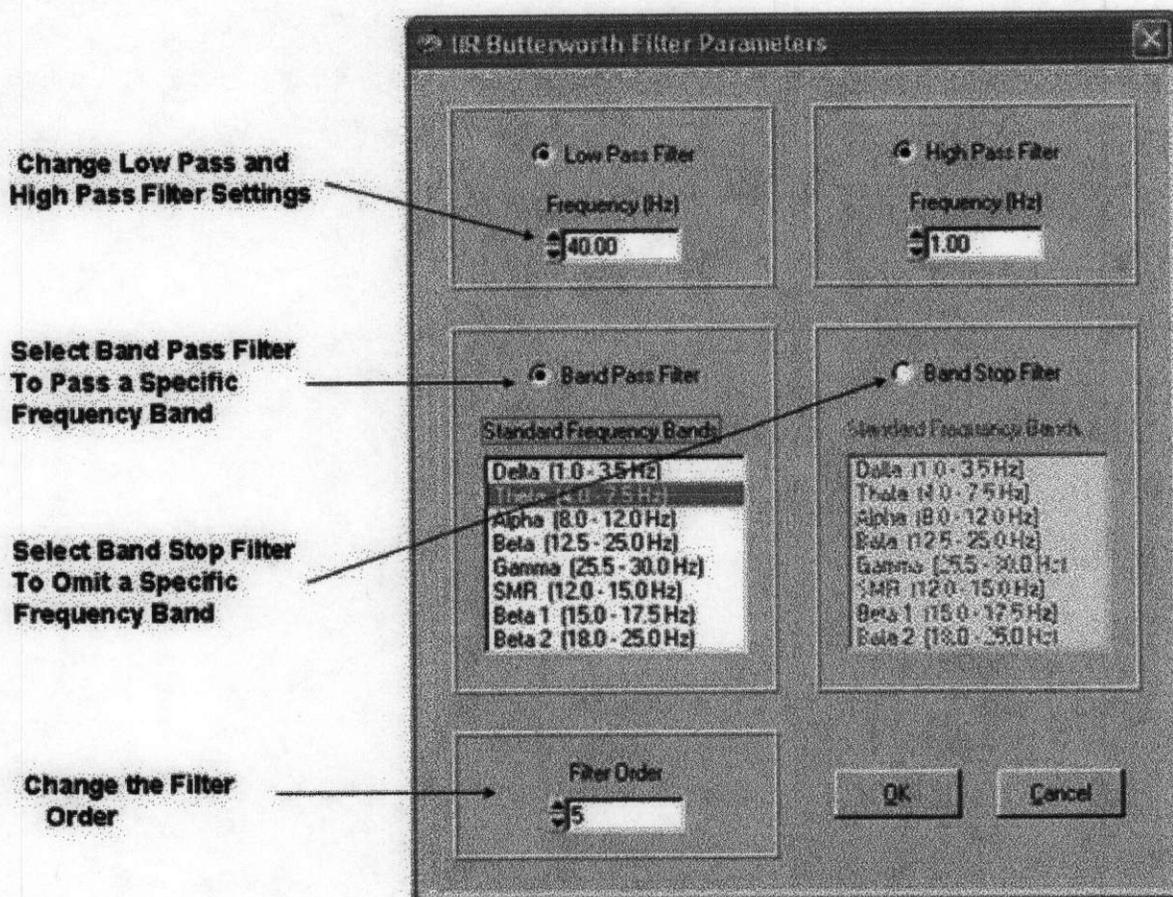
8a – Press the left mouse button and drag over the EEG segments of interest and read the instantaneous microvolt values (μV) or microampers (μA) in the CSD montage. To Erase the annotations, press the right mouse button and drag over the annotations to be erased.



Step # 9 – Digital Filter Viewer is a IIR ButterWorth Filter that only changes the appearance of the EEG tracings and does not have any impact on the FFT or normative database comparisons. This is a valuable visual tool to examine the time and frequency details of the EEG tracings themselves.

[Return to Top](#)

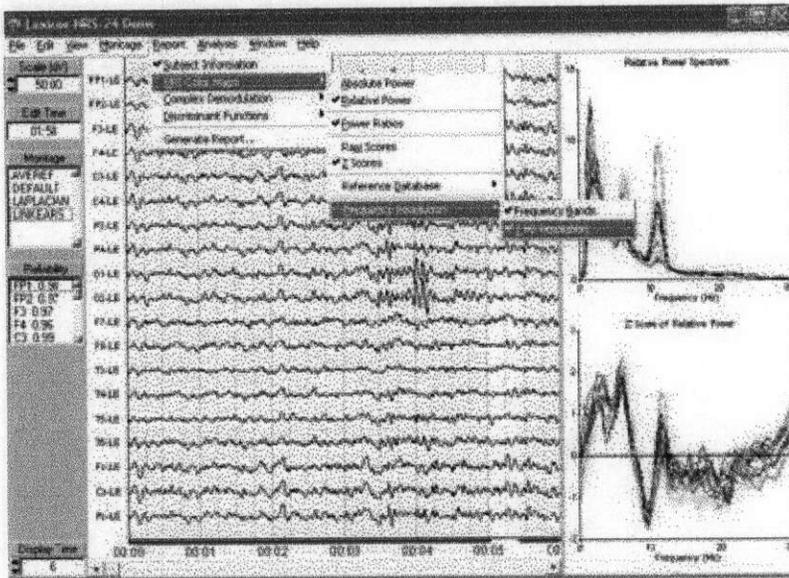
9a – Click View > Filters



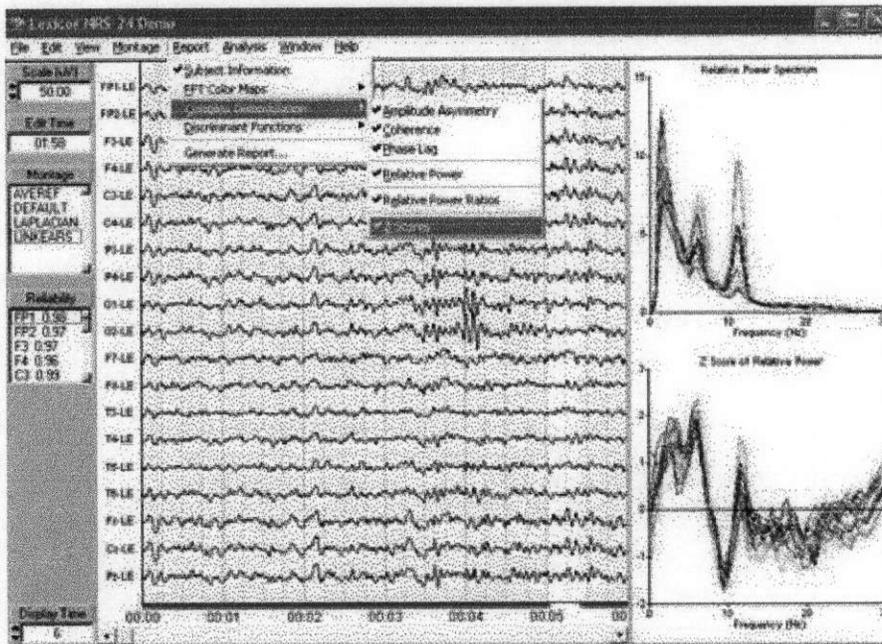
Step # 10 – Selecting Report Content

[Return to Top](#)

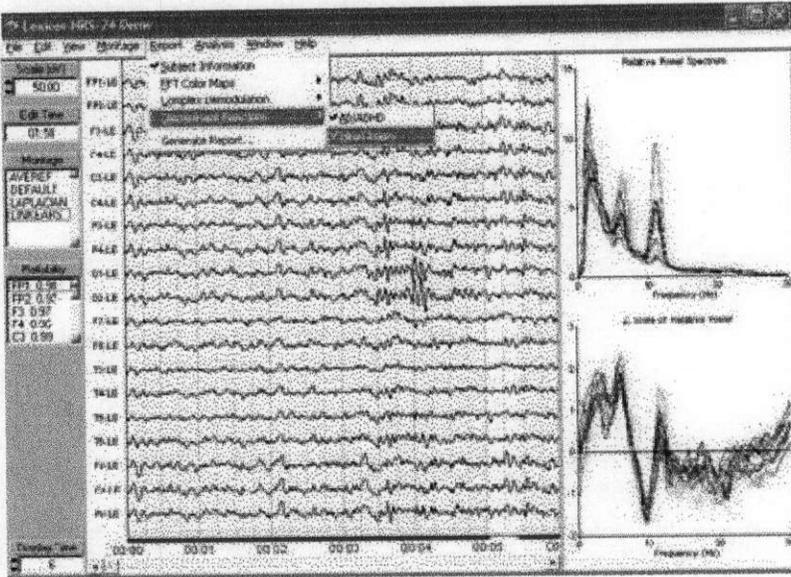
10a – Highlight “Report” in the Analysis Menu, then drag the mouse to FFT Color Maps > Frequency Resolution > 1 Hz Resolution to see the Default Selections. Uncheck and check those FFT Color Maps that you want in your Report.



10b – Highlight “Report” in the Analysis Menu. Uncheck and check those Analysis Results that you want in your Report.

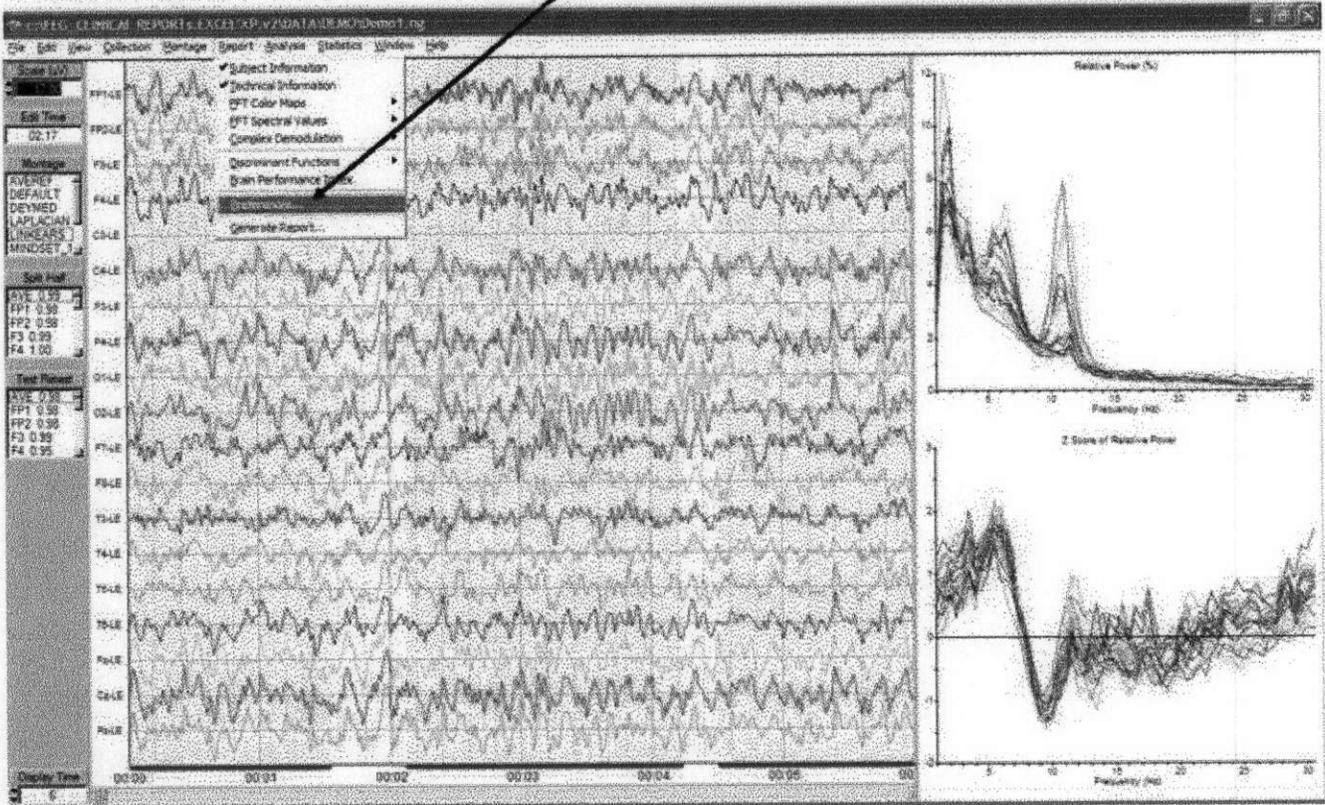


10c – Highlight “Report” in the Analysis Menu, then drag the mouse to Discriminant Functions> Learning Disabilities & Head Injury to see the Default Selections. Uncheck and check the Discriminant Functions that you want in your Report (Not a Diagnostic).



10d - Click: Report > Preferences to Select the range of Z scores and colors ranges in the Topographic Z score maps.

Click – Report > Preferences to select Color Topographic Z score preferences



10e - In the preferences window select the Z score range and color contrasts, then close the Report Preferences window.

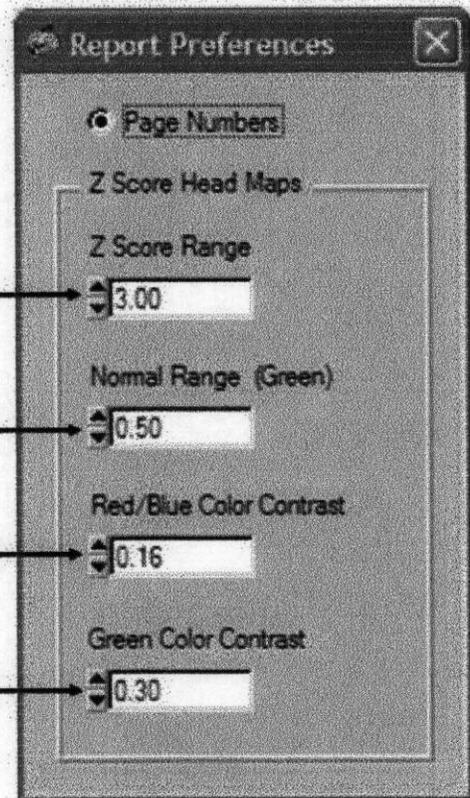
Select Topographic Color Scales and Contrasts for Different Z Score Ranges

Adjust Z Score \pm Std. Deviations

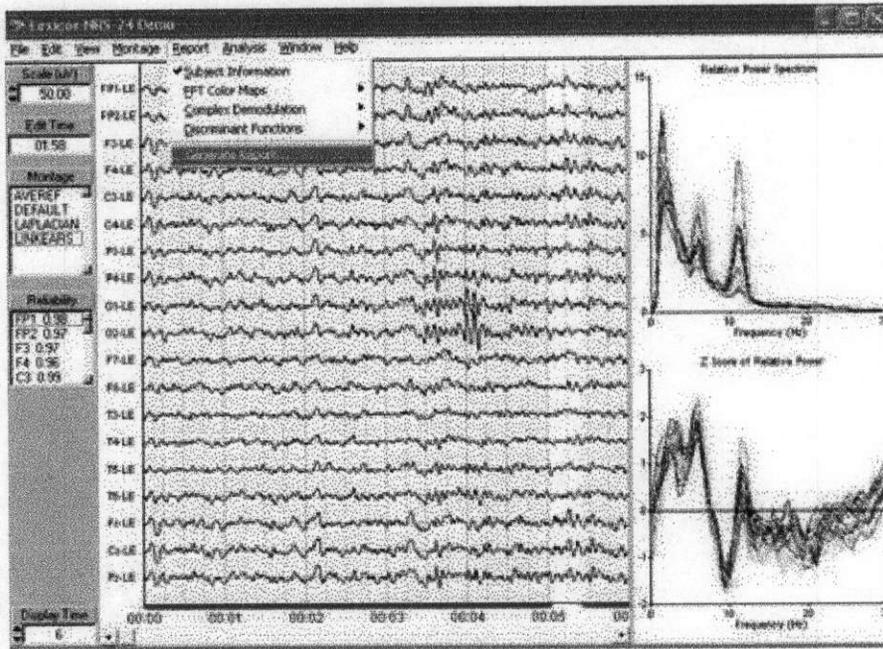
Select Range of Normal \pm Std. Deviations (Green Color)

Select Non-Linear Red/Blue Contrast

Select Non-Linear Green Contrast



10f – After making your Selections (Final Items Checked and Unchecked) Highlight Generate Report and Then Release the Mouse. Repeat 8a-8d with Different Montages and Conditions (Laplacian & Average Reference)



Step # 11 – Printing & Bit Map Export

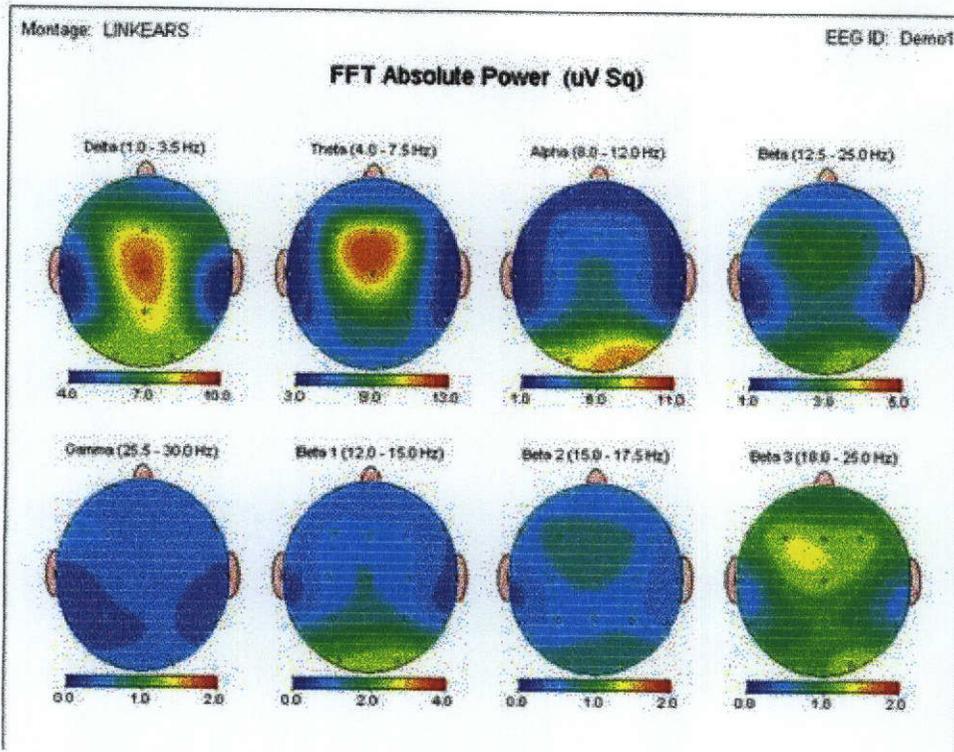
[Return to Top](#)

11a- First Page of Report is the Subject Information Page (see Step 1b)

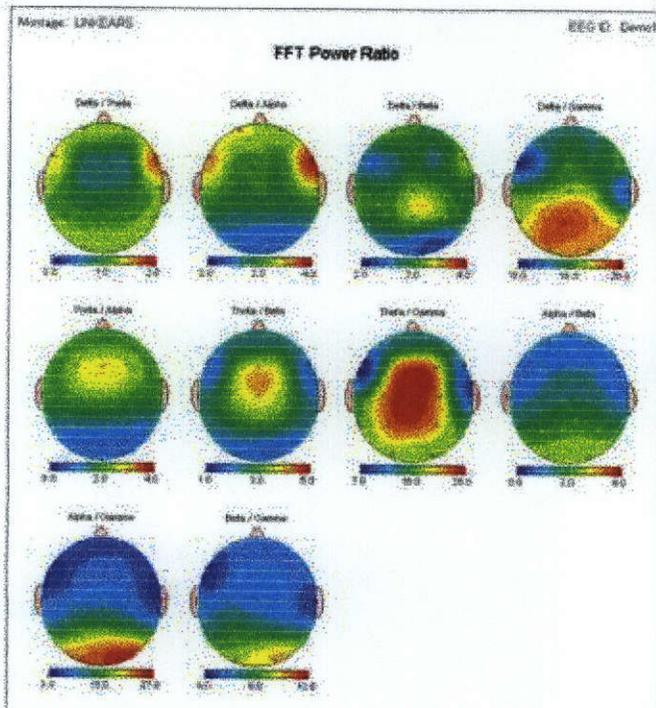
Subject Information	
Patient Name:	Joe TBI
Date of Birth:	11/20/1985
Age:	18:00
Gender:	Male
Handedness:	Right
EEG ID:	Demo1
Date of Test:	11/20/2003
Technician:	Mr. Competent
Doctor:	Dr. Competent
Medication:	None
Comments:	Electrode impedances were < 5K, patient was alert and rested. No drowsiness was noted.

11b – Example Page of Z Score Color Maps of Relative Power Frequency Bands

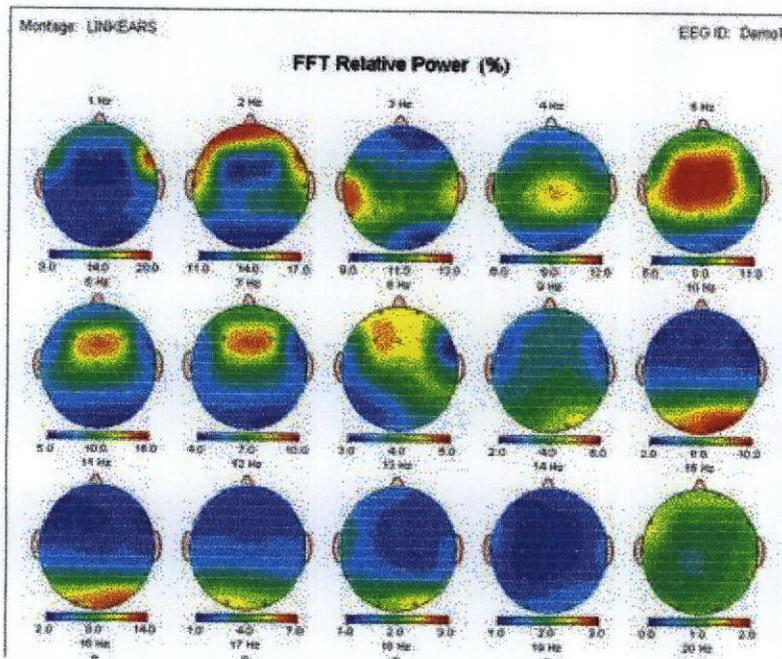
mk:@MSITStore:C:\Program%20Files\RoboHelp%20Office\RoboHTML\NEUROGUIDE\... 5/2/2004



11c - Example Page of Z Score Color Maps of Ratios of Relative Power



11d – Example Page of the 1 Hz Z Relative Power Z Score Maps



11e – Example Page of the Cross-Spectral Raw Scores

Analysis Output Window
File Report

Amplitude Asymmetry Raw Scores

Intrahemispheric: LEFT					Intrahemispheric: RIGHT				
	DELTA	THETA	ALPHA	BETA		DELTA	THETA	ALPHA	BETA
FP1-F3	-25.10	64.94	-89.05	-29.12	FP2-F4	-21.05	-69.53	-41.17	-23.01
FP1-C3	-21.27	-83.42	-80.66	-28.75	FP2-C4	-18.21	-41.83	-45.42	-28.21
FP1-P3	-16.25	-20.87	-85.83	-23.47	FP2-P4	-23.12	-31.18	-24.91	-40.37
FP1-O1	-28.55	-19.80	-137.40	-73.17	FP2-O2	-25.92	-18.40	-125.95	-78.24
FP1-F7	22.03	19.19	14.69	-10.23	FP2-F8	73.03	23.73	21.23	0.27
FP1-T9	-48.90	39.24	18.71	20.98	FP2-T4	26.53	51.83	28.42	37.12
FP1-T5	17.04	18.22	-60.46	-4.48	FP2-T8	9.59	27.84	-48.56	0.67
F3-C3	3.87	12.53	-14.77	10.60	F4-C4	3.78	19.18	-15.12	5.74
F3-P3	8.93	26.94	-25.19	5.84	F4-P4	-1.17	29.72	-58.56	-8.25
F3-O1	-1.38	-48.33	-107.67	-28.68	F4-O2	-4.02	43.28	-110.21	-48.24
F3-F7	47.24	81.49	60.51	29.15	F4-F8	24.74	80.42	51.11	24.08
F3-T9	71.59	97.08	84.25	67.63	F4-T4	67.62	103.38	67.61	68.79
F3-T5	42.65	89.69	-14.83	34.79	F4-T8	21.38	83.86	-9.28	-34.75
C3-P3	5.06	24.73	-41.20	-4.84	C4-P4	-4.95	19.69	-46.40	-12.51
C3-O1	-5.25	24.63	-97.06	-48.89	C4-O2	7.80	22.95	-69.22	-63.81
C3-F7	68.67	70.80	73.84	18.83	C4-F8	31.06	62.70	74.61	28.48
C3-T9	68.85	87.21	77.19	57.28	C4-T4	54.14	88.50	80.87	63.67
C3-T5	38.84	89.94	0.24	24.75	C4-T8	27.87	87.52	5.37	-29.25
F3-O1	-10.71	10.02	62.02	-42.20	F4-O2	-2.85	12.84	69.59	-41.89
F3-F7	39.92	48.18	108.76	23.42	F4-F8	25.87	83.92	119.61	-40.83
F3-T9	84.08	96.04	109.71	81.79	F4-T4	-8.70	73.79	115.64	-74.89
P3-T5	53.64	47.25	-41.40	29.19	P4-T8	-22.62	87.87	51.00	-41.29
O1-F7	-48.85	39.82	144.82	84.12	O2-F8	-22.63	-41.71	148.83	75.67
O1-T9	73.18	86.99	148.78	97.70	O2-T4	61.29	69.83	188.69	108.08
O1-T5	-49.67	-37.66	97.28	69.28	O2-T8	25.25	46.79	103.50	70.88
F7-T9	28.91	19.41	-4.14	32.81	F8-T4	24.09	38.89	7.21	-28.98
F7-T5	-9.05	0.88	-73.43	-5.79	F8-T8	-3.48	4.28	-58.59	0.69
T3-T5	-31.85	-20.38	-78.98	-24.23	T4-T8	-27.49	-24.79	-75.85	-26.18

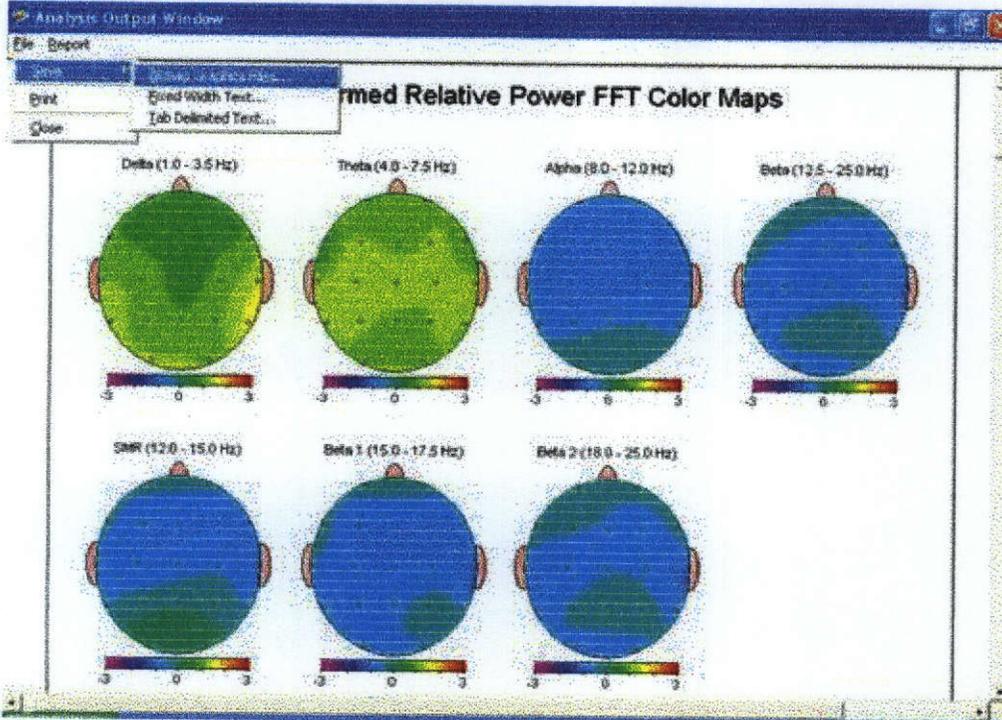
11f – Example Page of Cross-Spectral Z Scores

Analysis Output Window
File Report

Amplitude Asymmetry Z Scores

Intrahemispheric: LEFT					Intrahemispheric: RIGHT				
	DELTA	THETA	ALPHA	BETA		DELTA	THETA	ALPHA	BETA
FP1-F3	0.19	-0.84	-0.12	-0.04	FP2-F4	0.05	-0.89	-0.04	-0.11
FP1-C3	0.21	0.02	0.30	0.45	FP2-C4	0.19	0.22	0.44	0.29
FP1-P3	0.24	0.87	0.48	0.73	FP2-P4	0.32	0.70	0.38	0.24
FP1-O1	0.15	0.47	-0.22	0.18	FP2-O2	-0.04	0.25	-0.32	-0.22
FP1-F7	-0.46	-0.50	-0.73	-1.08	FP2-F8	-0.54	0.03	-0.84	-1.47
FP1-T3	-0.15	-0.10	-0.30	0.24	FP2-T4	-0.22	0.83	0.34	0.88
FP1-T5	0.33	0.72	0.38	0.84	FP2-T8	0.15	0.77	0.66	0.60
F3-C3	0.12	0.70	0.55	0.63	F4-C4	0.35	1.21	0.50	0.51
F3-P3	0.82	1.50	0.64	0.80	F4-P4	0.40	1.30	0.68	0.55
F3-O1	0.16	0.88	0.15	0.24	F4-O2	0.11	0.74	-0.15	-0.03
F3-F7	-0.43	0.23	-0.40	-1.15	F4-F8	-0.73	0.55	-0.05	-0.61
F3-T3	-0.33	0.34	-0.26	0.31	F4-T4	-0.38	1.00	-0.40	0.87
F3-T5	0.25	1.06	0.40	0.83	F4-T8	-0.29	1.30	0.67	1.01
C3-P3	1.00	1.60	-0.41	0.84	C4-P4	0.46	0.84	0.27	0.44
C3-O1	0.11	0.06	-0.35	-0.09	C4-O2	-0.04	0.32	-0.38	0.27
C3-F7	-0.53	-0.32	-0.67	-1.27	C4-F8	-0.55	-0.31	-0.80	-1.01
C3-T3	-0.46	-0.12	-0.67	-0.51	C4-T4	-0.70	0.32	-0.17	0.82
C3-T5	0.25	0.87	0.12	0.50	C4-T8	0.12	0.98	0.62	0.78
P3-O1	0.62	-0.21	-0.63	-0.50	P4-O2	-0.26	-0.12	-0.50	-0.51
P3-F7	-1.13	-1.06	-0.72	-1.52	P4-F8	-0.60	-0.78	-0.90	-0.87
P3-T3	-0.97	-1.09	-0.74	-0.37	P4-T4	-0.80	-0.30	-0.32	0.25
P3-T5	-0.50	-0.19	-0.22	-0.05	P4-T8	-0.19	0.56	0.41	0.51
O1-F7	-0.32	-0.80	0.12	-0.75	O2-F8	-0.30	-0.32	0.34	0.22
O1-T3	-0.30	-0.80	0.10	0.09	O2-T4	-0.30	-0.08	0.31	0.63
O1-T5	0.07	0.06	0.40	0.48	O2-T8	0.15	0.86	0.82	1.05
F7-T3	0.14	0.28	0.06	0.32	P3-T4	0.21	0.88	0.45	1.22
F7-T5	0.58	0.92	0.55	1.32	F5-T8	0.69	1.10	0.68	1.40
T3-T5	0.57	1.02	0.80	0.33	T4-T8	0.67	0.91	0.77	0.29

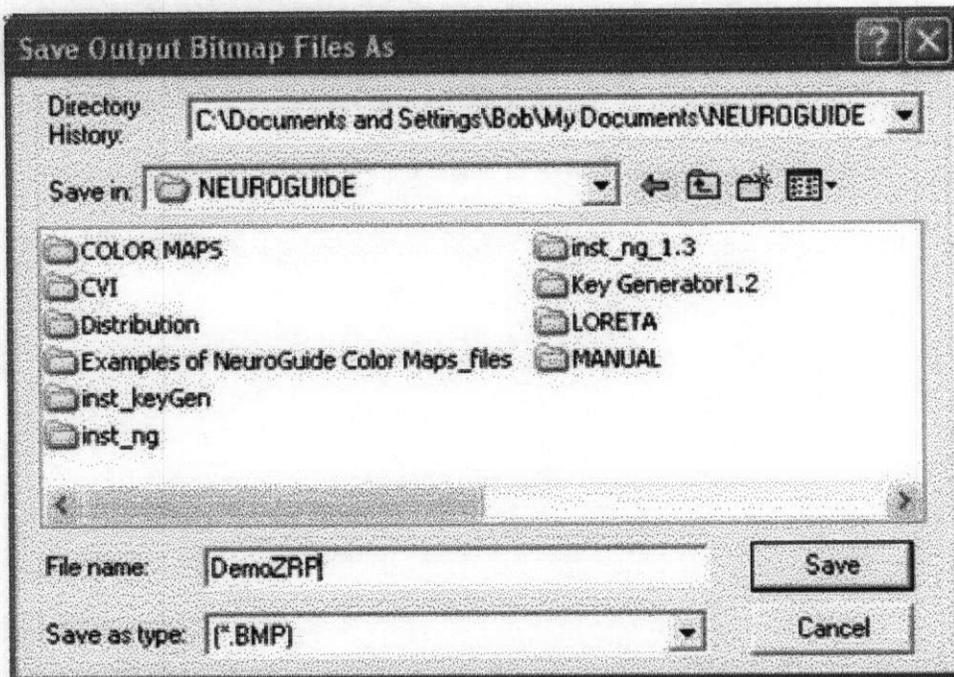
11g- Save the Results of the Color Maps in Bit Map Format or the numerical values in ASCII Tab Delimited Format to be Export to Excel or Database Management or Statistics Programs.



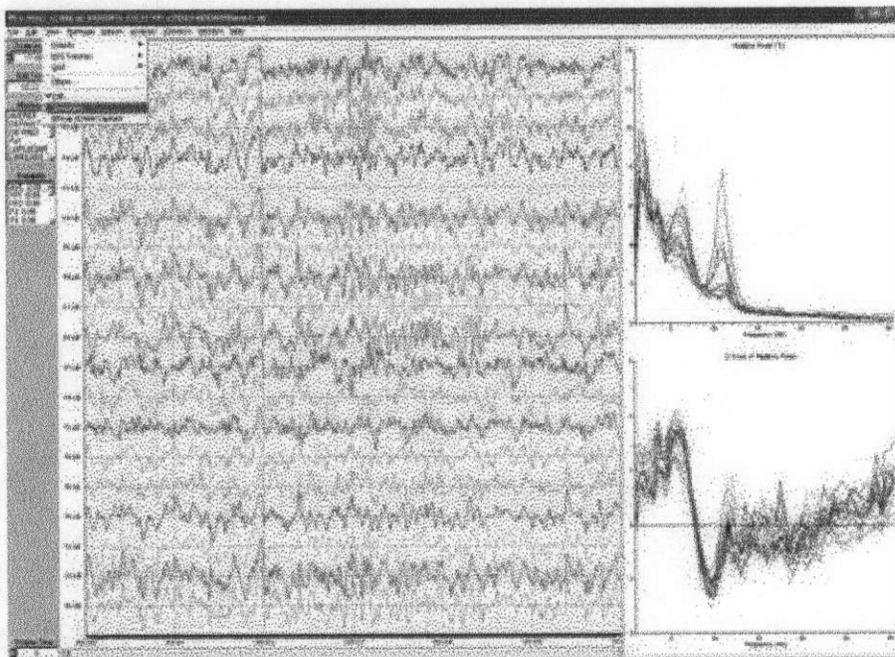
11h – Create a Folder, then open the folder and name the bitmap files before saving them in the folder. Later navigate to the Folder to Import directly into Word, or Power

mk:@MSITStore:C:\Program%20Files\RoboHelp%20Office\RoboHTML\NEUROGUIDE\... 5/2/2004

Point or Print Shop Pro, etc.



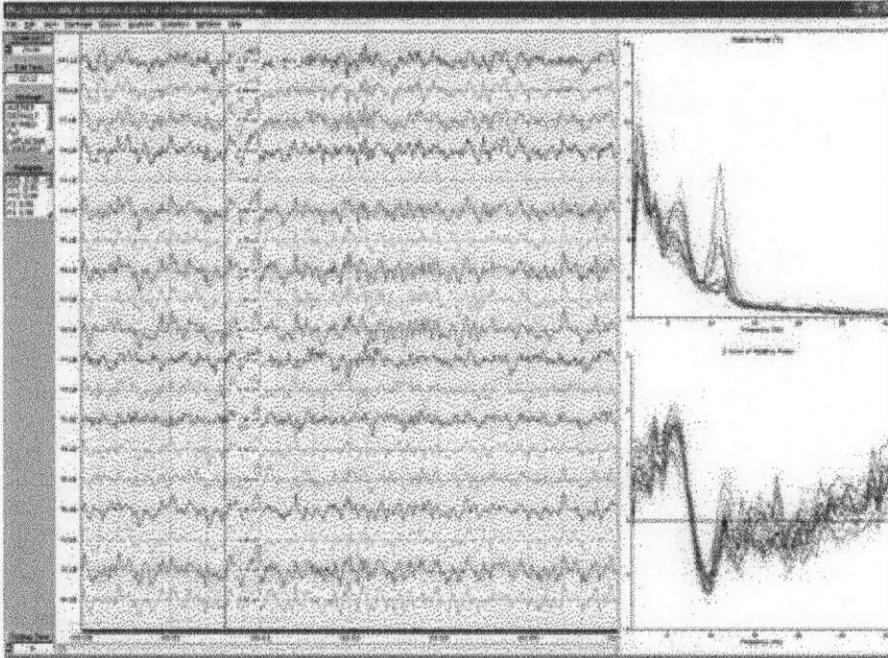
11j – Use Screen Capture Tool to Copy a Bit Map to the ClipBoard. Highlight “View” menu and check “Copy Bitmap to Clipboard”. When done with the screen capture tool, then highlight “View” and check “Edit” or “Annotate” to use the mouse for other functions. Click View > Annotate



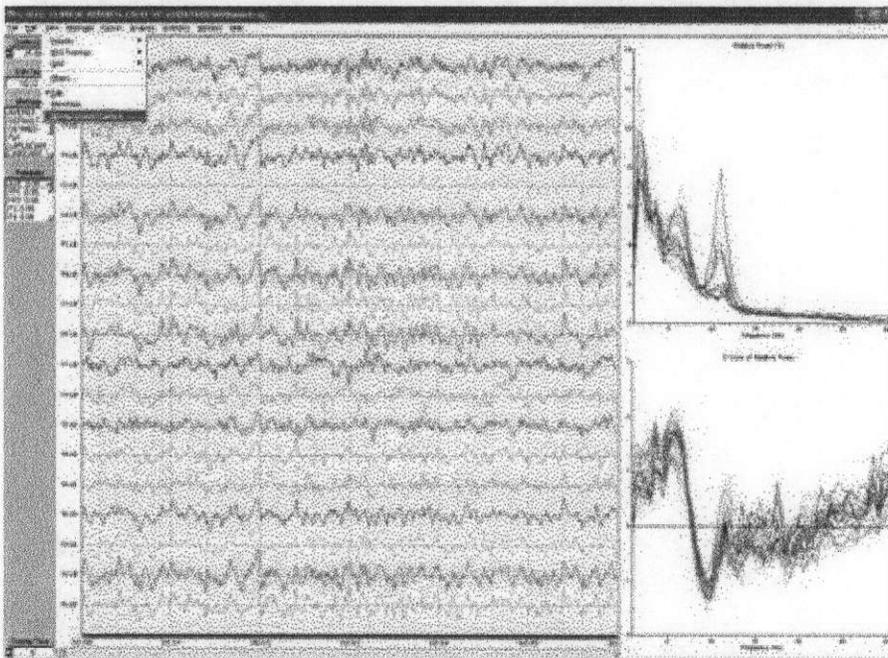
11j – Depress the left mouse button and drag the mouse over the EEG tracings and view the “Blue” vertical line and microvolt values of the digital EEG. To erase the annotation

mk:@MSITStore:C:\Program%20Files\RoboHelp%20Office\RoboHTML\NEUROGUIDE\... 5/2/2004

values, depress the right mouse button and drag over the annotation selections. Click **View > Edit** in order to restore the edit functions.



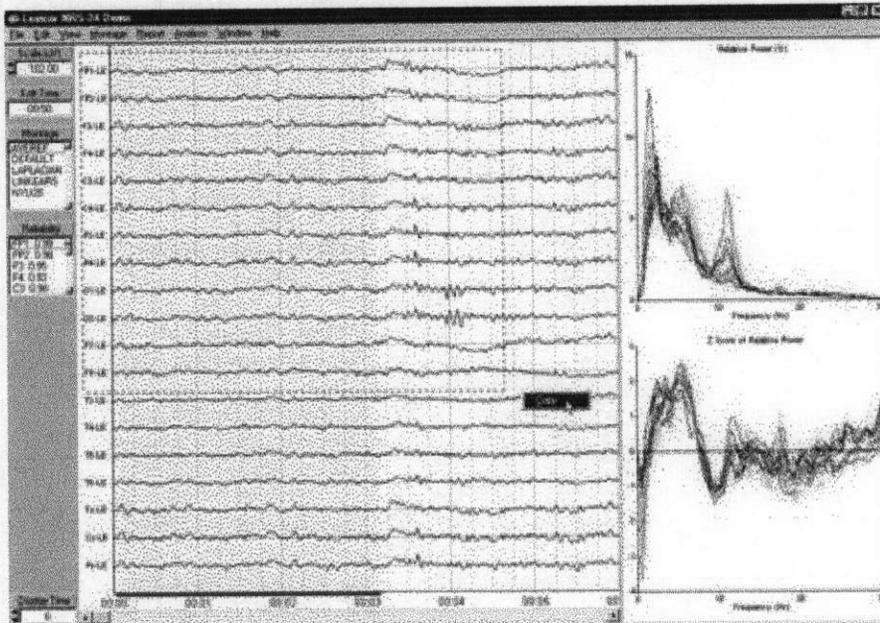
11k - Select screen region to copy, then depress the left mouse button and drag the mouse over the screen image that you want to copy to the clipboard.



11l - If a mistake is made click the left mouse button and the dashed rectangle will disappear. Start over again and click and drag the mouse over another screen region. To copy the selection to the clipboard, click the right mouse button and select "copy".

mk:@MSITStore:C:\Program%20Files\RoboHelp%20Office\RoboHTML\NEUROGUIDE\... 5/2/2004

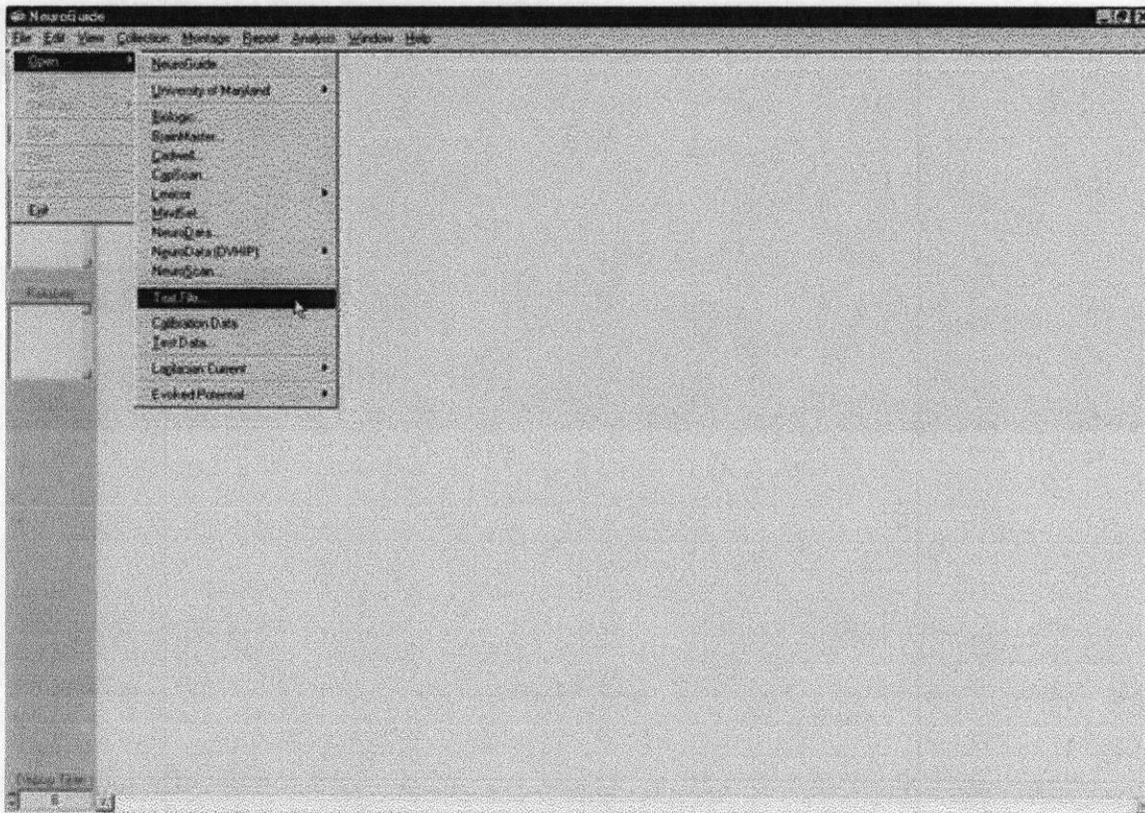
A second method is to highlight "Edit" and then select "Copy" at the bottom of the menu.



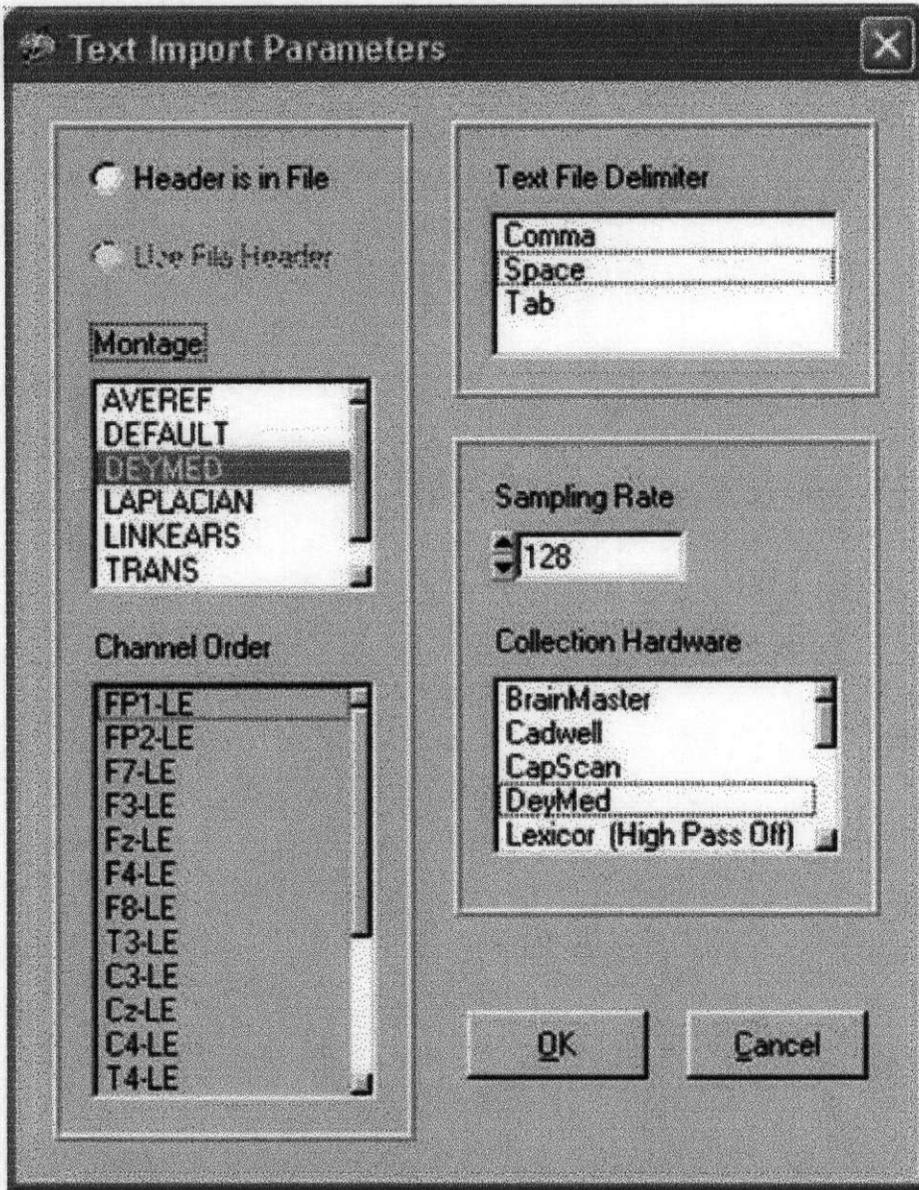
Step # 12 – Import EEG in ASCII Format and EDF

[Return to Top](#)

12a – Highlight "File > Open>Text file" in order to select an ASCII formatted EEG file.

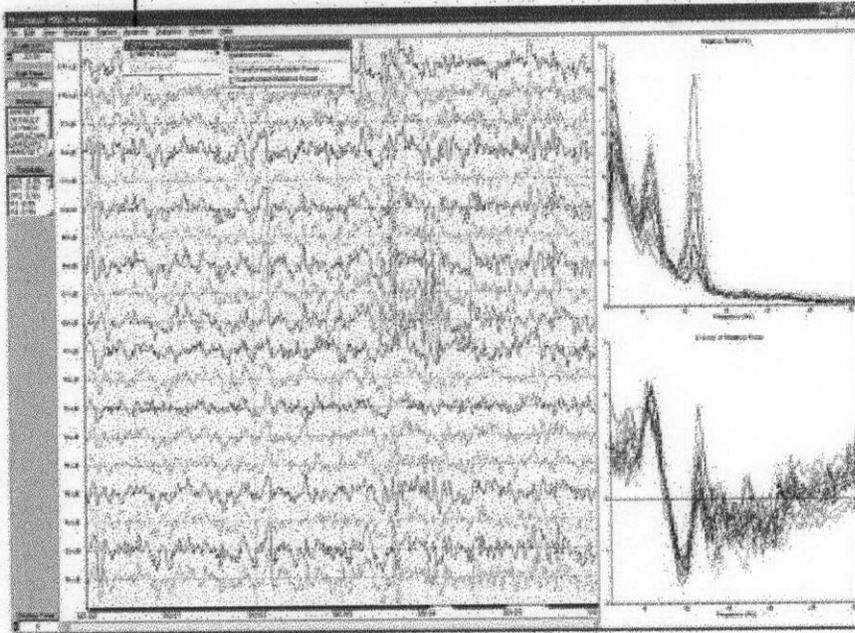


12b – Navigate to the ASCII file and open the file. The ASCII import window below appears. Open the ASCII file in Word or Excel and examine the file and determine the channel order and delimiters and whether or not there is a header in the file. One must know the Montage or order of the channels, the sample rate and the delimiters. NeuroGuide will search the file and help determine the delimiters or headers. If none is found then the default window below is opened. If a different channel order is used, then select “Montage” and “Create New Montage”. After creating a Montage to match the channel order, name the montage, save and close. Re-open the ASCII import window and select this new montage. A Default DeyMed Montage is available to import DeyMed ASCII-real EEG using the (A1+A2)/2 or linked ears reference.



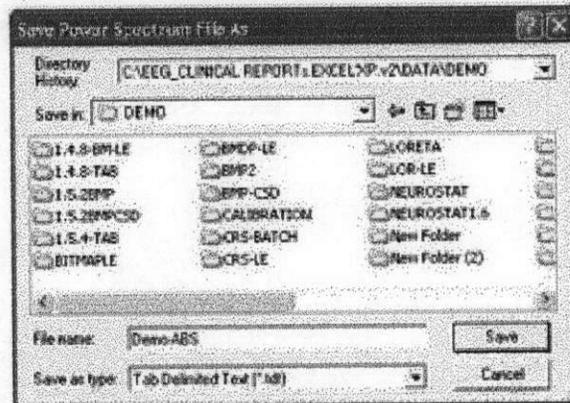
12c – Import EDF formatted files by Selecting File>Open/EDF. NeuroGuide assumes that all channels were digitized at the same rate. User’s must know the Montage or channel order, create a new montage to match the channel order of the EDF file that you are importing.

Click Analysis > FFT Power Spectra to Save 0.5 Hz Resolution FFT Results in Tab Delimited Format

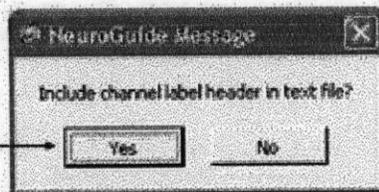


13b - Navigate to a Folder and Name the File

Navigate to Folder and Name the FFT File. Default extension is *.tdt To designate that it is Tab Delimited



Yes means that the Top row of the file will Be the channel labels



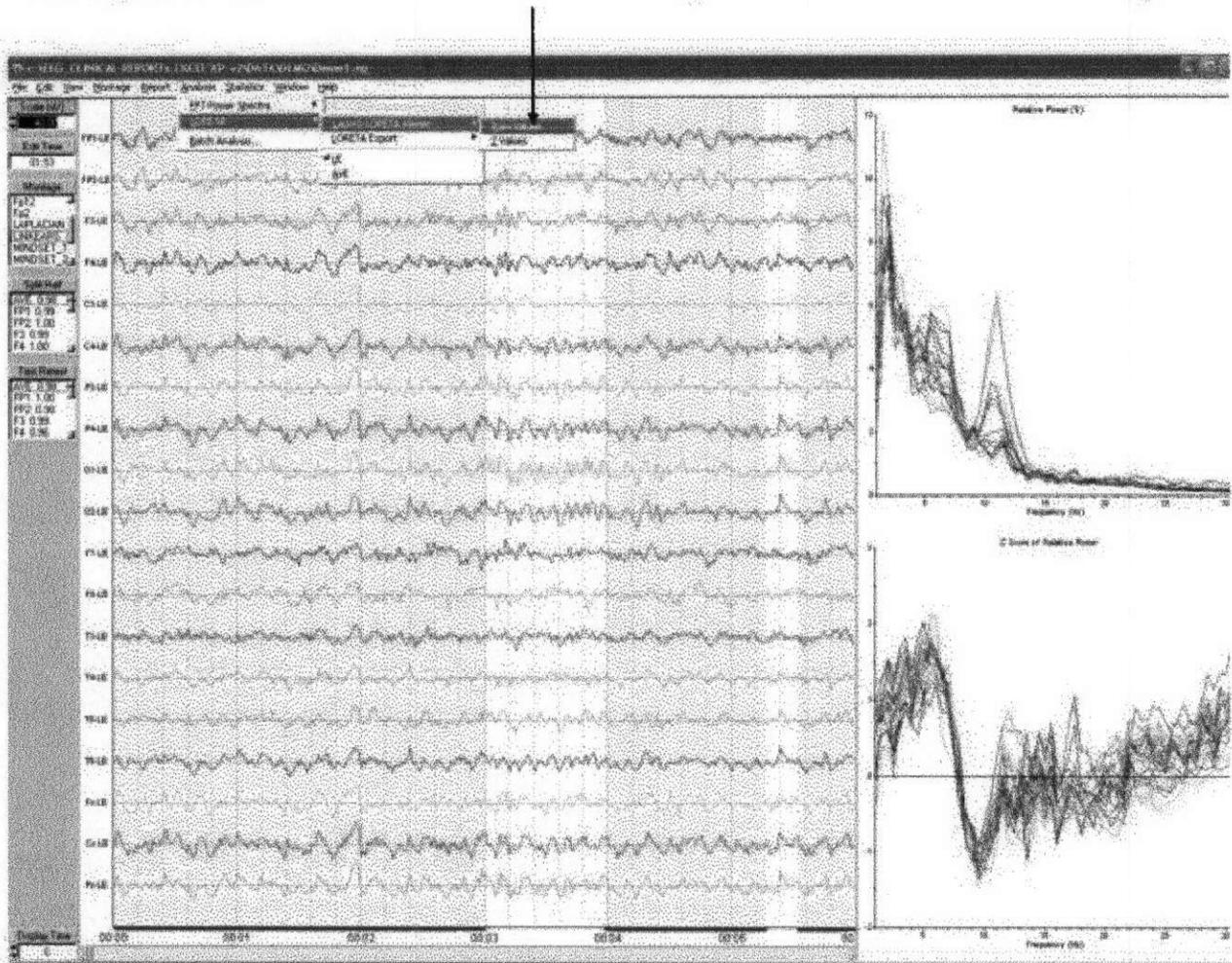
Step # 14 – Launch LORETA - Frequency Domain Raw Cross-Spectral Values and/or Normative Database Z Scores (z scores are not in the Demo they are an add on product).

[Return to Top](#)

14a - Download the free Key Institute LORETA programs at (www.unizh.ch/keyinst/NewLORETA/Software/Software.htm) and then request a copy of the Key Institute password. Once the Key Institute software is installed on the users computer then the LORETA viewer program can be launched directly from the NeuroGuide edit window.

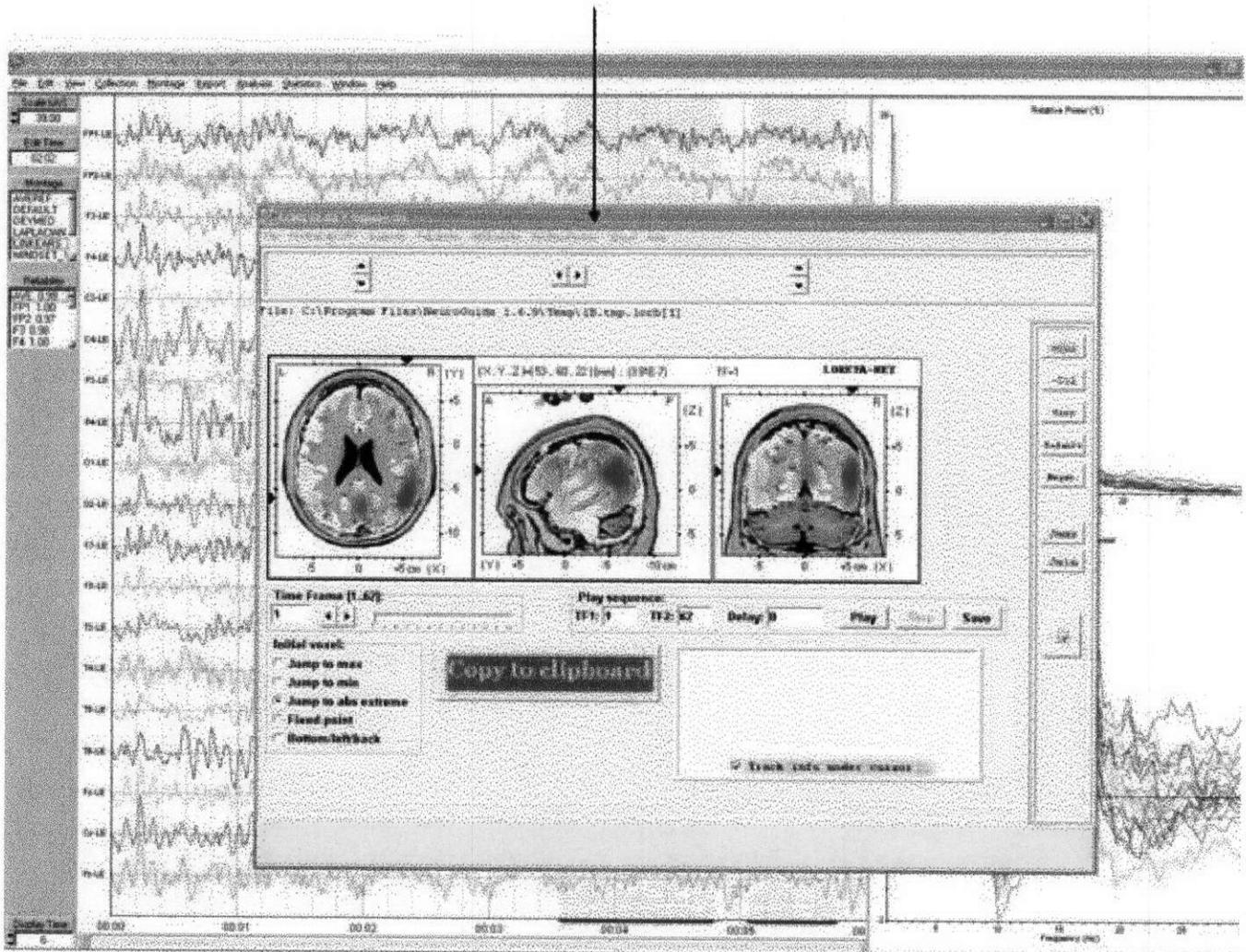
14b - Select artifact free EEG samples then Click Analysis > LORETA > Launch LORETA Viewer > Raw Values

Click - Analysis > LORETA > Launch LORETA Viewer > Raw Values to Export Cross-Spectral Raw Values and Launch the Key Institute LORETA Viewer Program

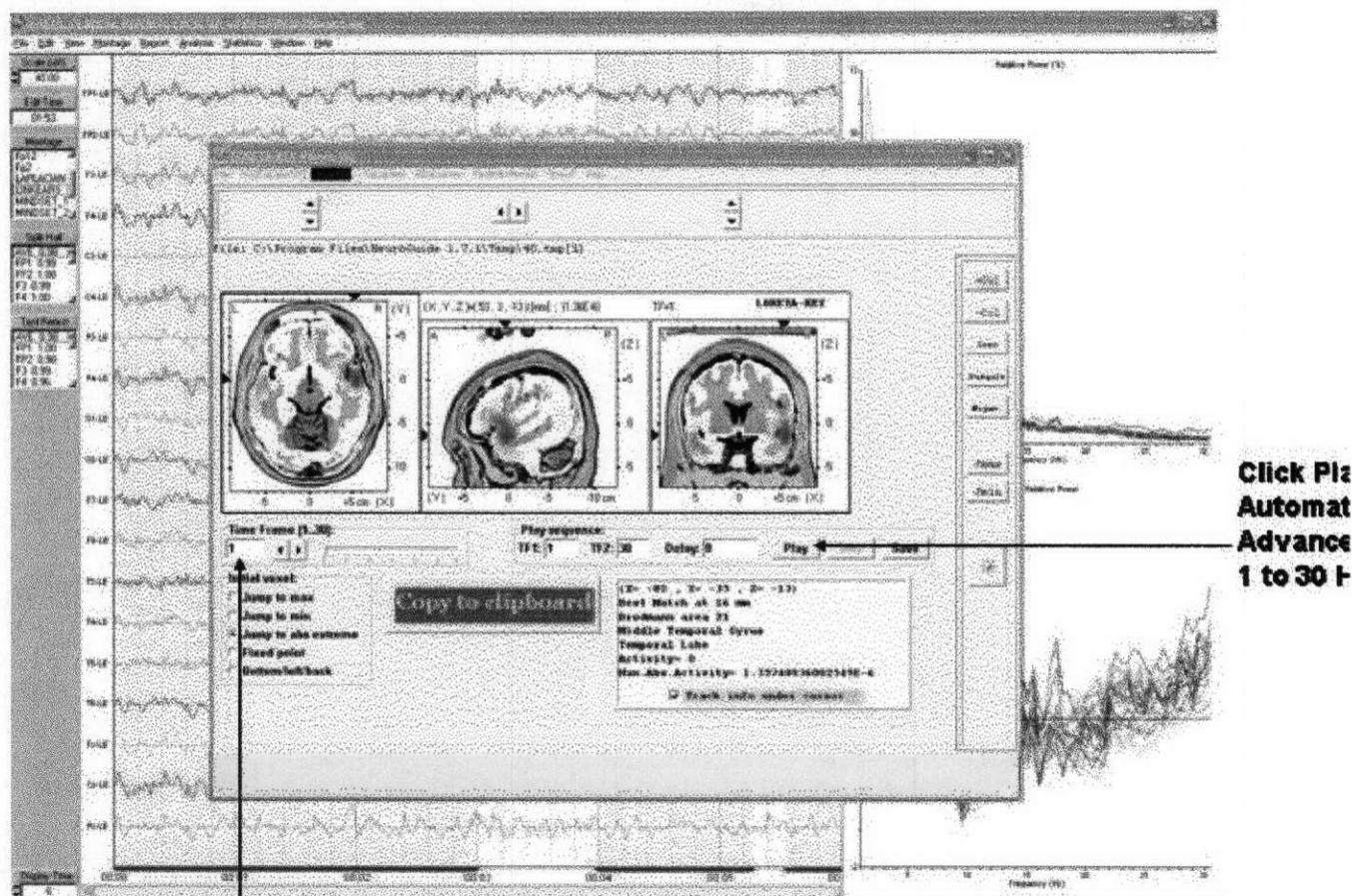


14c - Simultaneous NeuroGuide and LORETA Viewer

Example of Simultaneous LORETA Viewer and NeuroGuide. Clic Back and Forth between NeuroGuide and the LORETA Viewer



Step 14d - Time Frames are Frequencies from 1 to 30 Hz in 1 Hz increments.



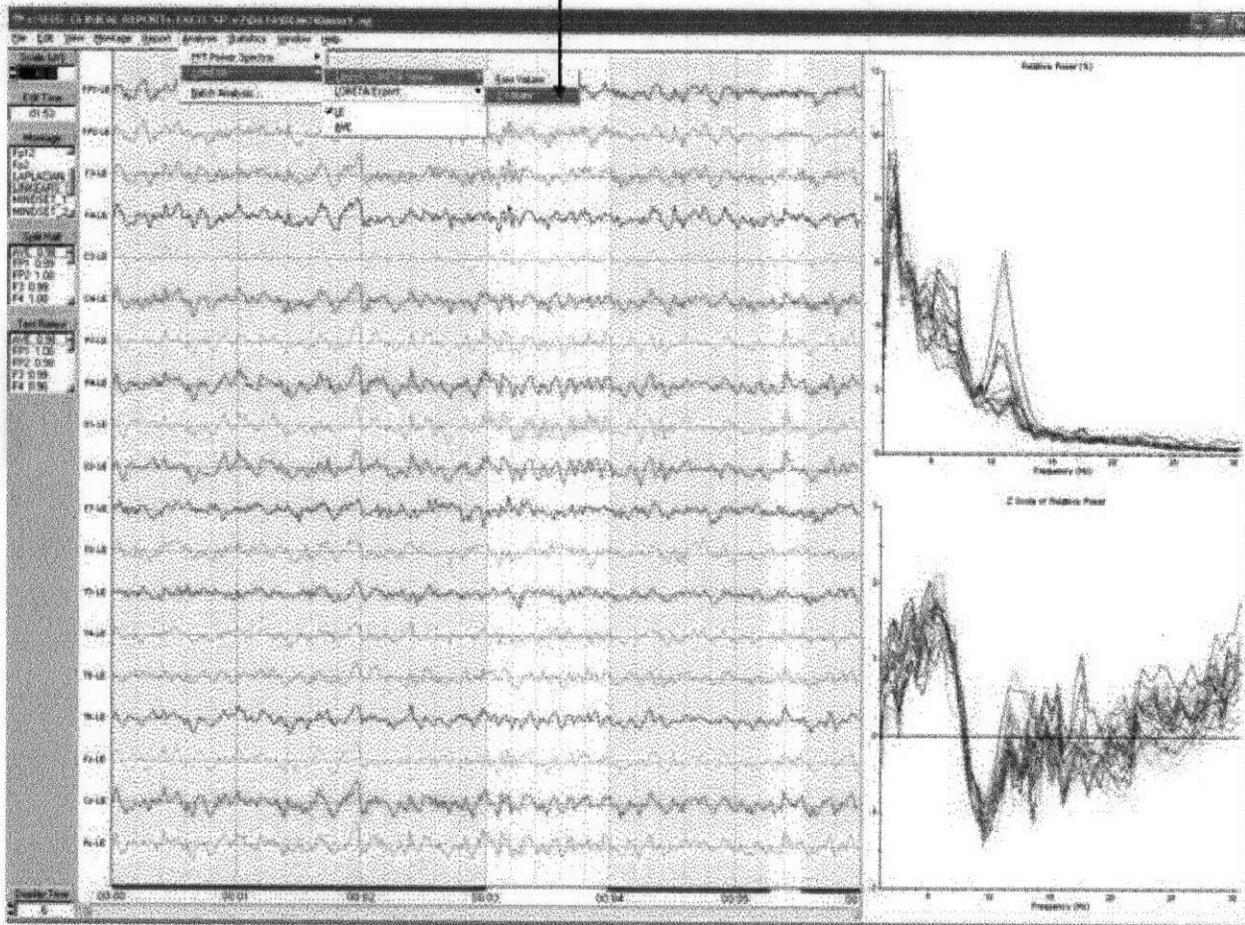
Time Frame is Frequency from 1 to 30 Hz

The cross-spectral values are computed according to the equations provided by the Key Institute for frequency domain analysis (i.e., Hermitian matrix multiplication without the 2π scaling and any unspecified scaling) and the spatial localization can be independently verified by exporting the same EEG selections in the time domain (see step # 15). See Step # 16 for further details and options involved in the use of the Key Institute LORETA software. The automatic launching of the LORETA viewer involves the use of the electrode coordinates and T- Matrix described in Step 16b, thus saving the user of NeuroGuide the trouble of using the time domain to cross-spectral steps described in steps 15 and 16. See the Key Institute documentation to learn how the *.crs file and the *.lorb are computed and then passed to the LORETA viewer by NeuroGuide.

14e - Select artifact free EEG samples then Click Analysis > LORETA > Launch LORETA Viewer > Z Scores (z scores are not available in the Demo

mode). This procedure exports normative database Z scores which is an add on feature of NeuroGuide. See [Appendix F](#) for details.

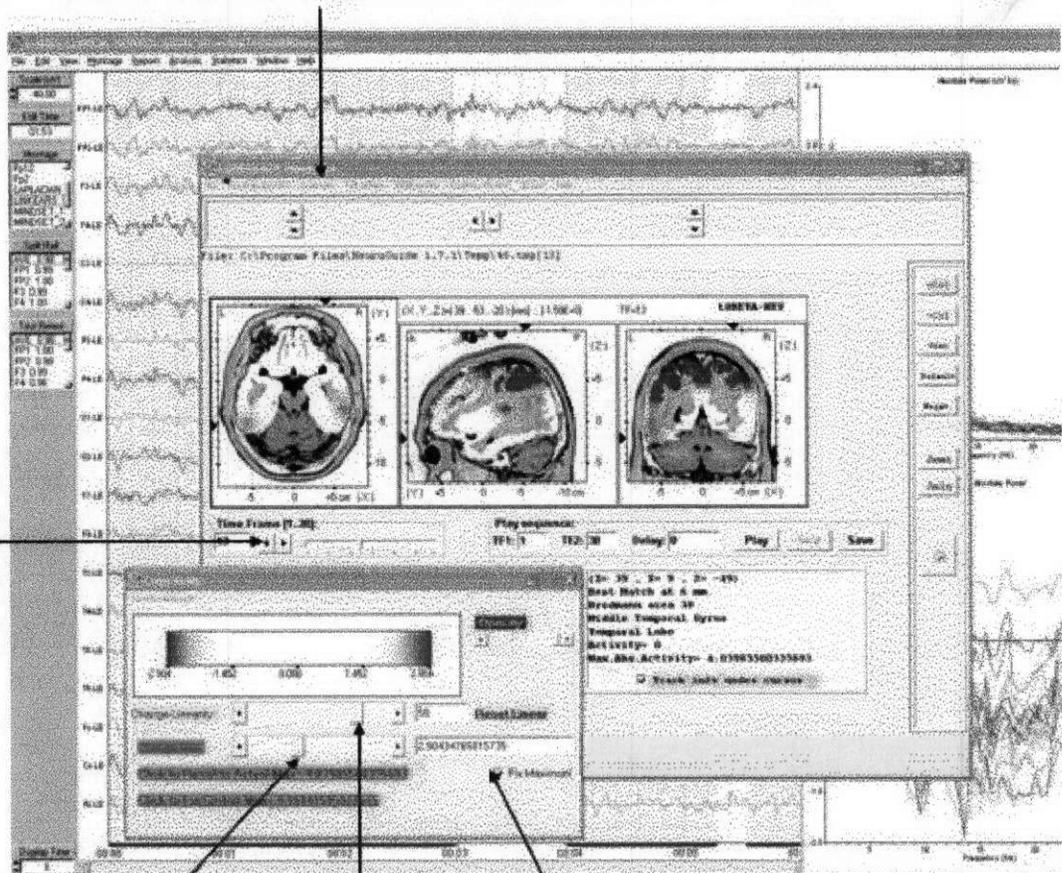
Click - Analysis > LORETA > Launch LORETA Viewer > Z Scores to Export Normative Database Z Scores and Launch the Key Institute LORETA Viewer Program



14f - Click ScaleWin and then click Time Frame > to advance from 1 to 30 Hz and view the default maximum Z Scores. Note that the Z scores of the maximum and minimum blue and red pixels in the MRI sequence may or may not be statistically significant (i.e., $Z > 2$ standard deviations). That is, the default ScaleWin only displays the "maximum" and "minimum" Z scores which may or may not be $Z > 2$ standard deviations. Click "Play" to automatically step through the entire spectrum of Z scores and note the Z score maxima and minima. Click the NeuroGuide edit window and identify the frequencies at which the maximum deviations from normal occur on the scalp surface and then type these frequencies into the Explorer Viewer time frame and examine the LORETA solution.

Click – ScaleWin and Adjust the Color Scale and Viewer Settings

Advance Time Frames Corresponding To the Surface EEG Z Scores in NeuroGuide Edit Window



Change Z Score Max & Min

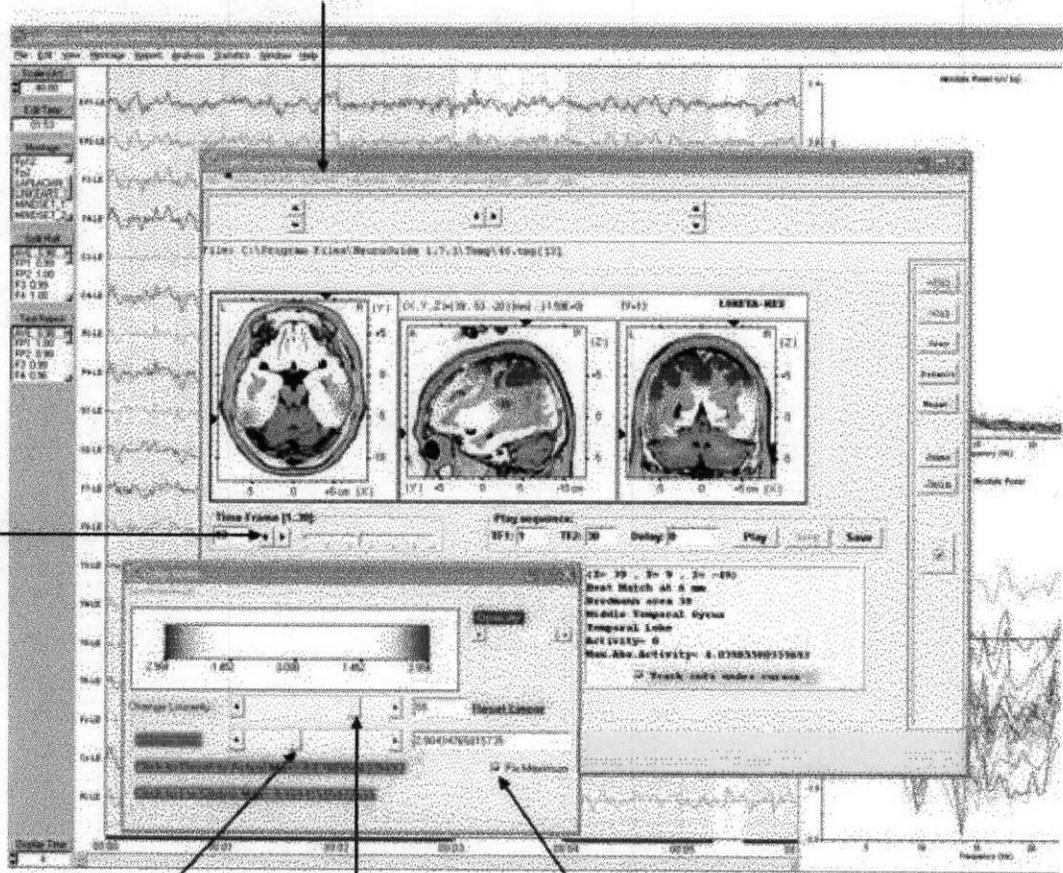
Adjust Color Extremes

DO Not Check "Fit Maximum" to For the Maximum Z Score Value

14g - Click - ScaleWin in the Viewer and then check "Fit Maximum" and move "Change Max" wiper to adjust Z score thresholds and move "Change Linearity" wiper to adjust color extremes. Z scores are only valid if they correspond to the surface EEG measures in the NeuroGuide edit window. Click the NeuroGuide EEG tracing and dynamic FFT window and determine the frequencies of maximum deviance from normal and then click the LORETA Viewer and change frequency and Z score settings accordingly. Details of normative database creation and validation using the Key Institute software and NeuroGuide computation of the Key Institute equations are provided in Appendix F.

Click – ScaleWin and Adjust the Color Scale and Viewer Settings

Advance Time Frames Corresponding To the Surface EEG Z Scores In NeuroGuide Edit Window



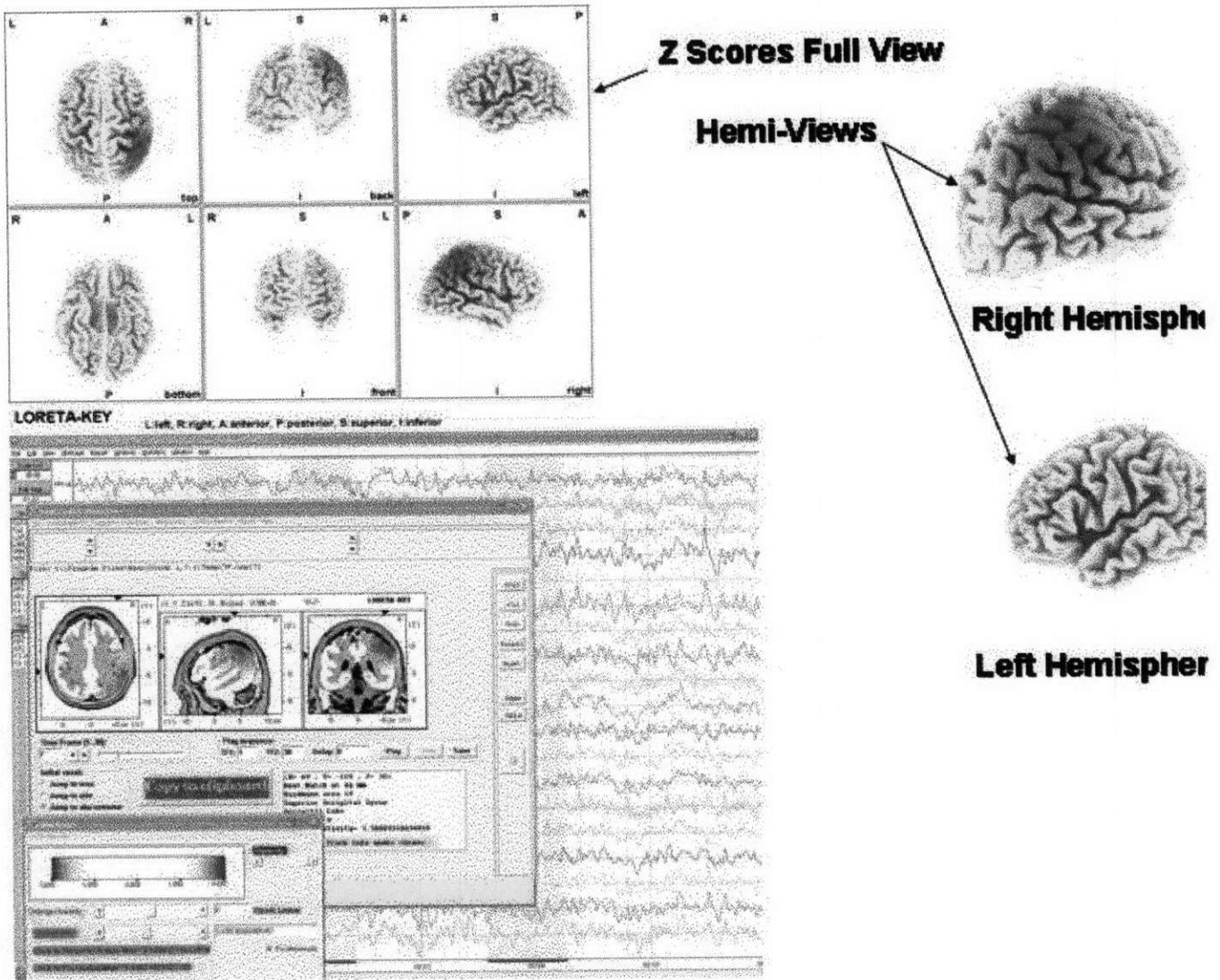
Change Z Score Max & Min

Adjust Color Extremes

Check "Fit Maximum" to scan For a Threshold Z Score Value

[Return to Top](#)

14h - In the LORETA Viewer Click "3DSurf" to Open the 3-Dimensional Rendered Brain. Click "Orthoview" to Produce a Full View of the Rendered Brain and the Location of Z Scores. Click "Left" or "Right" to View the Hemispheres.



[Return to Top](#)

Step # 15 – LORETA Export of EEG Time Series in ASCII Format – Easy Steps

[Return to Top](#)

NEUROGUIDE TIME SERIES EXPORT

1- After editing the 19 channels of digital EEG, in the NeuroGuide menu bar select "Analysis > LORETA Export" and click on "Overlapping Windows" and the "Save Export Files" window will appear.

2- In the "Save Export Files" window Click on the create folder button and name the folder "Overlap-LE"

mk:@MSITStore:C:\Program%20Files\RoboHelp%20Office\RoboHTML\NEUROGUIDE\... 5/2/2004

3- Double click on the new folder (i.e., Overlap-LE), name the files LE and then click Save.

LORETA – Key CROSS-SPECTRUM

1- Download the FREE Key Institute LORETA software (www.unizh.ch/keyinst/NewLORETA/Software/Software.htm) and then launch it and double click on “EEG cross-spectrum” (users must first obtain a password to use the FREE Key Inst. Software).

2- From the FREE Key Inst. EEG cross-spectral maker menu select “A1EEGs -> 1Spec (aut)” and navigate to where you saved the “LORETA Export” files from NeuroGuide (i.e., step #2). Click “Add this folder” and click “add all sub-folders”.

3- Type: Number of electrodes = 19, Number of time frames = 256, sample rate = 128, select “normalize each EEG file, select the top frequency option, click “GO”.

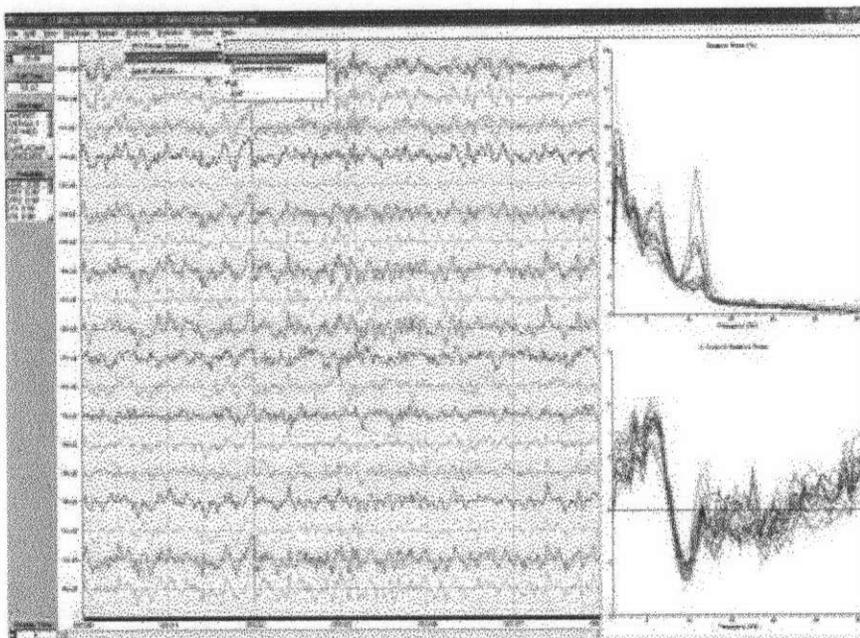
LORETA – Key 3-D IMAGES

1- Re-Activate the main LORETA window and double click “LORETA Explorer for cross-spectra” then in the menu bar select “File > Open EEG-crs” and select the crs file created in steps # 5 & 6 , “Open Electrode Coords” and select “Lex-TalairachCoord.xyz”, highlight File>Open TransfMatrix and select the file “LexTMatrix.tm file. These two files were created using the Key Institute “Electrode Coordinates Maker” and the Lexicor electrode order for the international 10/20 system of electrodes. Download the coordinate and transfer matrix files as www.appliedneuroscience and click the demo webpage to download.

2- Now click on the part of the spectrum that you are interested in and create the 3-D displays that you are interested in. Try “3Dsurf” and “ScaleWin” and please read the LORETA-Key manual pages 34 and 35.

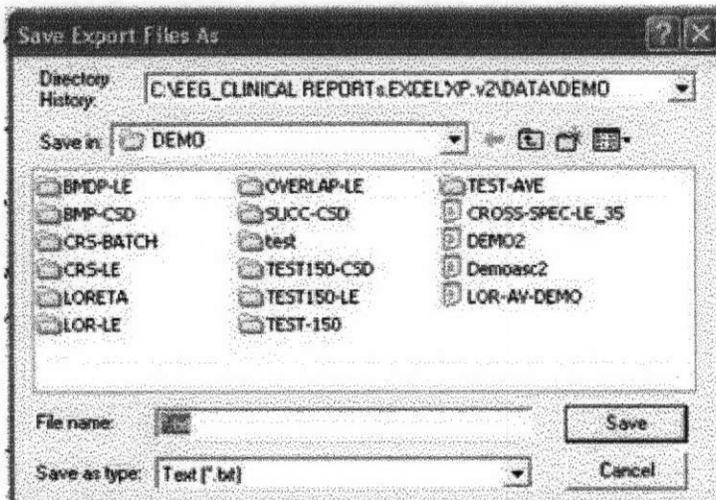
15a – Details of Export of ASCII EEG as a Time Series

After making your edit selections in the NeuroGuide edit window, highlight “Analysis” in the menu bar and select “LORETA Export”. There are two options: “Overlapping Windows” or “Successive Windows”. For purposes of this demo, select “Overlapping Windows” by highlighting with the left mouse button. Then click on “Overlapping Windows”.



15b – Save Key Inst. Formatted Files in a Folder

Click on the create folder button and name the folder Overlap-LE (e.g., for Cross-Spectral Linked Ears montage). Open the folder & type the file name LE.txt and click save. This will save the successive ASCII files in the Key Inst. Institute format for the “A1EEGs -> 1Spec(aut)” option.



Selection of the “Overlapping Windows” option minimizes the FFT windowing effects by overlapping 256 point x 19 channel EEG segments by 75% in ASCII format (see Kaiser & Sterman, J. of Neurotherapy, 4(3): 85-92, 2001). This is a standard procedure in NeuroGuide, including the method by which the normative EEG data was analyzed. The “Successive Windows” method saves successive 256 point data without overlapping which is not optimal as discussed by Kaiser & Sterman, 2001). The user is encouraged to compare and contrast the “Successive Windows” vs the “Overlapping”

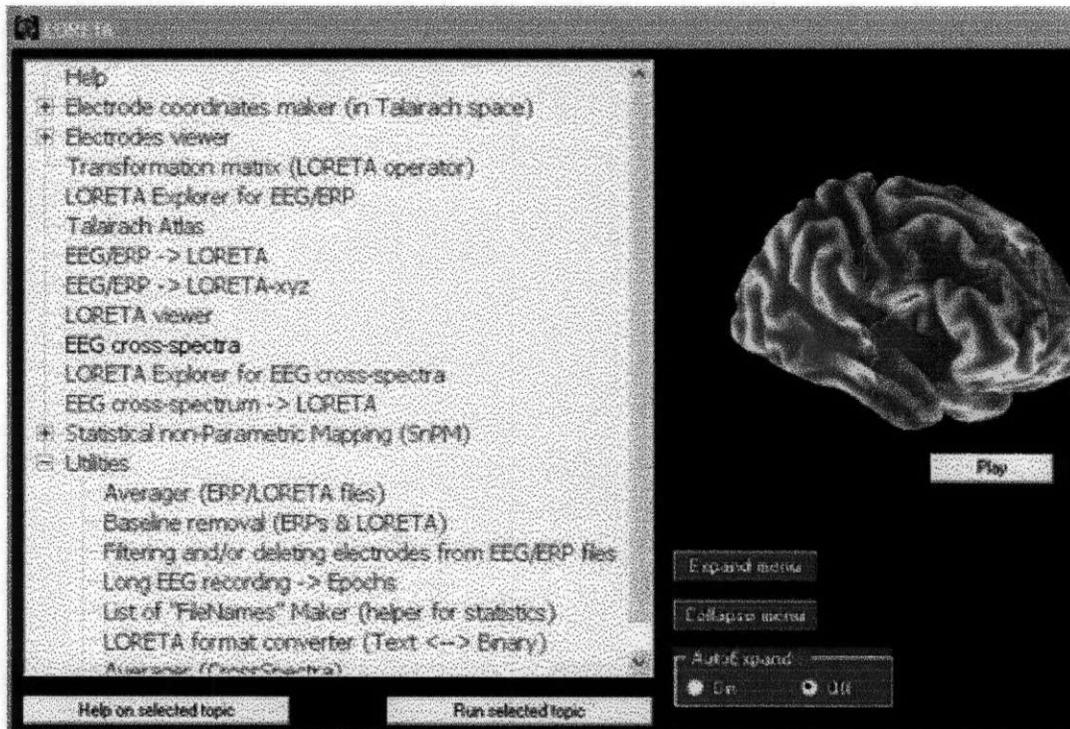
mk:@MSITStore:C:\Program%20Files\RoboHelp%20Office\RoboHTML\NEUROGUIDE\... 5/2/2004

methods in order to see the effects of the cosine taper windowing of a 256 point FFT.

16 – Import of ASCII EEG Time Series to LORETA – EEG Cross-Spectra

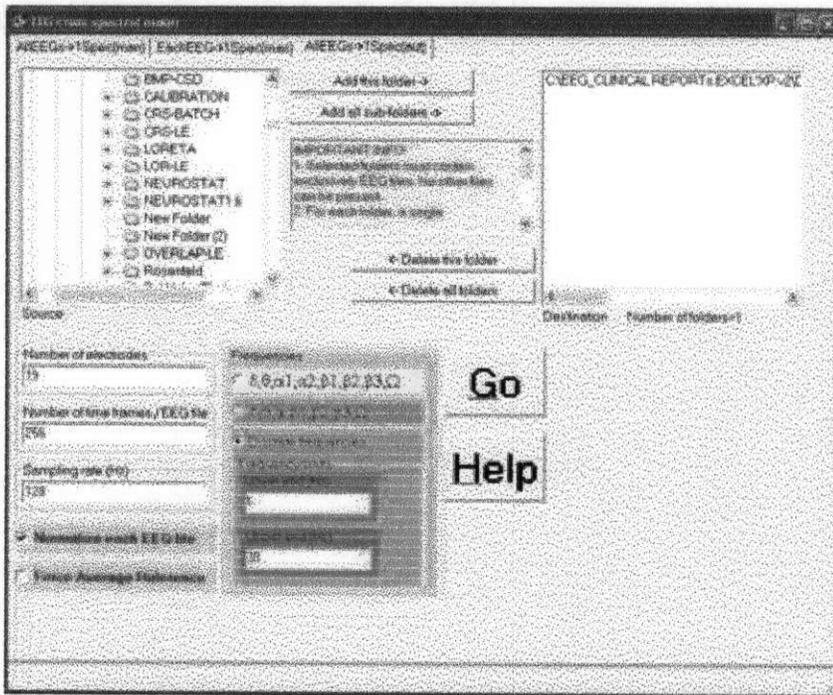
[Return to Top](#)

First download the “Lex-Talairachcoord.xyz” and the “Lex-TalairachTMatrix.tm” files from the Demo page of www.appliedneuroscience.com and save these files in a convenient location. The user must download the free Key Institute LORETA Internet software by going to <http://www.unizh.ch/keyinst/NewLORETA/Software/Software.htm>. Once the Key Inst. Software is installed, launch the LORETA program and double click on “EEG Cross-Spectra”



16a – Activate the EEG Cross-spectral maker > AIEEGs ->1Spec(aut)

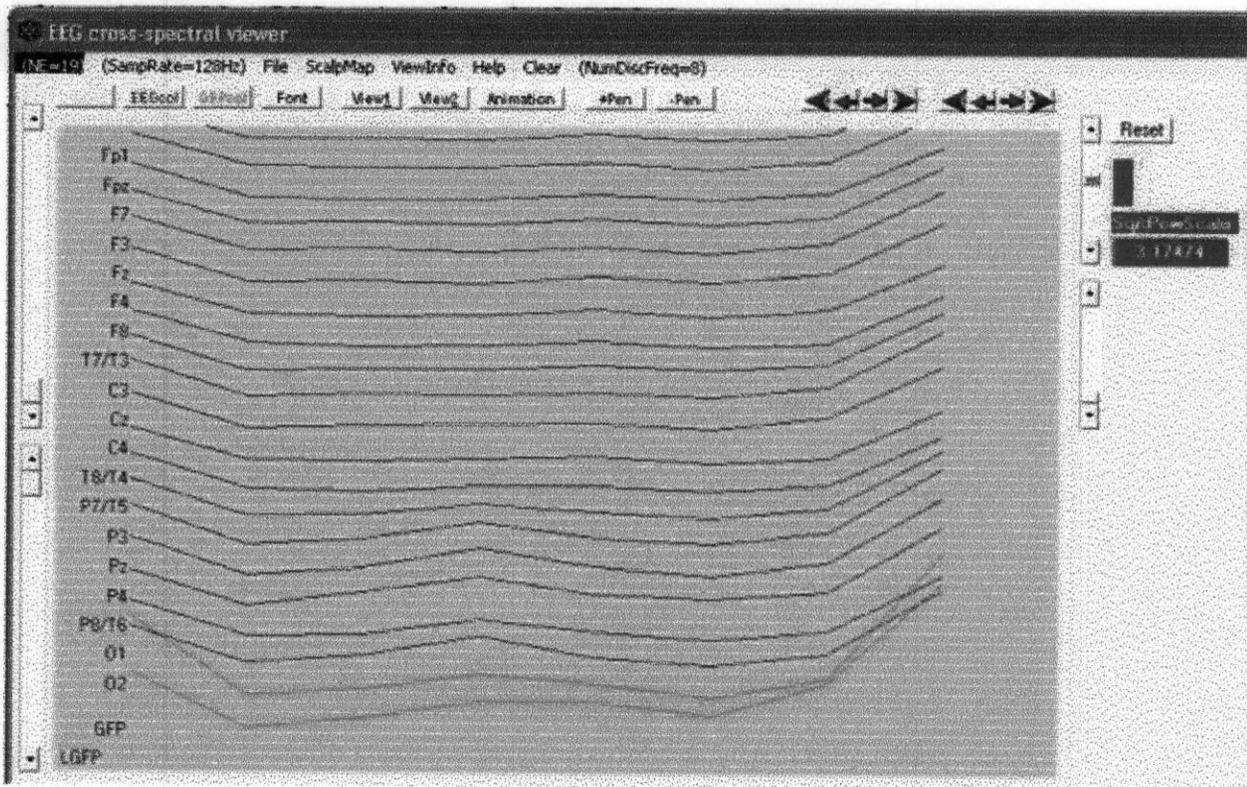
As described on page 34 of the Key Inst. Documentation the A1EEGs -> 1Spec (aut) option computes 1 single cross-spectral file for each and every 256 point NeuroGuide time series file that the user previously saved as described in section 11a. The window below will appear:



Navigate to the location where you created the folder “Overlap-LE” described in 11a and then click “Add this folder ->” and “add all sub-folders ->”. Type 19 as the number of electrodes, type 256 as the number of time frames/EEG file, type 128 as the sampling rate (Hz), click Normalize each EEG file (deselect “Force Average Reference” users are encouraged to repeat these steps using “Force Average” to compare and experiment), click the Discrete frequency selection and set the lower end = 1 Hz and the Upper end = 30 Hz then click “Go”. A cross-spectral file with a *.crs extension will be saved with the same folder name of “Overlap-LE” that you created in section 11a.

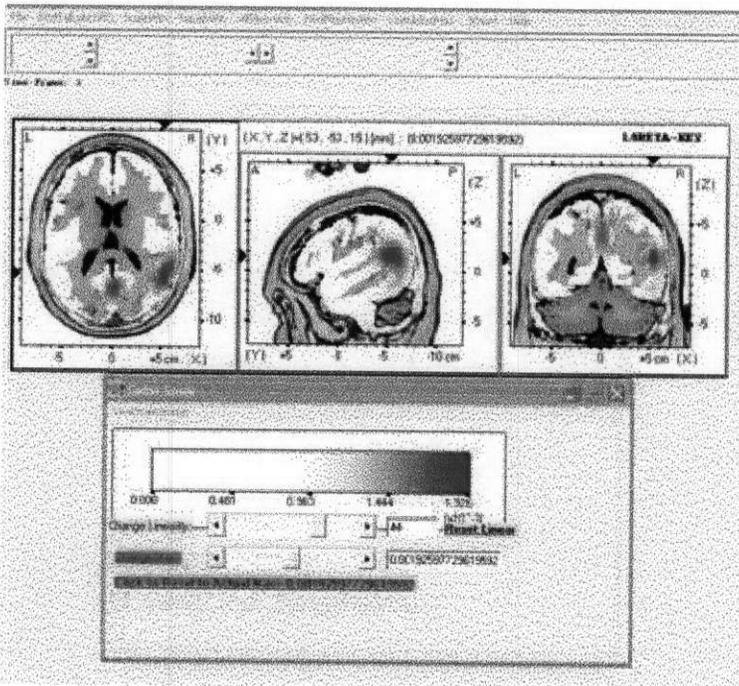
16b – LORETA Explorer for EEG Cross-Spectrum

Double click “LORETA Explorer for Cross-Spectrum” in the main LORETA Key Institute window. Highlight File > Open EEG – crs and navigate to the folder where the *.crs file was saved in section 15b and select the cross-spectral file that you created. Highlight File > Open Electrode Coords and navigate to select the electrode coordinate file for Lexicor. NeuroGuide uses the “Lex-Talairachcoord.xyz” file which was produced by the Key Inst. Talairach Electrode Coordinate Maker and is compatible with the Lexicor order of electrodes using the LORETA Export menu. Repeat this step and highlight File>Open TransfMatrix and select the file “and the “Lex-TalairachTMatrix.tm” which was also produced by the Key Inst. Software using the Lexicor electrode order. The following window will appear:

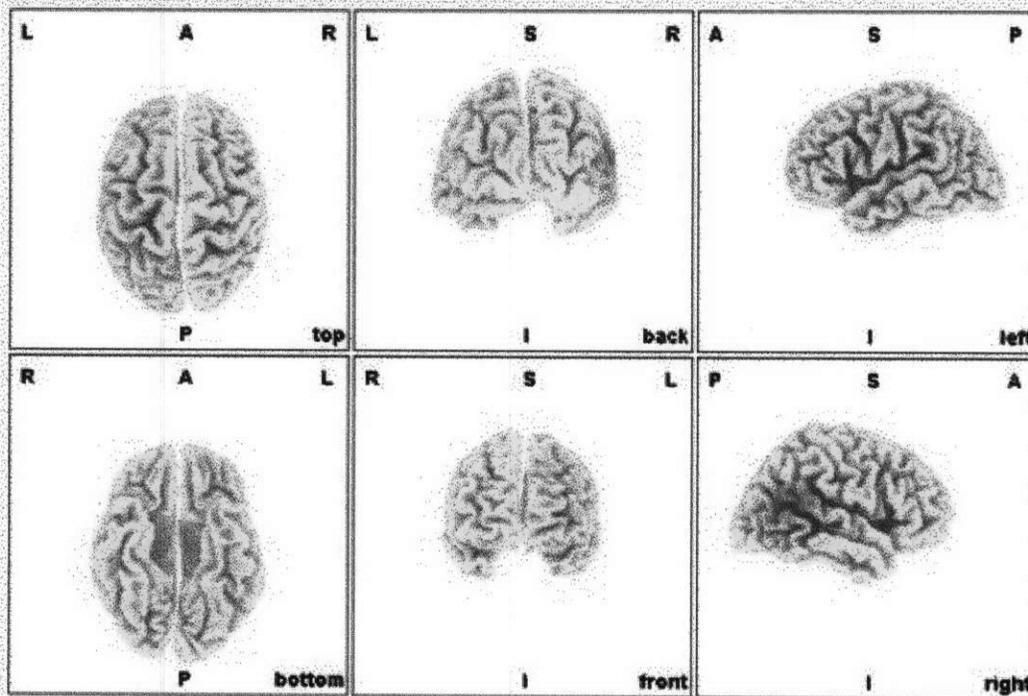


16c – Create 3-D Maps

To create 3-D LORETA maps use your left mouse button to select one of the eight frequency bands and then click "View1". 3-D LORETA source localization will appear at the top of the screen.



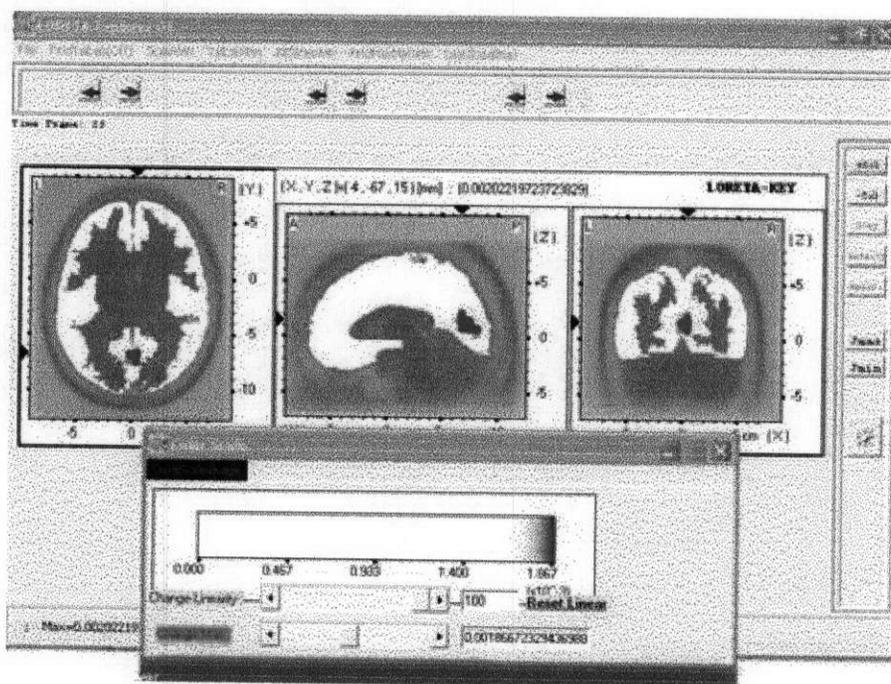
Click "3Dsurf" at the top of the LORETA Explorer menu to activate the cortical surface images. Click "Orthoview" to produce the 9 different views below:



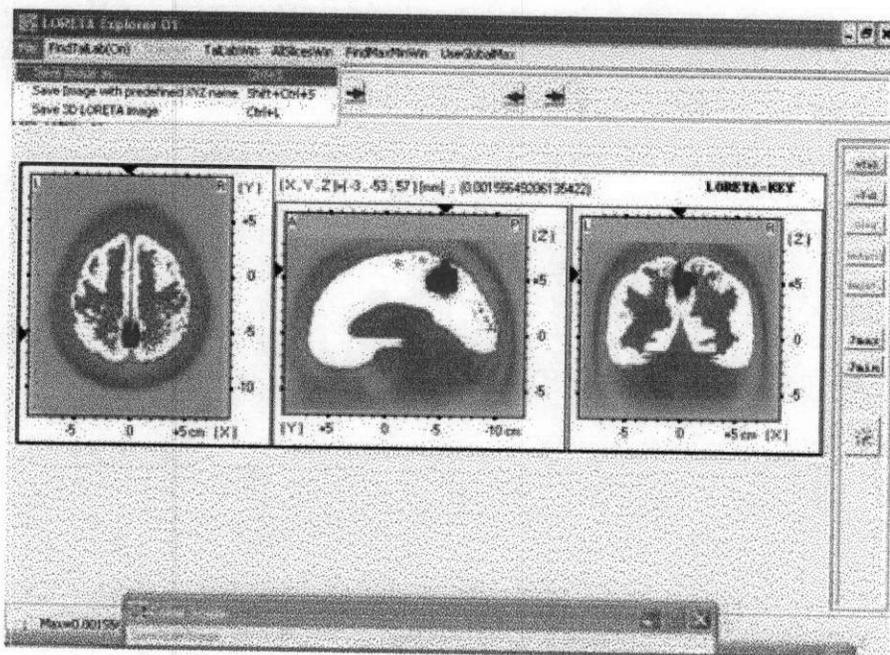
LORETA-KEY

L:left, R:right, A:anterior, P:posterior, S:superior, I:inferior

16d – In LORETA Explorer Place the Color Scale Window Below the 3-Dimensional Images. Set the "Change Linearity" Wiper to the far right and then move the "Change Max" Wiper to the right and left. Observe how the absolute power values spatially extend from the Midline Visual Cortex or the Midline Occipital Cortex (near to Visual Area 17) and then spreads to Visual Area 18 as the "Change Max" Wiper.

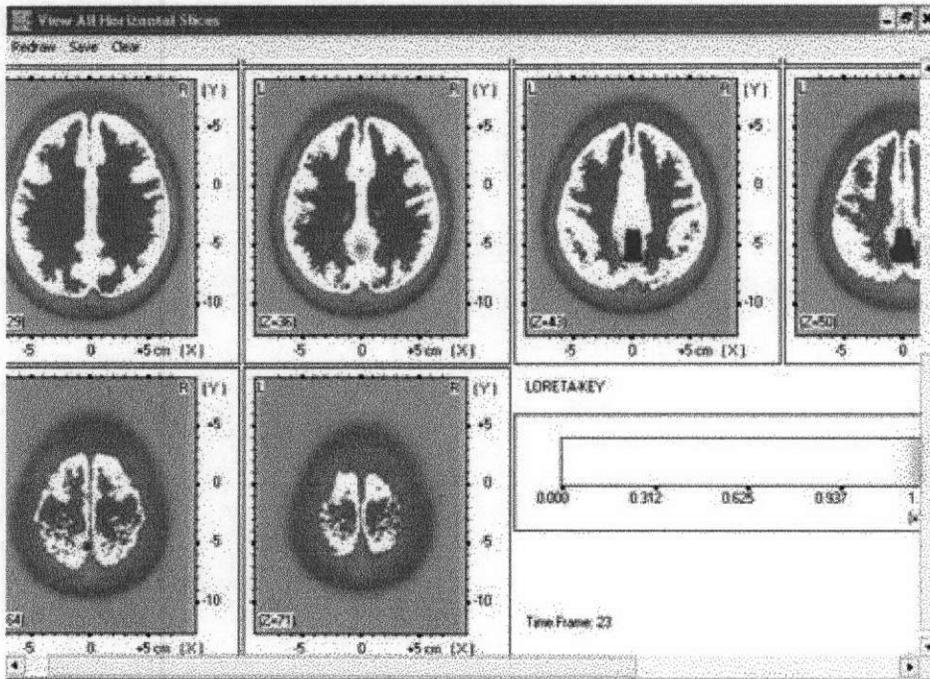


16e – Save the LORETA Images in jpeg format. Click File and then Save As.

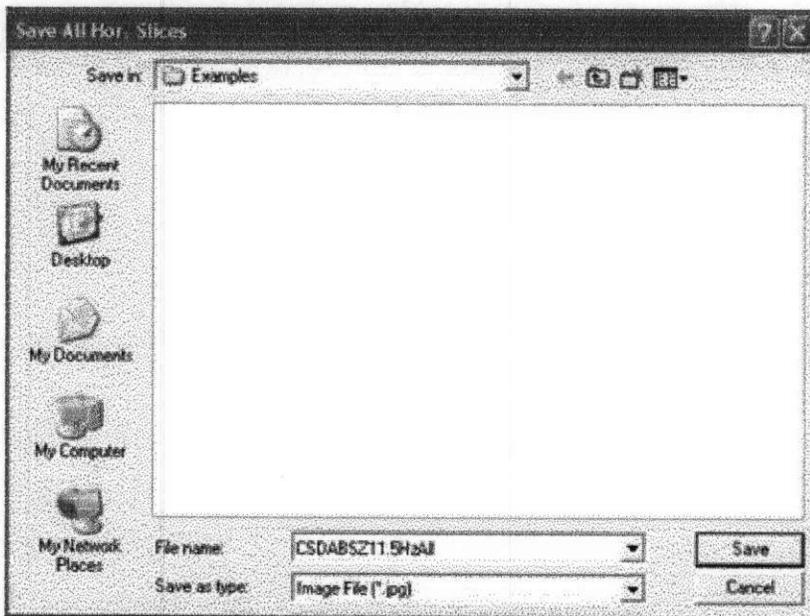


16f – Examine All of the LORETA Slices. Click “AllSlicesWin” in the LORETA Explorer Menu.

mk:@MSITStore:C:\Program%20Files\RoboHelp%20Office\RoboHTML\NEUROGUIDE\... 5/2/2004



16g – Save the All Slices LORETA images in jpeg format by Clicking “Save”.



16h – Repeat Step 15a to 16g by importing a different NeuroGuide Output file into the LORETA Explorer by clicking on the “Open EEG/ERP” menu. Repeat Steps 16b – 16g with a different NeuroGuide ASCII time series output, for example, an Eyes Open condition from the same subject and explore the fine details of the 3-Dimensional Sources of the EEG. Enjoy exploring relationships between frequency and 3-D space

mk:@MSITStore:C:\Program%20Files\RoboHelp%20Office\RoboHTML\NEUROGUIDE\... 5/2/2004

Appendix - A: Warning about Digital and Statistical Analyses of the EEG

Return to Top

Warning: NeuroGuide does not diagnose and only provides displays of the digital EEG and statistical analyses of selected EEG segments. NeuroGuide requires competent human intervention for its many mathematical tools and NeuroGuide is only considered as an adjunct and/or as a supplement to other measures that may aid in evaluating the status of the EEG by a competent person. Clinical use of NeuroGuide requires a competent medical or clinical professional. NeuroGuide is a standalone software package that uses "look up" table functions to create Z scores which are a reference based on published scientific selection criteria of samples of EEG (Thatcher et al 1987; 1986; 1989; 2003) and the use of these tables is at the discretion of the competent professional. It is advised that reliability measurements and validity tests using different montages and different selections of EEG be conducted as a routine procedure when using NeuroGuide. NeuroGuide was designed to allow for mouse click selections and testings of hypotheses and reliability and validity using digital analyses of the EEG.

Contra indications: EEG artifact can invalidate analyses and improper positioning of electrodes or significant deviations from accepted standards of electroencephalographic recording methodology can invalidate EEG recordings or erroneous storage of data and falsification of data, improper manipulation of data or unlawful uses of NeuroGuide including violations of copyright law and other improper uses of NeuroGuide are all contra indicated.

Appendix – B:

Return to Top

Computation of the auto-spectral and cross-spectral densities, Coherence, Phase Delays and Amplitude Asymmetry of the edited EEG selections

Use the Signal Generator to Calibrate the Digital Signal Processing

1- Import of digital EEG data involves the following steps: 1- Down-sample or up-sample to 128 Hz, 2- Baseline the EEG by filtering at < 1 Hz and > 40 Hz (5th order Butterworth filters and creating values from zero time to negative time to allow the filter to start at time point = 0); 3- After each edit selection baseline the spliced selections of EEG by filtering a second time at < 1 Hz and > 40 Hz.

2- Amplifier equilibration is computed as the difference between the normative database amplifier characteristics in microvolts based on the frequency response of a calibrated sine wave from 1 to 40 Hz. The equilibration ratio for each EEG machine manufacturer is a coefficient in all of the subsequent spectral computations in the list of EEG

mk:@MSITStore:C:\Documents%20and%20Settings\Owner\Desktop\NeuroGuide_Deluxe.... 5/4/2004

machines in the File > Open window. The FFT (Fast Fourier Transform) parameters are: epoch = 2 seconds at a sample rate of 128 sample/sec = 256 digital time points and a frequency range from 0.5 to 40 Hz at a resolution of 0.5 Hz using a cosine taper window.

Each 2 second FFT is 81 rows (frequencies 0 to 40 Hz) X 19 columns (electrode locations) = 1,539 element cross-spectral matrix for each subject. NeuroGuide uses the same equations as used by the Key Institute and Bendat and Piersol, 1980; Otnes and Enochson, 1978 which are standard equations. The N in the Key Institute cross-spectrum equations 16 and 17 is the number of 2 second windows that are used in the computation of the average FFT which is the number of 2 second windows/N over all EEG selections. The last whole integral of 256 points marks the end of window summation and averaging. The N sub T (Key Inst. equation 17) is the number of time frames per FFT window = 256 at 128 samples per second.

3- In order to minimize the effects of windowing in the FFT (Kaiser and Sterman, J. Neurotherapy, 4(3): 85-92, 2001) a EEG sliding average of the 256 point FFT cross-spectral matrix was computed for each normal subject's edited EEG by advancing in 64 point steps (75% overlap) and recomputing the FFT and continuing with the 64 point sliding window of 256 point FFT cross-spectrum for the entire edited EEG record. Each of the 81 frequencies for each 19 channels is log₁₀ transformed to better approximate a normal distribution. The total number of 2 second windows is the number that is entered into the analysis of variance and t-tests and it is used to compute the degrees of freedom for a given statistical test.

4- A mean, variance, standard deviation, sum of squares, and squared sum of the real (cosine) and imaginary (sine) coefficients of the cross-spectral matrix is computed across the sliding average of edited EEG for all 19 leads for the total number of 81 and 1,539 log transformed elements for each subject. This creates the following seven basic spectral measurement sets and their derivatives 1- Cross-Spectral Power (square root of the sums of squares of the real and imaginary coefficients); 2- Auto-Spectral Power which is the diagonal of the cross-spectral matrix where the imaginary coefficient = 0 and power = sine square; 3- Amplitude asymmetry of auto-spectral power = $(A-B)/(A+B)$ x 200 where A = EEG channel 1 and B = EEG channel 2; 4-Coherence = square of the cross-spectrum divided by the product of the two auto-spectra; 5- Phase = arctangent of the ratio of the real/imaginary components for frequencies from 0.5 to 40 Hz.; 6- Real coefficients; 7 - Imaginary coefficients (Bendat and Piersol "Engineering applications of correlation and spectral analysis", John Wiley & Sons, NY, 1980; Otnes and Enochson "Digital time series analysis", Wiley-Interscience, 1978; Press et al, "Numerical recipes in C").

Appendix - C: Warning about Exporting Edited Digital EEG in Lexicor Format

Return to Top

Warning: NeuroGuide uses a splicing method of appending edited selections of EEG (minimum segment length = 600 msec.) and then baselines using a Butterworth high

mk:@MSITStore:C:\Documents%20and%20Settings\Owner\Desktop\NeuroGuide_Deluxe.... 5/4/2004

and brain anatomy using NeuroGuide's Exports to LORETA.

LORETA is a special and excellent program and the user needs to read the LORETA Explorer manual that is provided with the program from the Key Institute before using it.

A number of different tools are available after you launch the Key Institute LORETA programs. Validation of LORETA is necessary before one can trust the solutions that are provided. Try validating by comparing Eyes Open vs Eyes Closed changes in amplitude of the alpha rhythms. It is expected that if the visually observed alpha is maximal in O1 and O2, then it should also be maximal in LORETA in the posterior cortical regions and not in the midline Pz lead or in anterior cortical regions, etc. Users must be cautious to validate LORETA to the extent that LORETA is consistent with physiological information and the re-montaged digital EEG.

All comments and feedback are welcome.

Contact us at qeeg@appliedneuroscience.com and tell us what you think.

Appendix - A: Warning about Digital and Statistical Analyses of the EEG

[Return to Top](#)

Warning: NeuroGuide does not diagnose and only provides displays of the digital EEG and statistical analyses of selected EEG segments. NeuroGuide requires competent human intervention for its many mathematical tools and NeuroGuide is only considered as an adjunct and/or as a supplement to other measures that may aid in evaluating the status of the EEG by a competent person. Clinical use of NeuroGuide requires a competent medical or clinical professional. NeuroGuide is a standalone software package that uses "look up" table functions to create Z scores which are a reference based on published scientific selection criteria of samples of EEG (Thatcher et al 1987; 1986; 1989; 2003) and the use of these tables is at the discretion of the competent professional. It is advised that reliability measures and validity tests using different montages and different selections of EEG be conducted as a routine procedure when using NeuroGuide. NeuroGuide was designed to allow for mouse click selections and testings of hypotheses and reliability and validity using digital analyses of the EEG.

Contra indications: EEG artifact can invalidate analyses and improper positioning of electrodes or significant deviations from accepted standards of electroencephalographic recording methodology can invalidate EEG recordings or erroneous storage of data and falsification of data, improper manipulation of data or unlawful uses of NeuroGuide including violations of copyright law and other improper uses of NeuroGuide are all contra indicated.

mk:@MSITStore:C:\Program%20Files\RoboHelp%20Office\RoboHTML\NEUROGUIDE\... 5/3/2004

Appendix – B:

Return to Top

Computation of the auto-spectral and cross-spectral densities, Coherence, Phase Delays and Amplitude Asymmetry of the edited EEG selections

Use the Signal Generator to Calibrate the Digital Signal Processing

- 1- Import of digital EEG data involves the following steps: 1- Down-sample or up-sample to 128 Hz, 2- Baseline the EEG by filtering at < 1 Hz and > 40 Hz (5th order Butterworth filters and creating values from zero time to negative time to allow the filter to start at time point = 0); 3- After each edit selection baseline the spliced selections of EEG by filtering a second time at < 1 Hz and > 40 Hz.

- 2- Amplifier equilibration is computed as the difference between the normative database amplifier characteristics in microvolts based on the frequency response of a calibrated sine wave from 1 to 40 Hz. The equilibration ratio for each EEG machine manufacturer is a coefficient in all of the subsequent spectral computations in the list of EEG machines in the File > Open window. The FFT (Fast Fourier Transform) parameters are: epoch = 2 seconds at a sample rate of 128 sample/sec = 256 digital time points and a frequency range from 0.5 to 40 Hz at a resolution of 0.5 Hz using a cosine taper window. Each 2 second FFT is 81 rows (frequencies 0 to 40 Hz) X 19 columns (electrode locations) = 1,539 element cross-spectral matrix for each subject. NeuroGuide uses the same equations as used by the Key Institute and Bendat and Piersol, 1980; Otnes and Enochson, 1978 which are standard equations. The N in the Key Institute cross-spectrum equations 16 and 17 is the number of 2 second windows that are used in the computation of the average FFT which is the number of 2 second windows/N over all EEG selections. The last whole integral of 256 points marks the end of window summation and averaging. The N sub T (Key Inst. equation 17) is the number of time frames per FFT window = 256 at 128 samples per second.

- 3- In order to minimize the effects of windowing in the FFT (Kaiser and Serman, J. Neurotherapy, 4(3): 85-92, 2001) a EEG sliding average of the 256 point FFT cross-spectral matrix was computed for each normal subject's edited EEG by advancing in 64 point steps (75% overlap) and recomputing the FFT and continuing with the 64 point sliding window of 256 point FFT cross-spectrum for the entire edited EEG record. Each of the 81 frequencies for each 19 channels is log₁₀ transformed to better approximate a normal distribution. The total number of 2 second windows is the number that is entered into the analysis of variance and t-tests and it is used to compute the degrees of freedom for a given statistical test.

- 4- A mean, variance, standard deviation, sum of squares, and squared sum of the real (cosine) and imaginary (sine) coefficients of the cross-spectral matrix is computed across the sliding average of edited EEG for all 19 leads for the total number of 81 and 1,539 log transformed elements for each subject. This creates the following seven basic spectral measurement sets and their derivatives 1- Cross-Spectral Power (square root of the sums of squares of the real and imaginary coefficients); 2- Auto-Spectral Power

mk:@MSITStore:C:\Program%20Files\RoboHelp%20Office\RoboHTML\NEUROGUIDE\... 5/3/2004

which is the diagonal of the cross-spectral matrix where the imaginary coefficient = 0 and power = sine square; 3- Amplitude asymmetry of auto-spectral power = $(A-B)/(A+B) \times 200$ where A = EEG channel 1 and B = EEG channel 2; 4-Coherence = square of the cross-spectrum divided by the product of the two auto-spectra; 5- Phase = arctangent of the ratio of the real/imaginary components for frequencies from 0.5 to 40 Hz; 6- Real coefficients; 7 – Imaginary coefficients (Bendat and Piersol "Engineering applications of correlation and spectral analysis", John Wiley & Sons, NY, 1980; Otnes and Enochson "Digital time series analysis", Wiley-Interscience, 1978; Press et al, "Numerical recipes in C".

Appendix - C: Warning about Exporting Edited Digital EEG in Lexicor Format

[Return to Top](#)

Warning: NeuroGuide uses a splicing method of appending edited selections of EEG (minimum segment length = 600 msec.) and then baselines using a Butterworth high pass filter at 1 Hz and a low pass filter at 40Hz so as to minimize splicing artifact. When NeuroGuide exports the edited selections in Lexicor format there is an approximation to baseline adjustment and possible splice artifact may occur when the edited data are imported into other software platforms. Another warning about cross-platform comparisons are possible differences in FFT epoch lengths (NeuroGuide uses 2 second epoch lengths), windowing methods (NeuroGuide uses cosine taper windowing), successive vs. overlapping epochs (NeuroGuide uses 75% sliding epoch overlapping while other platforms do not use overlapping epochs, see Appendix B), etc. Within platform analyses using calibration sine waves are recommended and cross-platform comparisons are not recommended unless the same analytical procedures are used.

Appendix – D: Default LORETA Electrode Coordinates and T Matrix

[Return to Top](#)

ASCII Electrode Order and Spherical Coordinates for Use of the NeuroGuide Output Files with the Key Inst. LORETA Explorer. If the "Lex-TalairachCoord.xyz" file is not available then create this file by copying the values in the Table below and save as an ASCII file (tab delimited, free space or comma delimited). You will need this file in order to use the NeuroGuide output files with the LORETA Explorer. The user of course can always create their own electrode coordinate files and 'T' matrices by using the Key Institute's "Talairach Electrode Coordinate Maker 01

mk:@MSITStore:C:\Program%20Files\RoboHelp%20Office\RoboHTML\NEUROGUIDE\... 5/3/2004

	A	B	C	D
1	19.0000000			
2	-32.8106500	81.0014200	-3.6996630	Fp1
3	32.8106500	81.0014200	-3.6996630	Fp2
4	-50.9022100	48.1851900	50.4379300	F3
5	50.9022100	48.1851900	50.4379300	F4
6	-61.1154100	-13.0630900	69.4728100	C3
7	61.1154100	-13.0630900	69.4728100	C4
8	-51.4187000	-77.4712400	63.7236800	P3
9	51.4187000	-77.4712400	63.7236800	P4
10	-31.6591500	-116.3994000	16.3618900	O1
11	31.6591500	-116.3994000	16.3618900	O2
12	-70.6373800	31.5961900	1.3213170	F7
13	70.6373800	31.5961900	1.3213170	F8
14	-82.4581900	-19.4618900	6.5102720	T7/T3
15	82.4581900	-19.4618900	6.5102720	T8/T4
16	-73.4313200	-72.5394700	11.9044600	P7/T5
17	73.4313200	-72.5394700	11.9044600	P8/T6
18	0.0000000	56.9681500	71.0918800	Fz
19	0.0000000	-10.3126900	96.5361000	Cz
20	0.0000000	-80.1928200	83.6937200	Pz

Appendix – E: University of Maryland Amplifier Characteristics

Return to Top

Normative reference EEG was acquired using 20 identical amplifiers mounted in a rack at the Baltimore campus and another rack of 20 identical amplifiers at the Eastern Shore campus. Each of the amplifiers and A/D systems were calibrated before and after each subject's EEG and evoked potential acquisition.

- 1- **Gain = 10^4 v/v switchable to 10^5 v/v**
- 2- **Gain Stability = 0.5%**
- 3- **Common Mode Rejection = 100 db**
- 4- **Bandwidth: 0.5 Hz to 29 Hz 3db point with notch filter at 60 Hz. Notch Q = 10, Notch rejection = 40 db, flatness less than 0.25 db.**
- 5- **Input Impedance = 100 meg (differential or common mode).**
- 6- **Noise Level = 0.5 uv p-p at 10^4 v/v & 1.5 uv p-p at 10^5 v/v.**

mk:@MSITStore:C:\Documents%20and%20Settings\Owner\Desktop\NeuroGuide_Deluxe.... 5/4/2004

- 4- Bandwidth: 0.5 Hz to 29 Hz 3db point with notch filter at 60 Hz. Notch Q = 10, Notch rejection = 40 db, flatness less than 0.25 db.
- 5- Input Impedance = 100 meg (differential or common mode).
- 6- Noise Level = 0.5 uv p-p at 10^4 v/v & 1.5 uv p-p at 10^5 v/v.
- 7- Nominal Output Level = $\pm 0.5v$ at 10^4 v/v & $\pm 5v$ at 10^5 v/v.
- 8- Supply Voltage = $\pm 15vdc$.
- 9- Supply Current = +15vdc: 37ma $\pm 10\%$ & -15vdc: 37ma $\pm 10\%$
- 10- A to D conversion = 12 bit, sample and hold (Analog Devices).
- 11- Sample Rate = 100 Hz.

Appendix – F:

[Go to launch LORETA Normative database](#)

Low Resolution Electromagnetic Tomography (LORETA) Normative Reference Database: Birth to 82 years

1.0- Introduction

There are many potential uses of a normative EEG database among the most important being a statistical “guess” as to the “error rate” or to the probability of finding a particular subject’s EEG measure within a reference normal population. Most other uses of a reference EEG database also involve statistics and the same statistics that all of modern clinical medicine relies upon. For example, null hypothesis testing, measures of reliability, sensitivity, power, predictive validity, content validity, etc. all depend on specific assumptions and statistical procedures.

Low Resolution Electromagnetic Tomography (LORETA) (Pascual-Marqui et al, Int. J. Psychophysiol., 18: 49-65, 1994; Pascual-Marqui, Internat. Journal of Bioelectromagnetism 1: 75-86, 1999) is a distributed inverse model of 2,394 gray matter pixels to estimate the current sources in 3-dimensions that give rise to the surface EEG.

The use of a normative LORETA database depends upon the statistical distribution of the 3-dimensional sources. The statistical stability of a normative database is directly related to the extent that the distribution of sources in a large population of normal individuals approximates a Gaussian distribution. This appendix demonstrates how the use of the FFT cross-spectrum of 2,394 sources from a large population of normal subjects provides a reasonable approximation to Gaussian and how leave-one-out cross-validation statistics demonstrate sensitivities > 95% accurate in the statistical estimation of values based on the NeuroGuide normative database. Expertise in the use of the Key Institute LORETA Viewer is necessary and validation of the maximum Z scores by the surface EEG in frequency and scalp location are important. The user of the NeuroGuide LORETA normative database is encouraged to read the Key Institute documentation and always validate the LORETA solutions based on the surface EEG.

1.1 – Key Institute and Applied Neuroscience, Inc. LORETA Normative EEG Database comparative validation

Four different normative reference databases were computed: eyes open and

mk:@MSITStore:C:\Program%20Files\RoboHelp%20Office\RoboHTML\NEUROGUIDE\... 5/2/2004

eyes closed for linked ears and for average reference montages. Five sequential age groupings of 625 normal subjects (Thatcher et al, J. Neurotherapy, 7(3/4): 87-121, 2003) were selected to cover the age range from 2 months to 82 years. The age groupings were: 1- Two months to 5.99 years; 2- 6.0 years to 9.99 years; 3- 10 to 13 years); 4- 13 to 16 years and 16 to 82 years. The details of the selection/exclusion criteria, clinical validation using neuropsychological tests and other aspects of normative reference database creation are described in Thatcher et al (J. Neurotherapy, 7(3/4): 87-121, 2003).

To make sure that the calculations of the 2,394 LORETA currents were correct, two different procedures were compared: 1- the Key Institute computation of currents followed by leave-one-out cross-validation and, 2- NeuroGuide computation of currents followed by cross-validation. Figure 1 is an illustration of a step by step procedure by which the ASCII digital time series was exported to the Key Institute and then the Key Institute software was used to compute *.crs files that were transformed into *.LOR files from which means and standard deviations of the 2,394 gray matter pixels were computed. In order to approximate Gaussian distributions, skewness and kurtosis were calculated and then the individual subject values were transformed by log10 and skewness and kurtosis were re-calculated. Other transforms such as square root and loge were used but these transforms were not as affective in reducing skewness and kurtosis. The left side of the figure is the edited and artifact clean and reliable Digital EEG Time Series which may be re-referenced or re-Montaged to average reference, which is then analyzed using the Key Institute software.

LORETA Normative Database Cross-Validation Tests Using the Key Institute Cross-Spectral Software

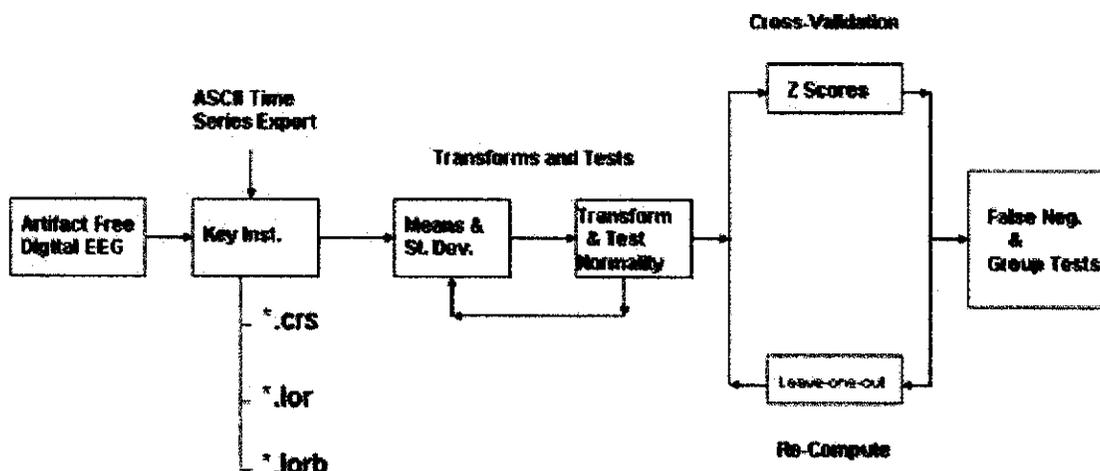


Fig. 1 – Illustration of cross-validation procedures using the Key Institute software to

mk:@MSITStore:C:\Program%20Files\RoboHelp%20Office\RoboHTML\NEUROGUIDE\... 5/2/2004

compute the cross-spectrum and means and standard deviations of the 2,394 LORETA currents. Leave-one-out cross-validation procedures were followed and parametric and non-parametric sensitivities were compared.

The second method which yielded essentially the same results as obtained using the Key Institute software involved computing the cross-spectrum in NeuroGuide and then multiplying the diagonal of the cross-spectral matrix (19 columns) by the Key Institute 'T' matrix of 2,394 x, y & z rows for each frequency (1 to 30 Hz), then computing J or the current source density as the square root of the sum of the squares for each frequency and each of the 2,394 pixels (same procedure as described by the Key Institute manual for the computation of *.crs files). Figure 2 illustrates the cross-validation procedures using the NeuroGuide software and the Key Institute 'T' matrix.

LORETA Normative Database Cross-Validation Tests Using the NeuroGuide Cross-Spectral Software

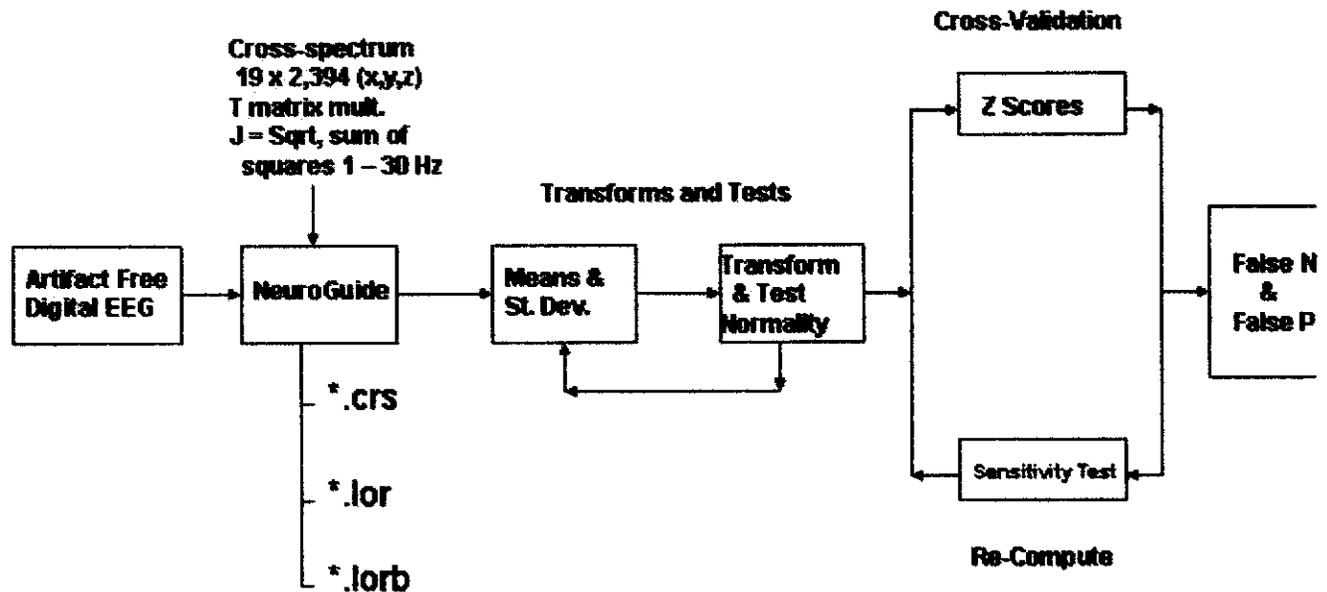


Fig. 2 - Illustration of cross-validation procedures using the NeuroGuide software to compute the cross-spectrum and means and standard deviations of the 2,394 LORETA currents. Approximations to Gaussian were achieved and statistical sensitivities of the Z scores were computed.

2.0 Results

2.1 – Gaussian Distributions and Affects of Log transforms

Figure 3 shows examples of the pre and post log10 distribution of LORETA Z scores in the adult subjects for different frequency bands.

zLORETA NORMs_Histogram Distributions_LE_EC_N=43 ADULTs

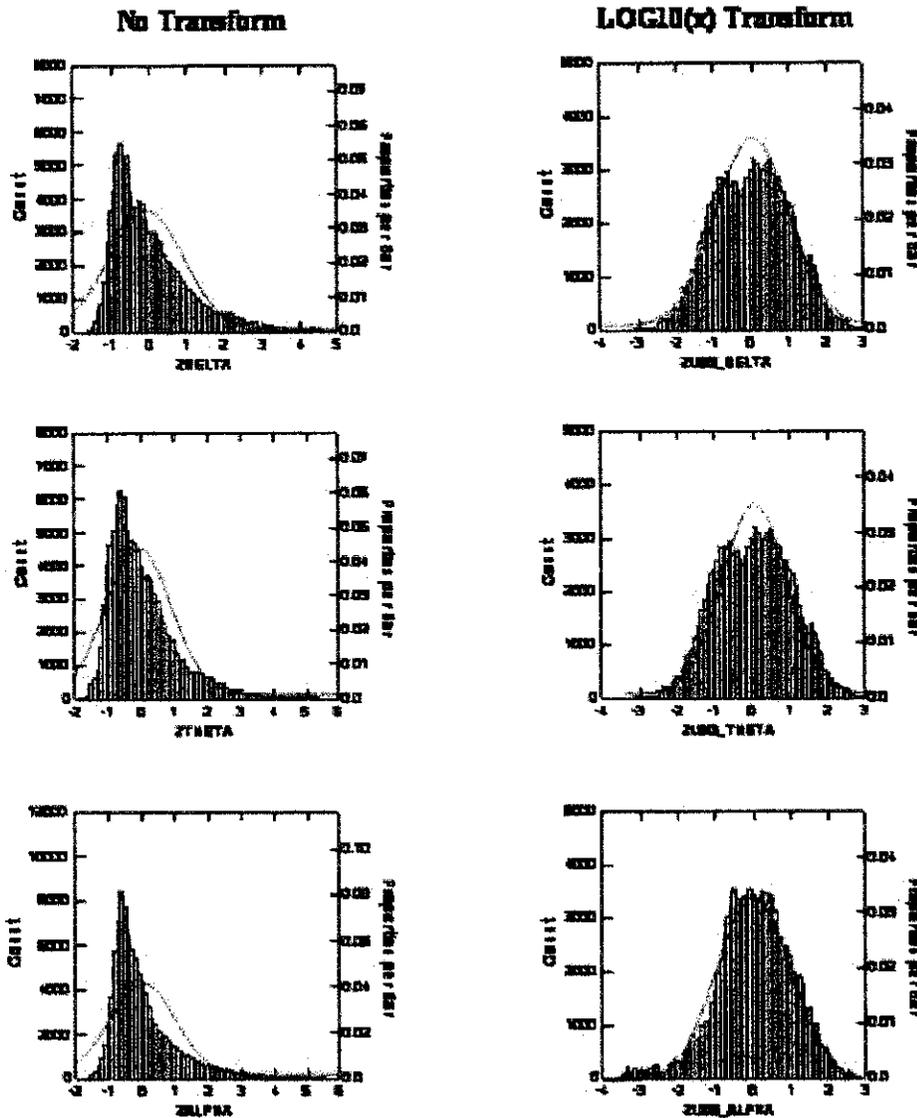


Fig. 3 - Distribution of the 2,394 LORETA currents in the delta (0.5 – 3 Hz), theta (3 – 7 Hz) and alpha (8 – 13 Hz) without transforms (left) and with log10 transform (right). The log transform adequately approximated a normal Bell Shaped distribution.

mk:@MSITStore:C:\Program%20Files\RoboHelp%20Office\RoboHTML\NEUROGUIDE\... 5/2/2004

The ideal Gaussian and the average cross-validation values of the database by which estimates of statistical sensitivity can be derived were published in Thatcher et al, J. Neurotherapy, 7: 121, 2003. True positives (TP) = the percentage of Z scores that lay within the tails of the Gaussian distribution, False negatives (FN) = the percentage of Z scores that fall outside of the tails of the Gaussian distribution. The error rates or the statistical sensitivity of a QEEG normative database are directly related to the deviation from a Gaussian distribution. These facts provide a mathematical method of estimating the statistical sensitivity of a normative EEG database in terms of the deviation from Gaussian for the NeuroGuide normative database of surface EEG values as well as for the 2,394 gray matter pixel LORETA norms.

LORETA zCROSS-VALIDATION_EC(A)_zLOG10(x)

LE										
SUMMARY	SKEW	KURT	< -1 SD	> 1 SD	< 2 SD	> 2 SD	< 3 SD	> 3 SD	SEN 2SD	SEN 3SD
DELTA	0.03	-0.46	17.37%	16.84%	1.45%	1.59%	0.03%	0.00%	95.63%	99.74%
THETA	0.06	-0.08	15.93%	15.77%	2.30%	1.78%	0.12%	0.08%	95.64%	99.74%
ALPHA	-0.37	0.71	13.26%	15.55%	3.12%	1.48%	0.80%	0.00%	95.64%	99.75%
BETA1	0.15	-0.12	15.68%	16.24%	1.23%	2.58%	0.83%	0.14%	95.63%	99.74%
BETA2	0.48	0.35	13.74%	14.50%	0.82%	4.57%	0.00%	0.16%	95.65%	99.74%
BETA3	0.73	0.40	13.77%	14.98%	0.23%	4.09%	0.00%	0.15%	95.65%	99.74%
OMEGA	-0.35	0.21	15.31%	15.48%	3.12%	0.83%	0.34%	0.00%	95.64%	99.74%

AVE										
SUMMARY	SKEW	KURT	< -1 SD	> 1 SD	< 2 SD	> 2 SD	< 3 SD	> 3 SD	SEN 2SD	SEN 3SD
DELTA	0.09	0.46	18.56%	16.19%	1.77%	1.26%	0.86%	0.00%	95.63%	99.74%
THETA	-0.26	0.19	15.86%	14.92%	3.21%	1.58%	0.16%	0.01%	95.64%	99.74%
ALPHA	-0.62	1.34	12.31%	14.78%	3.74%	1.12%	1.09%	0.00%	95.64%	99.75%
BETA1	0.07	-0.06	15.25%	16.10%	2.38%	1.71%	0.10%	0.08%	95.64%	99.74%
BETA2	0.25	0.32	13.94%	14.36%	1.74%	3.65%	0.00%	0.10%	95.65%	99.74%
BETA3	0.54	0.23	15.76%	15.12%	0.50%	4.37%	0.00%	0.89%	95.64%	99.74%
OMEGA	0.64	0.65	14.98%	14.24%	4.37%	0.88%	0.56%	0.00%	95.65%	99.75%

Fig. 4 - Statistical sensitivities based on the equations in Figure 4 for the eyes closed condition in a group of adult subjects for linked ears and average reference.

LORETA zCROSS-VALIDATION_EO(B)_zLOG10(x)

LE

SUMMARY	SKEW	KURT	< -1 SD	> 1 SD	< 2 SD	> 2 SD	< 3 SD	> 3 SD	SEN 2SD	SEN 3SD
DELTA	0.27	0.26	15.15%	14.55%	3.19%	1.38%	0.00%	0.00%	95.64%	99.74%
THETA	0.11	-0.05	16.00%	16.44%	1.45%	2.83%	0.00%	0.07%	95.63%	99.74%
ALPHA	0.38	-0.74	15.56%	18.30%	0.25%	2.74%	0.00%	0.16%	95.62%	99.74%
BETA1	0.37	-0.03	16.04%	16.76%	0.64%	3.18%	0.00%	0.00%	95.64%	99.74%
BETA2	0.36	0.79	13.73%	13.35%	1.80%	4.20%	0.00%	0.24%	95.66%	99.74%
BETA3	0.90	0.99	11.87%	14.57%	0.80%	5.26%	0.00%	0.31%	95.65%	99.74%
OMEGA	0.11	-0.36	16.15%	17.34%	1.15%	1.59%	0.00%	0.00%	95.63%	99.74%

AVE

SUMMARY	SKEW	KURT	< -1 SD	> 1 SD	< 2 SD	> 2 SD	< 3 SD	> 3 SD	SEN 2SD	SEN 3SD
DELTA	-0.43	0.60	14.28%	13.61%	3.81%	1.36%	0.06%	0.00%	95.65%	99.74%
THETA	-0.02	0.16	14.87%	15.92%	2.60%	1.99%	0.00%	0.06%	95.64%	99.74%
ALPHA	0.49	0.00	15.50%	17.76%	0.18%	2.70%	0.00%	0.35%	95.63%	99.74%
BETA1	0.38	0.07	15.90%	16.75%	0.68%	3.42%	0.00%	0.00%	95.64%	99.74%
BETA2	0.37	0.71	14.23%	13.90%	1.33%	3.91%	0.00%	0.31%	95.65%	99.74%
BETA3	0.89	0.96	12.29%	14.83%	0.80%	5.05%	0.00%	0.46%	95.65%	99.75%
OMEGA	0.12	0.18	14.83%	16.81%	2.53%	1.53%	0.09%	0.00%	95.64%	99.74%

Fig. 5 - Statistical sensitivities based on the equations in Figure 4 for the eyes open condition in a group of adult subjects for linked ears and average reference.

[Go to launch LORETA Normative database](#)

Appendix – G:

[Return to Top](#)

Computation of the auto-spectral and cross-spectral densities, Coherence, Phase Delays and Amplitude Asymmetry of the edited EEG selections

1- The FFT parameters are: epoch = 2 seconds at a sample rate of 128 sample/sec = 256 digital time points and a frequency range from 0.5 to 40 Hz at a resolution of 0.5 Hz using a cosine taper window to minimize leakage. Each 2 second FFT is 81 rows (frequencies 0 to 40 Hz) X 19 columns (electrode locations) = 1,539 element cross-spectral matrix for each subject.

2- In order to minimize the effects of windowing in the FFT (Kaiser and Serman, J. Neurotherapy, 4(3): 85-92, 2001) a EEG sliding average of the 256 point FFT cross-spectral matrix was computed for each normal subject's edited EEG by advancing in 64 point steps (75% overlap) and recomputing the FFT and continuing with the 64 point sliding window of 256 point FFT cross-spectrum for the entire edited EEG record. Each of the 81 frequencies for each 19 channels is log₁₀ transformed to better approximate a normal distribution. The total number of 2 second windows

mk:@MSITStore:C:\Program%20Files\RoboHelp%20Office\RoboHTML\NEUROGUIDE... 5/2/2004

is the number that is entered into the analysis of variance and t-tests and it is used to compute the degrees of freedom for a given statistical test.

3- A mean, variance, standard deviation, sum of squares, and squared sum of the real (cosine) and imaginary (sine) coefficients of the cross-spectral matrix is computed across the sliding average of edited EEG for all 19 leads for the total number of 81 and 1,539 log transformed elements for each subject. This creates the following seven basic spectral measurement means and standard deviations: 1- Cross-Spectral Power (square root of the sums of squares of the real and imaginary coefficients using the complex conjugate Hermitan Matrix); 2- Auto-Spectral Power which is the diagonal of the cross-spectral matrix where the imaginary coefficient = 0 and power = sine square; 3- Real coefficients; 4 – Imaginary coefficients; 5- Coherence = square of the cross-spectrum divided by the product of the two auto-spectra; 6- Phase = arctangent of the ratio of the real/imaginary components for frequencies from 0.5 to 40 Hz; and 7- Amplitude Asymmetry defined as the ratio of absolute power $(A-B)/A+B$ x 200, that is absolute power in channel A minus channel B divided by the sum of A + B times 200.

Appendix – H: A Few of the Normative Database Publications, Replications and Validations (see the National Library of Medicine database for more citations)

[Return to Top](#)

Bell, M.A and Fox, N.A. (1992), The relations between frontal brain electrical activity and cognitive development during infancy. Child Dev. 63(5): 1142-63.

Boldyreva GN, Zhavoronkova LA. (1991). Interhemispheric asymmetry of EEG coherence as a reflection of different functional states of the human brain. Biomed Sci.; 2(3): 266-70.

Cantor DS, Thatcher RW, Hrybyk M, Kaye H. (1986). Computerized EEG analyses of autistic children. J. Autism Dev. Disord., 16(2):169-87.

Cantor, D.S., Thatcher, R.W. and Kaye, H. (1987). Computerized EEG Analyses of Autistic Children. Int. J. Autism, 114: 21-36.

Case, R. (1992). The role of the frontal lobes in the regulation of cognitive development.

mk:@MSITStore:C:\Program%20Files\RoboHelp%20Office\RoboHTML\NEUROGUIDE\... 5/2/2004

Brain Cogn. 20(1): 51-73.

Dawson G, Panagiotides H, Klinger LG, Hill D. (1992). The role of frontal lobe functioning in the development of infant self-regulatory behavior. Brain Cogn. 20 (1): 152-75.

Fishbein, D. and Thatcher, R.W. (1986). New Diagnostic Methods in Criminology: Assessing Organic Sources of Behavioral Disorders. Research on Crime and Delinquency, 23 (3): 240 - 267.

Fisher, K.W. (1987), Relations between brain and cognitive development. Child Dev. 58 (3): 623-32.

Hanlon, H. W. (1996). Topographically different regional networks impose structural limitations on both sexes in early postnatal development. In: K. Pribram & J. King (Eds.), Learning as self-organization (pp. 311-376). Mahwah, NJ: Lawrence Erlbaum Assoc., Inc.

Hanlon, H. W., Thatcher, R. W. & Cline, M. J. (1999). Gender differences in the development of EEG coherence in normal children. Developmental Neuropsychology, 16 (3), 479-506.

John, E.R. Karmel, B., Corning, W. Easton, P., Brown, D., Ahn, H., John, M., Harmony, T., Prichep, L., Toro, A., Gerson, I., Bartlett, F., Thatcher, R., Kaye, H., Valdes, P., Schwartz, E. Neurometrics: Numerical taxonomy identifies different profiles of brain functions within groups of behaviorally similar people. Science, 196, :1393 1410, 1977.

John, E.R., Prichep, L.S. and Easton, P. Normative data banks and neurometrics: Basic concepts, methods and results of norm construction. In: Remond A. (ed.), Handbook of Electroencephalography and Clinical Neurophysiology, Vol. III, Computer Analysis of the EEG and Other Neurophysiological Signals. 1987, Amsterdam: Elsevier, pp. 449-495.

Ito Y, Teicher MH, Glod CA, Ackerman E. (1998). Preliminary evidence for aberrant cortical development in abused children: a quantitative EEG study. J Neuropsychiatry Clin Neurosci. 10(3): 298-307.

Kaiser J, Gruzelier JH. (1996). Timing of puberty and EEG coherence during photic stimulation. Int J Psychophysiol. 21(2-3): 135-49.

Matsuzawa J, Matsui M, Konishi T, Noguchi K, Gur RC, Bilker W, Miyawaki T. (2001). Age-related volumetric changes of brain gray and white matter in healthy infants and children. Cereb Cortex. 11(4): 335-42.

McAlaster, R. (1992). Postnatal cerebral maturation in Down's syndrome children: a developmental EEG coherence study. Int J. Neurosci. 65(1-4): 221-37.

Thatcher, R. W., McAlaster, R., Lester, M. L., Horst, R. L. & Cantor, D.S. (1983). Hemispheric EEG asymmetries related to cognitive functioning in children. In A.

mk:@MSITStore:C:\Program%20Files\RoboHelp%20Office\RoboHTML\NEUROGUIDE\... 5/2/2004

- Perecuman (Ed.), *Cognitive processing in the right hemisphere* (pp. 125-145). New York: Academic Press.
- Thatcher, R. W., Krause, P. and Hrybyk, M. (1986). Corticocortical association fibers and EEG coherence: A two compartmental model. *Electroencephalography and Clinical Neurophysiology*, 64, 123-143.
- Thatcher, R. W., Walker, R. A. & Guidice, S. (1987). Human cerebral hemispheres develop at different rates and ages. *Science*, 236, 1110-1113.
- Thatcher, R. W., Walker, R. A., Gerson, I. & Geisler, F. (1989). EEG discriminant analyses of mild head trauma. *Electroencephalography and Clinical Neurophysiology*, 73, 93-106.
- Thatcher, R. W. (1991). Maturation of the human frontal lobes: Physiological evidence for staging. *Developmental Neuropsychology*, 7 (3), 370-394.
- Thatcher, R. W. (1992). Cyclic cortical reorganization during early childhood. *Brain and Cognition*, 20, 24-50.
- Thatcher, R. W. (1994). Psychopathology of early frontal lobe damage: Dependence on cycles of postnatal development. *Developmental Pathology*, 6, 565-596.
- Thatcher, R. W. (1998). EEG normative databases and EEG biofeedback. *Journal of Neurotherapy*, 2 (4), 8-39.
- Thatcher, R.W. (1999). EEG database guided neurotherapy. In: J.R. Evans and A. Abarbanel Editors, Introduction to Quantitative EEG and Neurofeedback, Academic Press, San Diego.
- Thatcher, R. W., Biver, C. & North, D. (2003) Quantitative EEG and the Frye and Daubert Standards of Admissibility. *Clinical Electroencephalography*, , 34(2), 1 – 15.
- Thatcher, R.W., Walker, R.A., Biver, C.J., North, D.M., and Curtin, R. Quantitative EEG Normative Databases: Validation and Clinical Correlation. *Journal of Neurotherapy* 7, 87-105, 2003.
- Trudeau, D.L., Anderson, J., Hansen, L.M., Shagalov, D.N., Schmoller, J., Nugent, S. and Barton, S. (1998). Findings of mild traumatic brain injury in combat veterans with PTSD and a history of blast concussion", *J. Neuropsychiatry Clin Neurosci*. 10 (3):308-313.
- Wolff, T. and Thatcher, R.W., (1990). Cortical reorganization in deaf children. *J. of Clinical and Experimental Neuropsychology*, 12: 209-221.
- van Baal, G. C. (1997). A genetic perspective on the developing brain: EEG indices of neural functioning in five to seven year old twins. *Organization for scientific research (NWO)*. The Netherlands: Vrije University Press.

van Baal, G. C., de Geus, E. J., & Boomsma, D.I. (1998). Genetic influences on EEG coherence in 5-year-old twins. *Behavioral Genetics*, 28 (1), 9-19.

van Beijsterveldt, C. E., Molenaar, P. C., de Geus, E. J., & Boomsma, D. I. (1996). Heritability of human brain functioning as assessed by electroencephalography. *American Journal of Human Genetics*, 58 (3), 562-573.

van Beijsterveldt, C. E., Molenaar, P. C., de Geus, E. J., & Boomsma, D. I. (1998). Genetic and environmental influences on EEG coherence. *Behavioral Genetics*, 28 (6), 443-453.

[Return to Top](#)

NeuroGuide Introduction Brochure

Appendix - A

Introducing NeuroGuide

NeuroGuide Deluxe is an informative and comprehensive digital EEG and QEEG post-hoc analysis system. NeuroGuide provides access to modern and simple to use Microsoft windows for automatic artifact rejection, Dynamic Lifespan Eyes Open and Eyes Closed Reference Normative Database, covering the age from Birth to 82 years of age (N = 625). NeuroGuide includes Re-Montaging to Average Reference or the Laplacian for eyes open and eyes closed conditions.

NeuroGuide is designed for use with the LORETA Key Institute Source Localization software for registration with the Talarich MRI Atlas from the Montreal Neurological Institute.

NeuroGuide provides tab delimited output files that can be imported into any statistical package or database management system. NeuroGuide does not diagnose nor render any clinical decisions and it is designed for use by trained and competent individuals.

NeuroGuide discriminant functions are add on products and include a Mild Head Injury discriminant function and a Learning Disabilities discriminant function. The discriminant functions are not intended to provide a clinical diagnosis but are only an adjunct to other measures.

NeuroGuide brain performance index is an add on product and includes predictive correlations between EEG and Neuropsychological function such as Block Design, Digit Span and I.Q. and other cognitive measures. The brain performance index is a correlative research tool and is not intended to diagnose or render clinical judgments.

NeuroStat is an add on program that computes pre-test vs. post test EEG comparisons as well as statistical group comparisons.

NeuroBatch is an add on program that automatically processes large batches of edited EEG and organizes EEG data for purposes of group statistics.

LORETA Normative reference database is an add on program that provides 3-Dimensional Z scores from birth to 82 years of age launched from the NeuroGuide edit window using the Key Institute Explorer Viewer.

NeuroGuide Signal Generator is not an add on but is a free educational tool distributed in the Demo at www.appliedneuroscience.com by which basic digital signal processing of EEG can be learned and LORETA and NeuroGuide and other programs can be tested.

NeuroGuide provides tools as analytical resources and as an EEG reference based on peer reviewed scientific publications. Any clinical use must be by qualified medical or clinical professionals restricted to the post-hoc statistical evaluation of the human electroencephalogram (EEG). NeuroGuide must be used only by competent and trained individuals. EEG artifact can invalidate analyses and improper positioning of electrodes or significant deviations from accepted standards of electroencephalographic recording methodology can invalidate EEG recordings or erroneous storage of data and falsification of data, improper manipulation of data or unlawful uses of NeuroGuide including violations of copyright law and other improper uses of NeuroGuide are all contra indicated.

mk:@MSITStore:C:\Program%20Files\RoboHelp%20Office\RoboHTML\NEUROGUIDE\... 5/9/2004

mk:@MSITStore:C:\Program%20Files\RoboHelp%20Office\RoboHTML\NEUROGUIDE\... 5/9/2004

Verification & Validation using Calibration Signals

Appendix - B

NEUROGUIDE SIGNAL GENERATOR MANUAL AND TUTORIAL

Copyright © 2003-2004 Applied Neuroscience, Inc.
(Sine Wave segments were selected for illustrative purposes only)

Introduction:

The signal generator is used to calibrate and test the digital signal processing properties of NeuroGuide as well as to serve as an educational program by which the principles of digital signal analyses can be learned and explored. Concepts such as frequency, time, phase delays, noise, amplitude and coherence can be tested and evaluated. EEG data can be simulated by approximating the selected mixtures of signals to match the signal parameters and scalp locations of the EEG.

TABLE OF CONTENTS

Step #1 - Launch NeuroGuide and click File>Open>Signal Generation

Step #2 - Use Mouse to Select EEG Channels, Sine Wave Frequencies and Amplitudes (uV) and Phase Delays (degrees) and “Noise” (% S/N ratio)

Step # 3- Click OK, then Click Edit>Select All to view FFT results

Step # 4 – Click File>Save As to save the signals in NeuroGuide or Lexicor format (*.ng or *.dat).

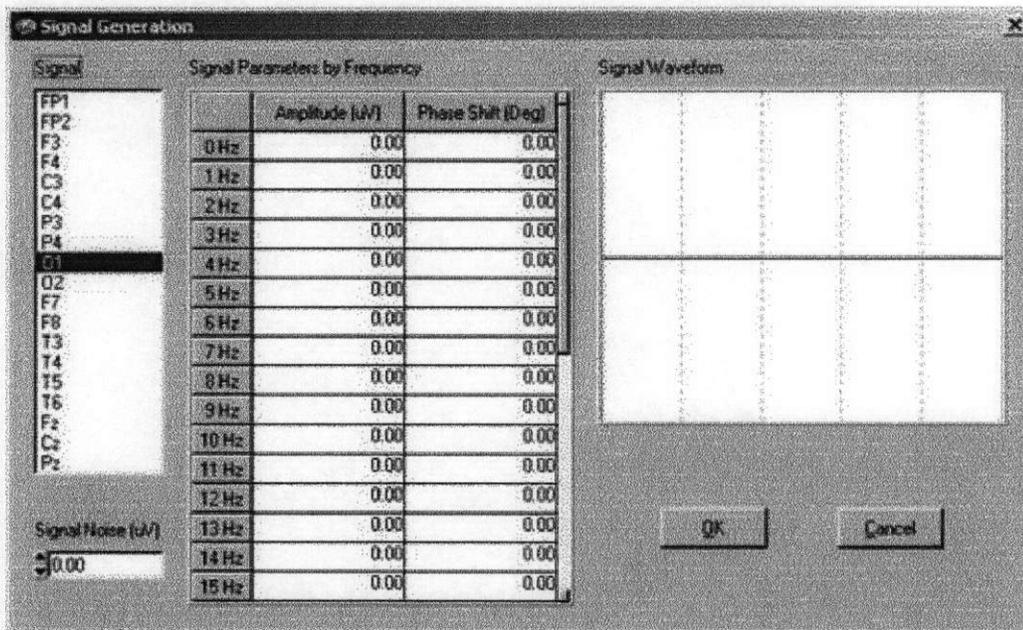
Step #5 - Example Tutorial of Replicating Peer Reviewed Publication: Gomez and Thatcher “Frequency domain equivalence between potentials and currents using LORETA.” *Int. J. of Neuroscience*, 107: 161-171, 2001.

Appendix – A - LORETA

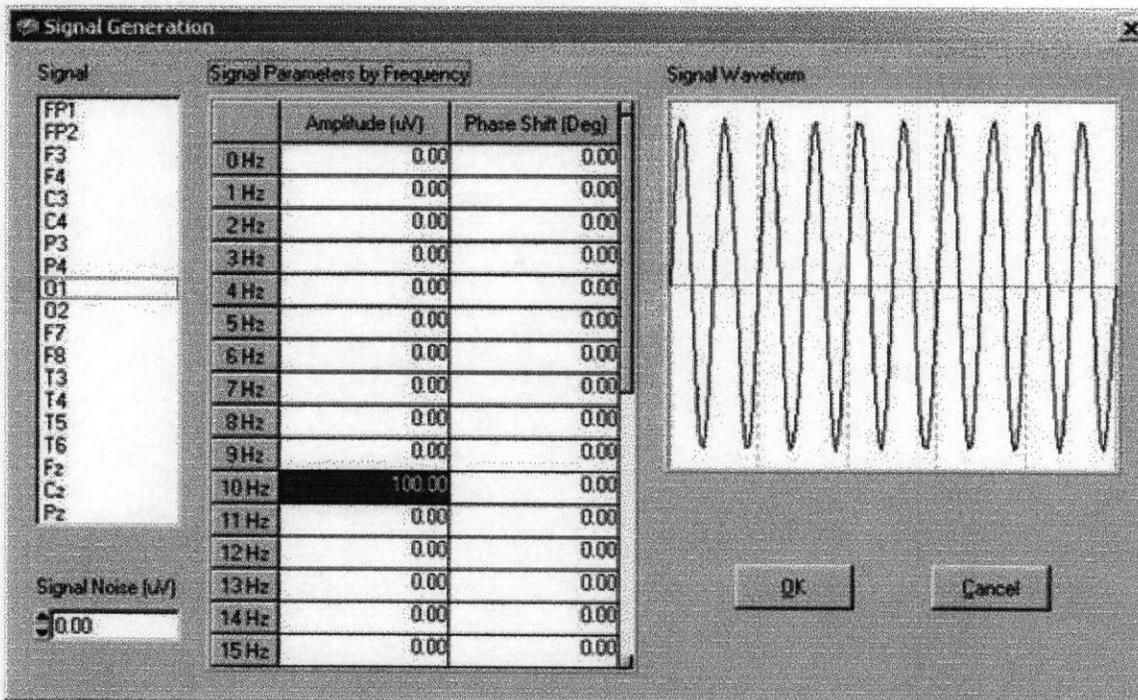
Appendix – B – Mathematics of Gomez and Thatcher, 2001

Appendix – C – References

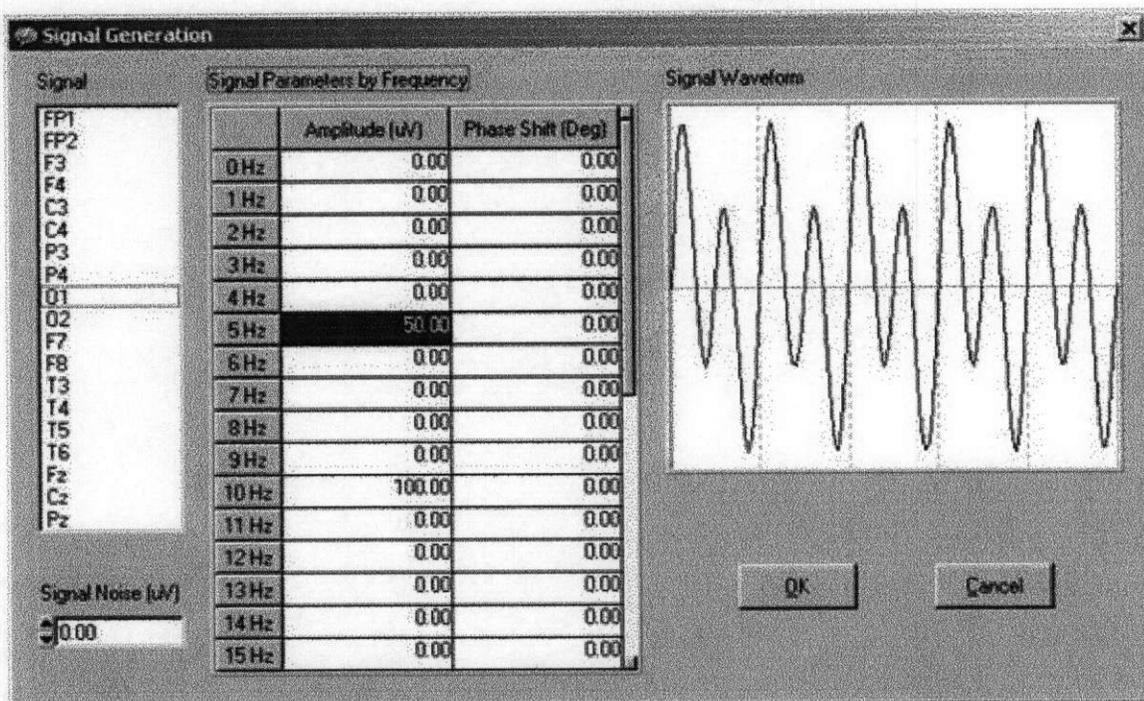
mk:@MSITStore:C:\Program%20Files\RoboHelp%20Office\RoboHTML\NEUROGUIDE\... 5/9/2004



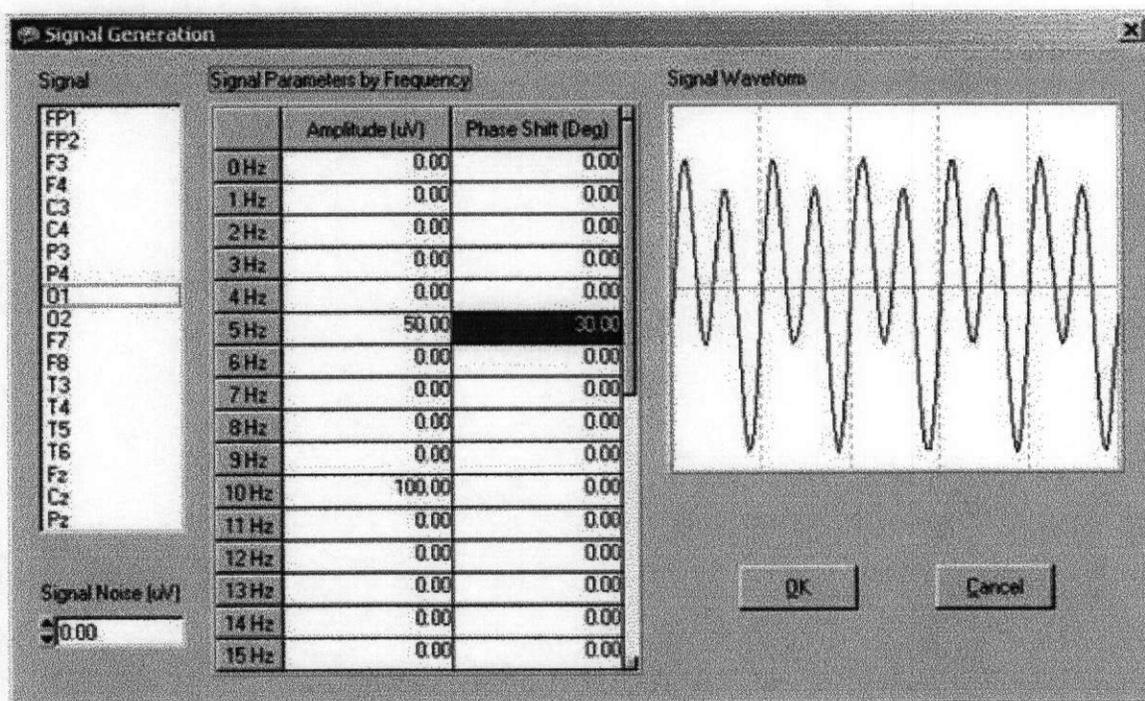
2a - Click a channel to select a location in Lexicor format (e.g., O1), then double click a Frequency (e.g., 10 Hz), then double click Amplitude (uV) and type in a value (e.g., 100 uV).



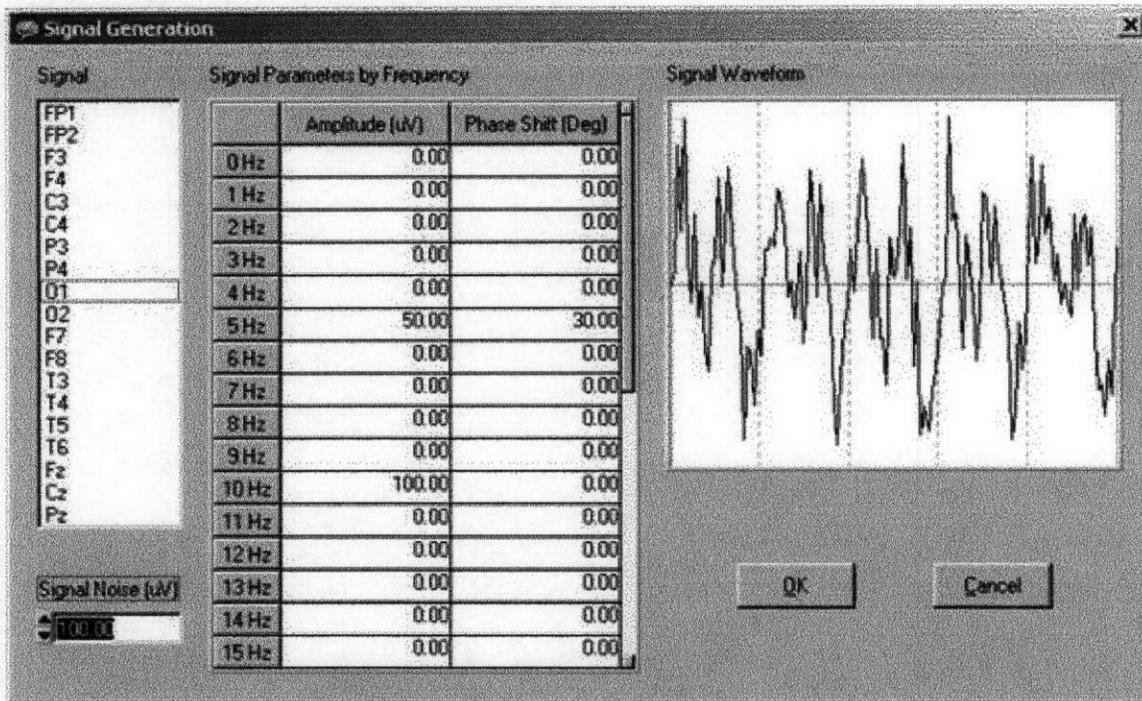
2b - Mix sine waves in by double clicking the amplitude of a different frequency, e.g., 5 Hz and type 50 uV.



2c – Shift the Phase of the 5 Hz signal by double clicking “Phase Shift (Deg)” at 5 Hz and type 30.



2d – Add “Noise” to the 5 Hz signal by double clicking the window below “Signal Noise (uV)” and type 100. This adds 100 microvolts of noise to the 5 Hz signal located at O1.



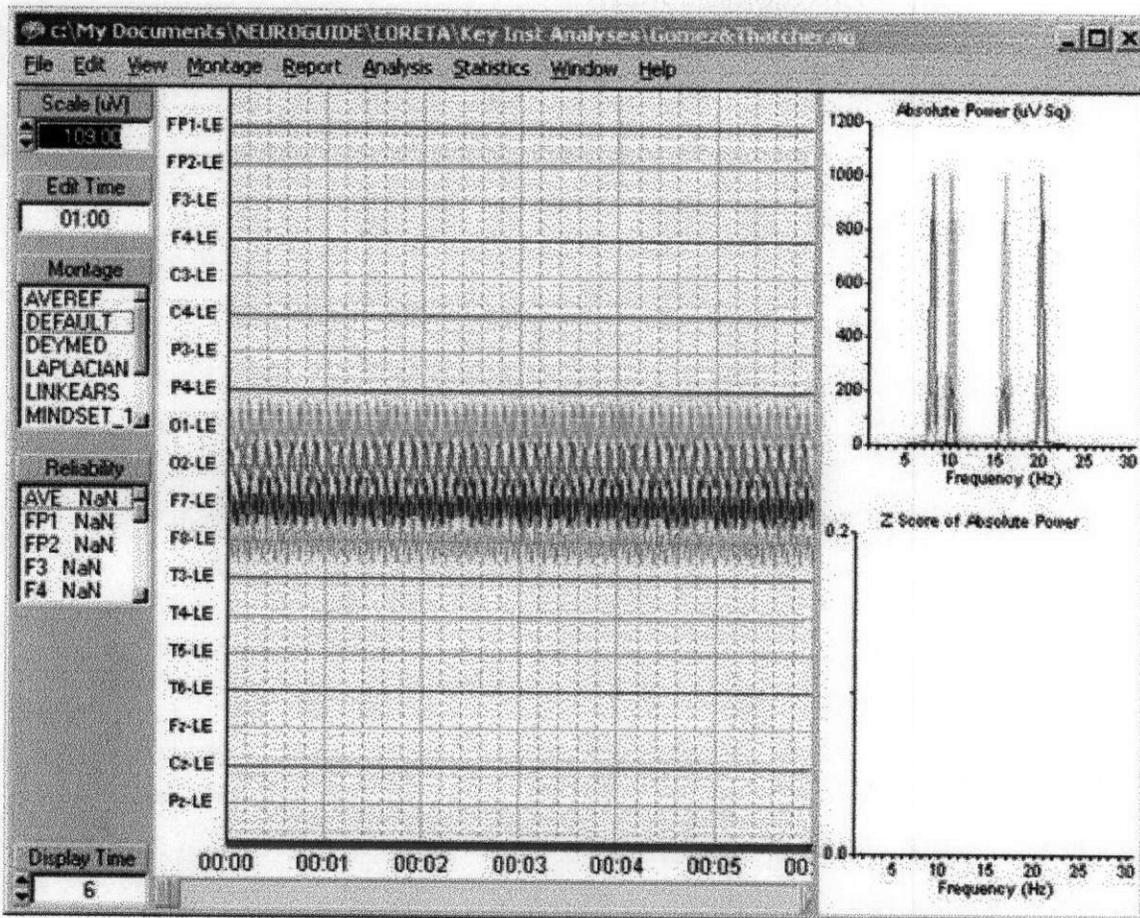
2e – Repeat Steps 2a to 2d for each channel with or without adding phase delays and/or noise or multiple frequencies, etc. Unselect any value by double clicking in the appropriate box and set the value = 0.

The Channel is the primary selection and then the amplitude, frequency or mixtures of frequencies and phases and noise are the secondary selections.

2f - Simulate any EEG by comparing the auto and cross-spectral values and then entering these values into the appropriate channels and appropriate parameter selection locations. Use the Signal Generator feature of NeuroGuide to learn about digital signal processing in general as well as various analytical programs including LORETA and other inverse solutions.

Step # 3- Click OK, then Click Edit>Select All to view FFT results

[Return to Top](#)



Step #4 - Click File>Save As to save the signals in NeuroGuide or Lexicor format (*.ng or *.dat).

Return to Top

Step – 4a - Follow the NeuroGuide Manual Instructions (step #6) to save as NeuroGuide (*.ng) or Lexicor (*.dat) files.

Step – 4b - Follow the NeuroGuide Manual Instructions (step # 6) to save Power Spectra and Cross-Spectra (Step # 6) and to Export to LORETA (Step # 11 in the NeuroGuide Manual).

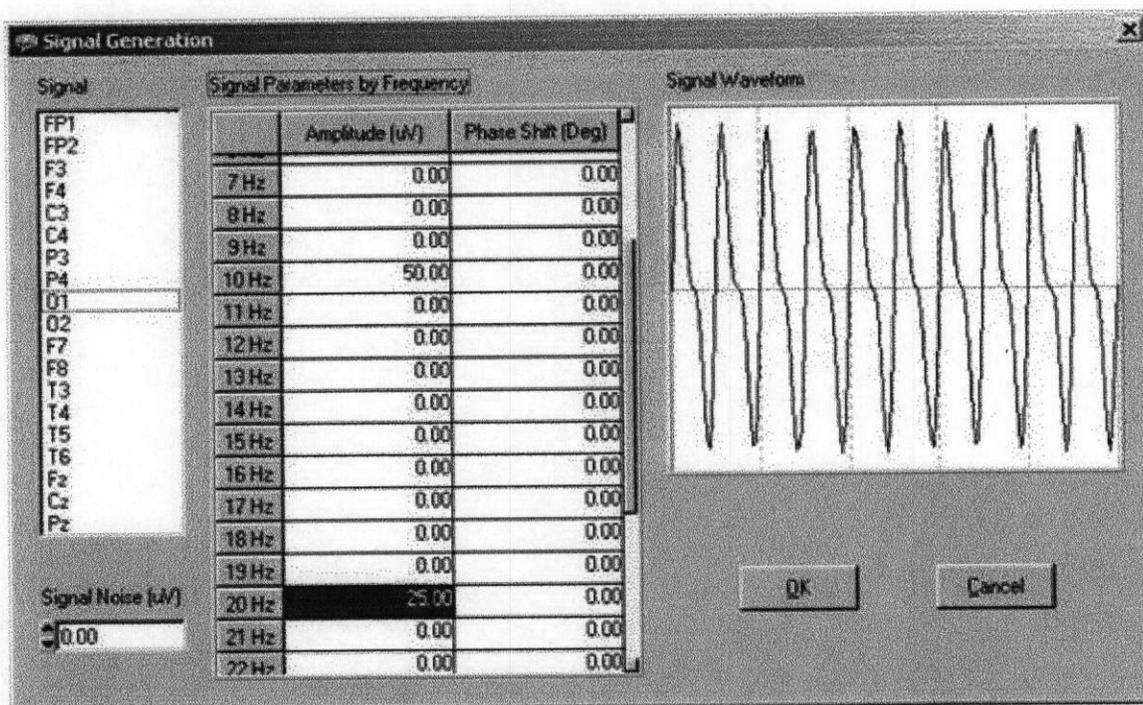
**Step #5 - Example Tutorial by replicating the publication:
Gomez and Thatcher “Frequency domain equivalence**

mk:@MSITStore:C:\Program%20Files\RoboHelp%20Office\RoboHTML\NEUROGUIDE\... 5/1/2004

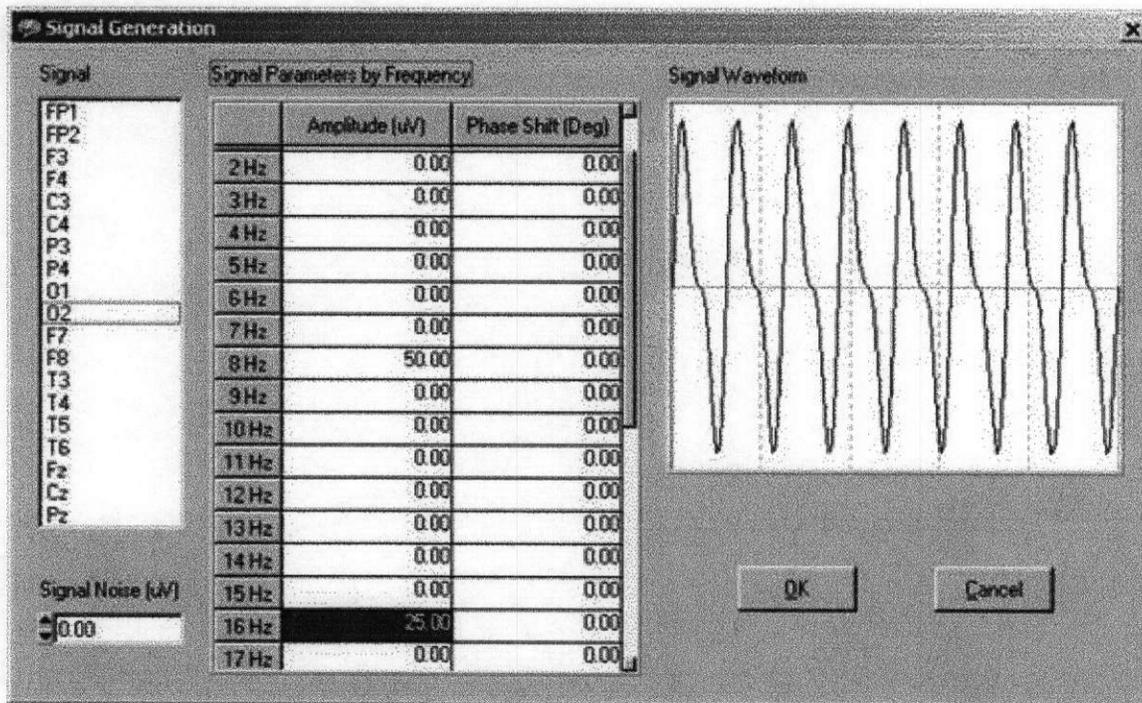
between potentials and currents using LORETA.” Int. J. of Neuroscience, 107: 161-171, 2001.

Return to Top

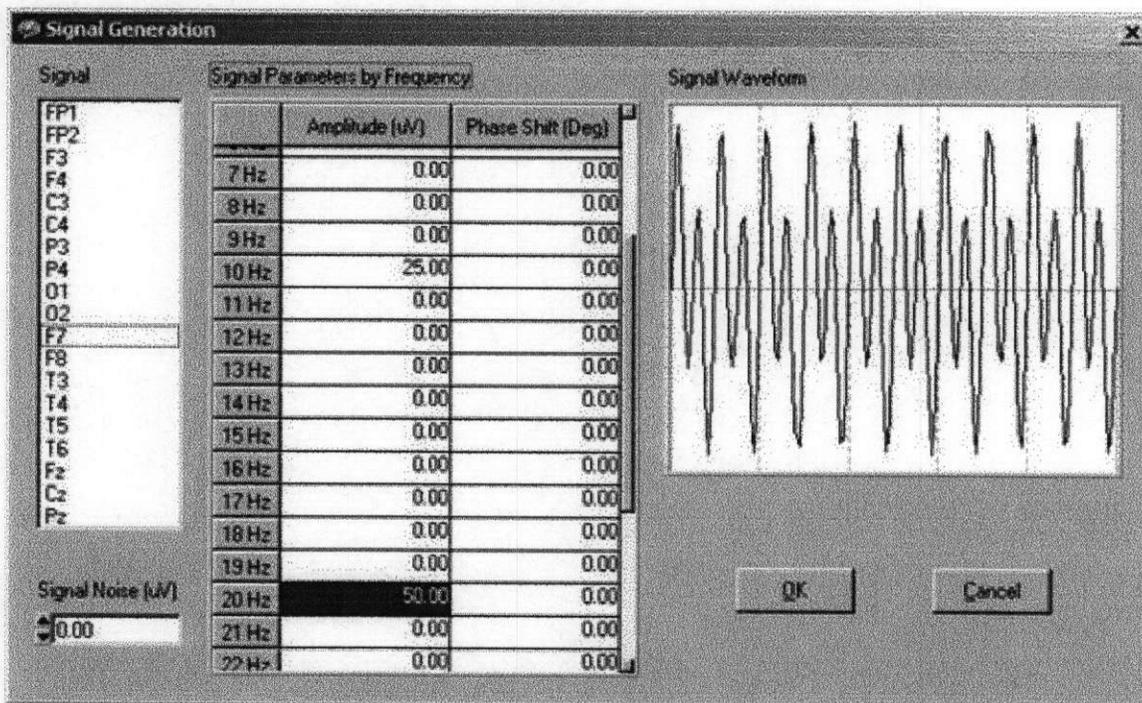
5a- Select O1 at 10 Hz at 50 uV and 20 Hz and 25 uV



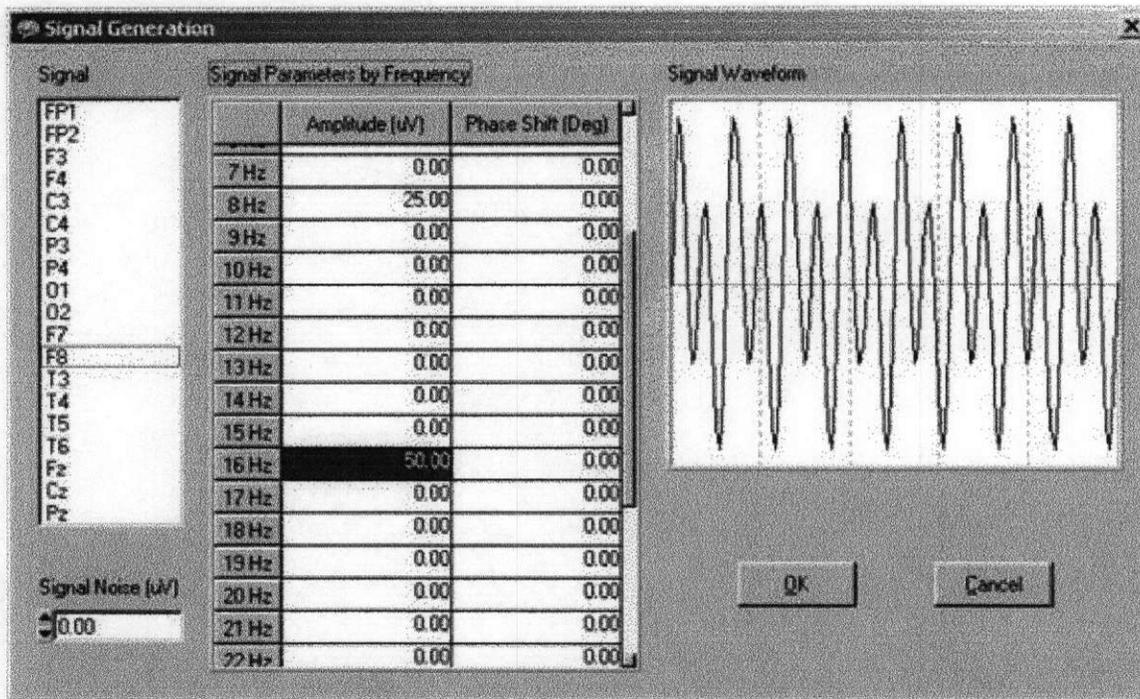
5b – Select O2 at 8 Hz 50 uV and 16 Hz at 25 uV



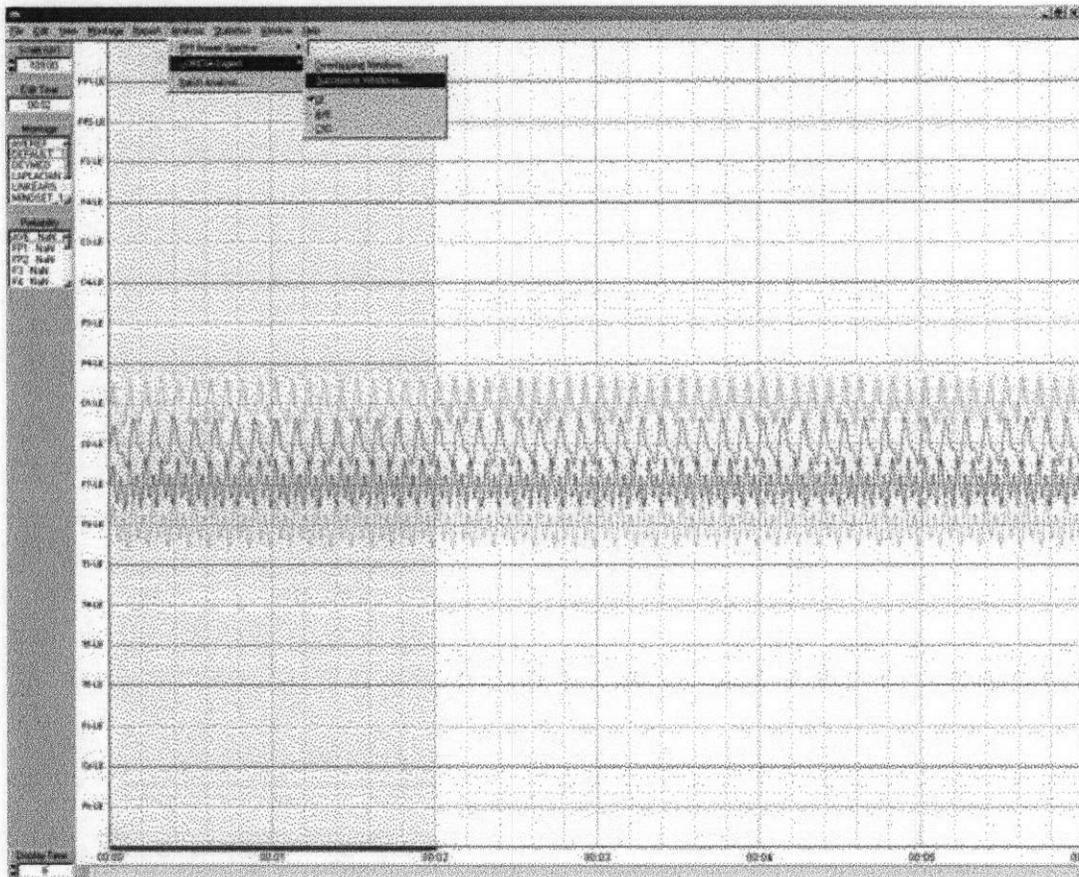
5c – Select F7 at 10 Hz 25 uV and 20 Hz 50 uV

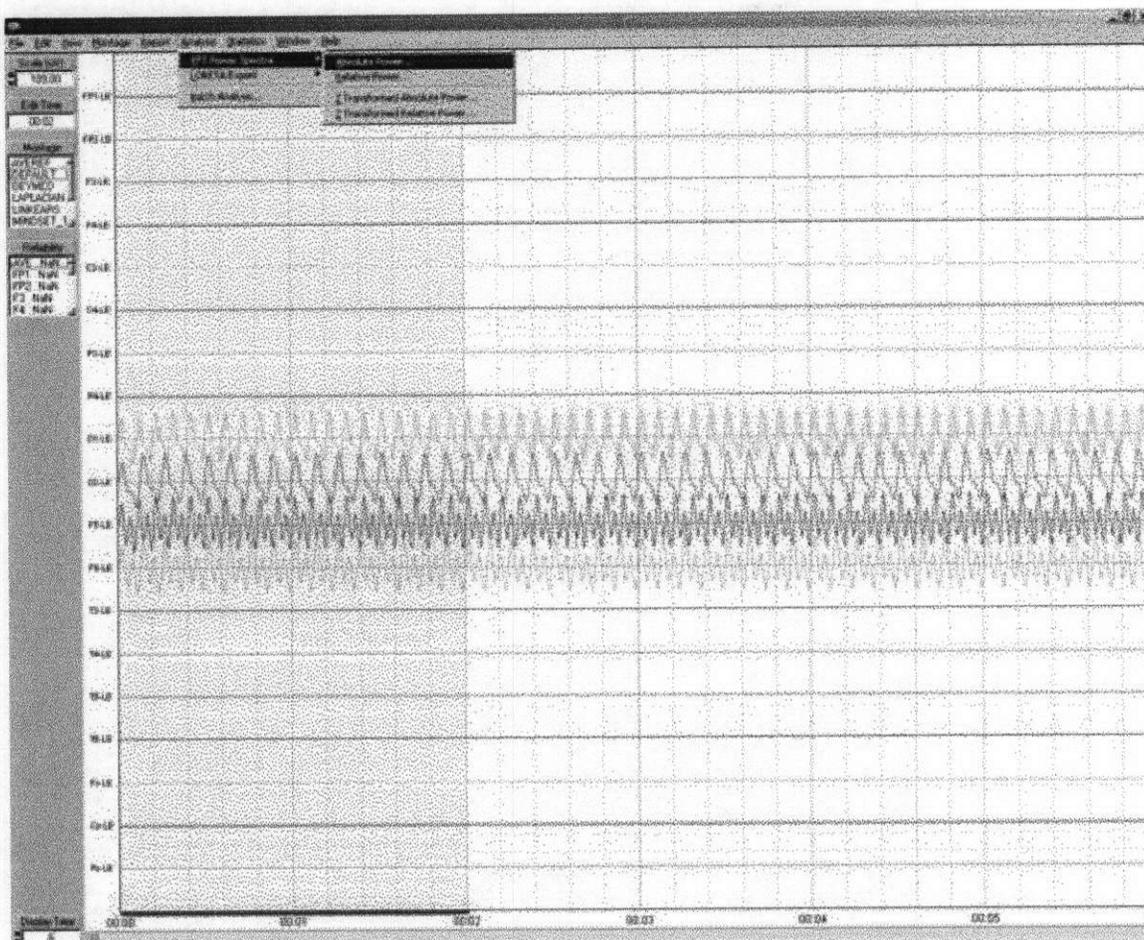


5d – Select F8 at 8 Hz 25 uV and 16 Hz at 16 uV



5e – Click OK and then click File>Save As NeuroGuide (*.ng) or Lexicor (*.dat) for purposes of further analysis. For example, save the power spectra and/or export the digital time series to LORETA.





APPENDIX – A

[Return to Top](#)

Gomez and Thatcher, 2001 used the Key Institute mathematical equations to validate LORETA and cross-validated their math by comparing the forward solution and the inverse solution using MRI 3-D voxel locations and the surface scalp EEG currents and potentials (Based on the Reciprocity Theorem, Helmholtz, 1853). The results of the Gomez and Thatcher, 2001 study is also consistent with Tesche, C. and Kajola, M. "A comparison of the localization of spontaneous neuromagnetic activity in the frequency and time domains." Electroencephalography and Clin. Neurophysiology, 87(6): 408-416, 1993.

One can test the facts and the science of LORETA for themselves using the NeuroGuide signal generator and the Gomez and Thatcher, 2001 frequencies and locations which is only one of several tools available to test LORETA (see Appendix B and C) not to mention the mathematical concepts of linearity between frequency and time and between electrical potentials and currents (Helmholtz, 1853 physics of "Reciprocity" and the "Lead Field", Malmivuo and Plonsey, 1995).

It makes no difference whether one exports signals in the time domain or in the frequency domain (as demonstrated in the Gomez & Thatcher, 2001 and the Tesche et al, 1993 publications as well as by mathematical simulation in step # 5). Caution must be exercised when using LORETA to be sure to physiologically validate using the surface linked ears, average reference and current source density data. This is not to indicate that LORETA is not a valid mathematical

and scientific methodology, to the contrary, it is an important contribution. We are emphasizing the fact that LORETA is valid when used by competent professionals who take the time to validate the source solutions by evaluating the surface EEG distributions in order to guard against possible ghost images and to take into consideration the inherent low resolution properties of LORETA (i.e., low resolution electromagnetic tomography).

APPENDIX – B

Mathematics and Results of Gomez & Thatcher, 2001

[Return to Top](#)

Note: There are three instances when multiplication of matrices is commutative: 1- by a null matrix, 2- by an identity matrix and, 3- multiplication by a scalar. The equation below is a valid equality when using a scalar as we do.

$$\lambda A = \{ \lambda a_{ij} \} = \{ a_{ij} \lambda \} = A \lambda \quad \text{Eq. 1}$$

We apply this commutative property in the following manner.

For $S = KJ$, where K is the lead field matrix, J = current and S = the sensitivity of the sensors (depending on the model used and the conductivity, etc.). S is an $N \times W$ matrix for the scalp potentials (EEG/MEG), where N is the number of sensors and W is the number of time samples. J is a $3M \times W$ matrix, where M is the number of sources and W is the same time samples as for S . Then the inverse solution is a linear combination of the signal S in the sensors

mk:@MSITStore:C:\Program%20Files\RoboHelp%20Office\RoboHTML\NEUROGUIDE\... 5/1/2004

$$\mathbf{J} = \mathbf{T} \cdot \mathbf{S} \quad \text{Eq. 2}$$

Where \mathbf{T} is some generalized inverse of \mathbf{K} , where the minimum norm solution is

$$\mathbf{T} = (\text{pinv}(\mathbf{K}' \cdot \mathbf{K} = \mathbf{K})) = \mathbf{K}' \quad \text{Eq. 3}$$

\mathbf{K}' is the transpose of \mathbf{K} , and \cdot represents matrix multiplication and $\text{pinv}(\mathbf{X})$ is the Moore-Penrose pseudoinverse (Menke, 1984). Pascual-Marqui et al, 1994 use the mathematical method that they refer to as “Low-Resolution Computed Tomography” (LORETA) to add physiological foundations and to avoid the minimum norms’s problems in localizing deep sources by using the Laplacian Operator \mathbf{B} and \mathbf{W} as a weighting matrix. The LORETA equation is

$$\mathbf{T} = \{\text{pinv}(\mathbf{W}\mathbf{B}'\mathbf{B}\mathbf{W})\}\mathbf{K}'[\text{pinv}(\mathbf{K} \text{ inv}(\mathbf{W}\mathbf{B}'\mathbf{B}\mathbf{W})\mathbf{K}')] \quad \text{Eq. 4}$$

The critical factor in these considerations is that the real number FFT computed by the cross-spectrum (Hermitian matrix as a scalar real number) as represented in equation 1 is a linear operator such that for any inverse solution of the form in equation 3 is equivalent to:

$$\text{FFT}(\mathbf{J}) = \text{FFT}[\mathbf{T} \cdot \mathbf{S}] = \mathbf{T} \cdot \text{FFT}[\mathbf{S}] \quad \text{Eq. 5}$$

Equation 5 is the formula that Gomez and Thatcher (2001) used. Gomez and Thatcher (2001) simulated the linear equivalence by a combination of sine waves and confirmed the linearity of equation 5 as any one can do by using the NeuroGuide signal generator as described in step # 5 for oneself.

Figure 1 – From Gomez & Thatcher, 2001. This is the three-shell spherical model of the head used to simulate LORETA. Four electrodes (F7, F8, O1, O2) and the reference electrode (A1) are indicated by black rectangles. The coordinates of the electrodes are according to the best-fitting sphere relative to cortical anatomy (Towel et al., 1993). The peaks of beta (for F7 and F8) and alpha activity (for O1 and O2) are indicated in parenthesis. Eight sources (1 to 3) indicated by black circles were located in the interior of the sphere to represent the equivalent current sources such as in the gray matter.

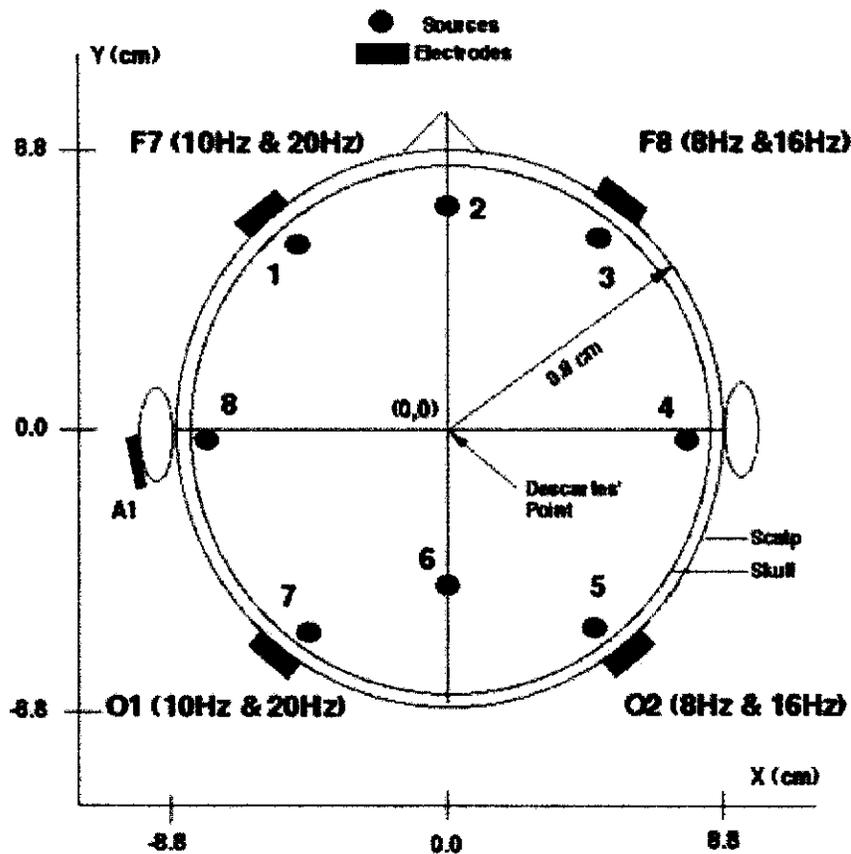
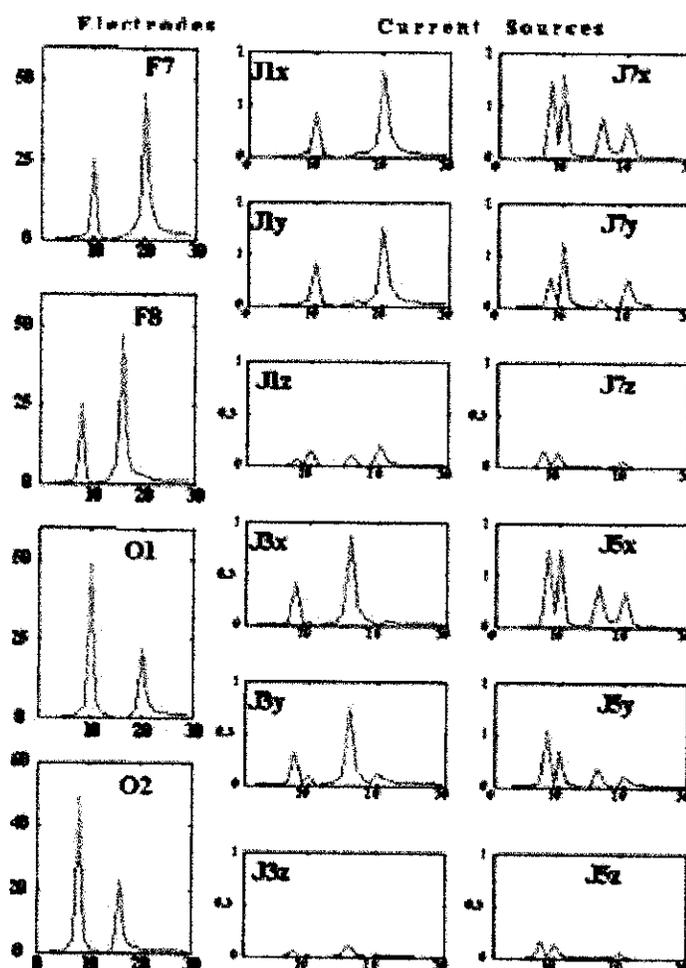


Figure 2 – From Gomez & Thatcher, 2001. Power spectrum of the signals used to simulate LORETA. The spectrum of the signals in the scalp electrodes is shown on the left (amplitude of beta is higher in the anterior regions, alpha amplitude is higher in the posterior regions and a frequency shift toward the lower frequencies in the right hemisphere). The center and right columns are the spectra of the current sources nearest to the electrodes J1, J3, J5 and J7 after calculating the inverse solution. Each source has three components x, y and z. The y-axis of the electrodes is $\mu V^2 / \text{cycle/sec}$ for the electrodes and $(\mu A / \text{cm}^2)^2 / \text{cycle/sec}$ for current density at each source location. The x-axis is frequency in Hz in all cases. This simulation confirms the mathematical statements and demonstrates a frequency domain equivalence between the spectra of electrical potentials at the scalp and the spectra of currents in the interior of the head model.



APPENDIX – D - REFERENCES

[Return to Top](#)

Baillet, S., et al, "Evaluation of inverse methods and head models for EEG source localization using a human skull phantom". *Physics in Medicine and Biology*, 46: 77-96, 2001.

Baillet, S. and Garnero, L. "A Bayesian approach to introducing anatomic-functional priors in the EEG, MEG inverse problem". *IEEE Trans. Biomed. Eng.* 44: 374-375, 1997.

Casper, et al. "Evaluation of inverse methods and head models for EEG source localization using a human skull phantom" at: <http://sipi.usc.edu/~silvin/docs/inversecasperthese2.pdf>

Gomez, J. F. and Thatcher, R.W. "Frequency domain equivalence between potentials and currents using LORETA." *Int. J. of Neuroscience*, 107: 161-171, 2001.

Helmholtz, HLF, *Ann. Physik und Chemie* 89: 211-233, 354-377, 1853 (see also "Helmholtz's Treatise on Physiological Optics" by Hermann Von Helmholtz, edited by J. P. Southal, Thoemmes, Press, 2000, ISBN 1855068311).

mk:@MSITStore:C:\Program%20Files\RoboHelp%20Office\RoboHTML\NEUROGUIDE\... 5/1/2004

Malmivuo, J. and Plonsey, R. "Bioelectromagnetism", Oxford University Press, 1995.

Menke, W. "Geophysical Data Analysis: Discrete Inverse Theory." Orlando: Academic Press, 1984.

Hämäläinen, M. "Discrete and distributed source estimates", *ISBET Newsletter* Edited by W. Skrandies, Giessen, Germany, No 6 / December 1995.

Pascual-Marqui, R. D. Review of methods for solving the EEG inverse problem. *Inter. J. of Bioelectromagnetism*, 1:75-86, 1999.

Tesche, C. and Kajola, M. "A comparison of the localization of spontaneous neuromagnetic activity in the frequency and time domains." *Electroencephalography and Clin. Neurophysiology*, 87(6): 408-416, 1993.

Towel, V. et al., The spatial location of EEG electrodes: locating the best-fitting sphere relative to cortical anatomy. *EEG & Clin. Neurophysiol.*, 103: 9 – 15, 1993.

[Return to Top](#)

Gaussian Distribution Verification & Validation Tests

Appendix - B

Normative Database Validation Steps

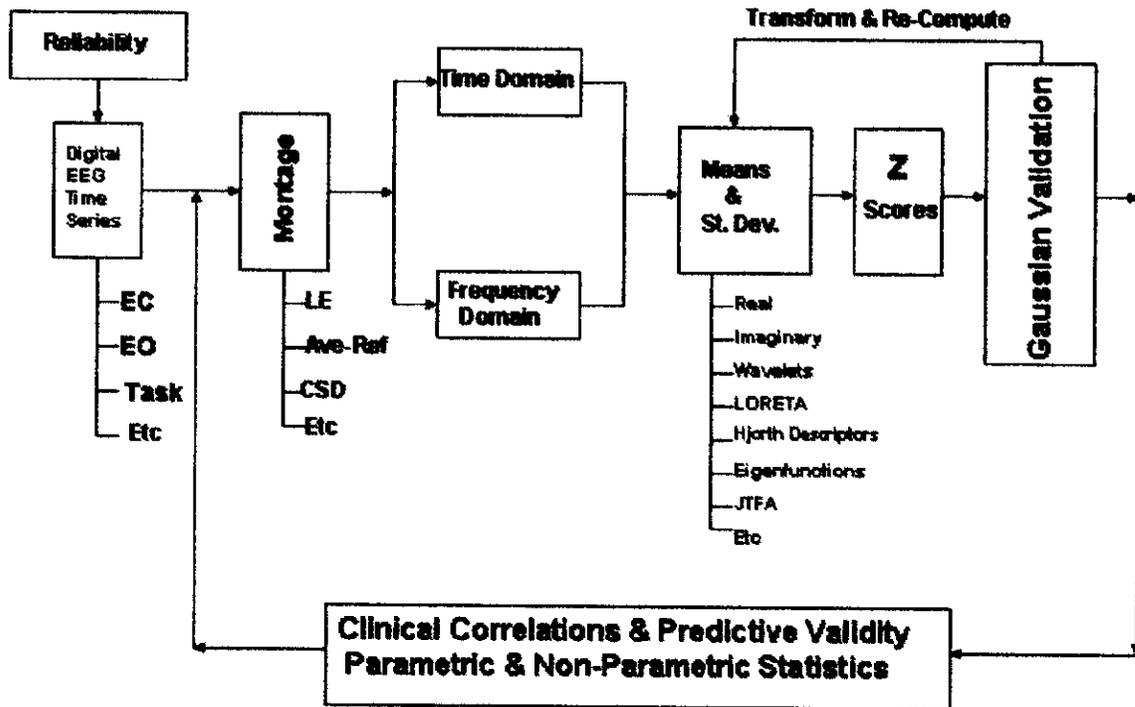
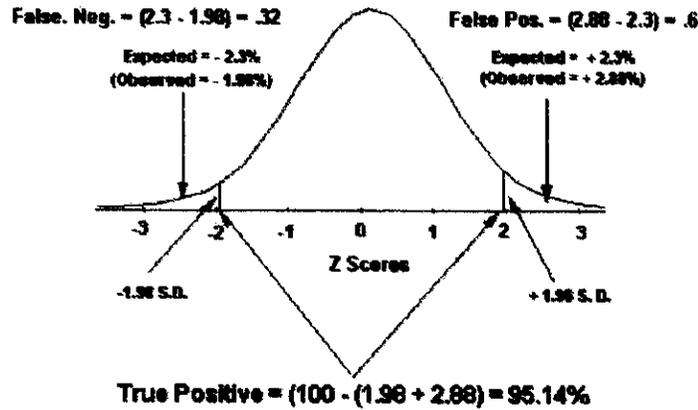


Illustration of the step by step procedure used in the design and development of the NAS to Gaussian cross-validate and then validate by correlations with clinical measures in order to estimate the predictive and content validity of the EEG normative reference database. The feedback connections between Gaussian cross validation and the means and standard deviations refers to transforms to approximate Gaussian if the non-transformed data is less Gaussian. The clinical correlation and validation arrow to the montage stage represents repetition of clinical validation to a different montage or reference or condition such as eyes-open and eyes-closed.

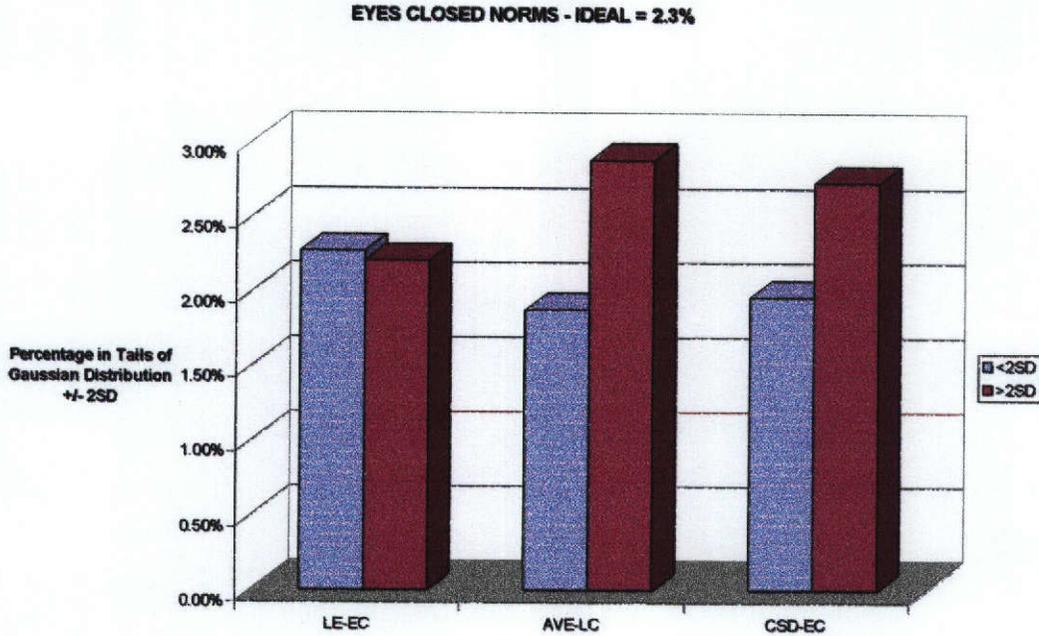
Sensitivity Based on Deviation from Gaussian
Cross-Validation Accuracy N = 625 Subjects



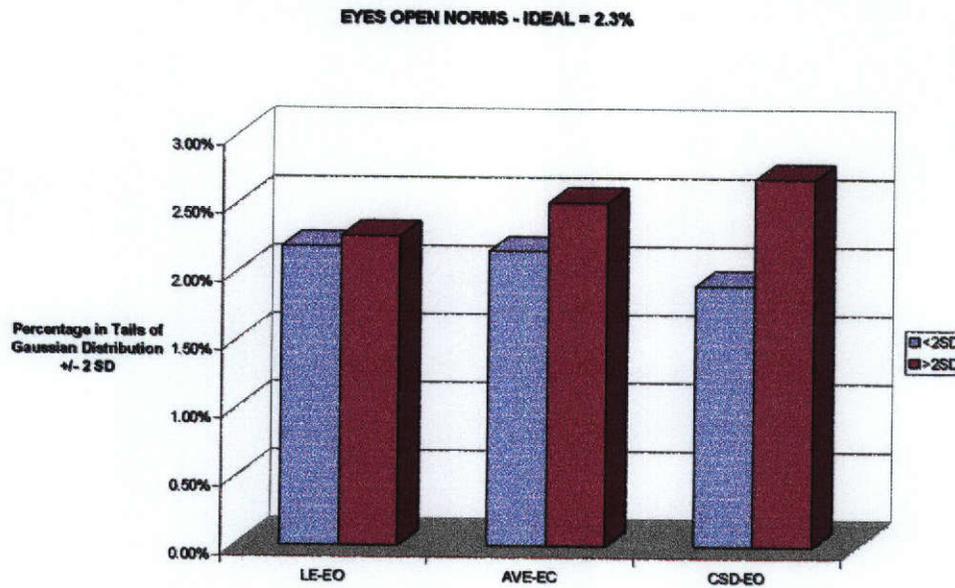
$$\text{Sensitivity} = \frac{TP}{TP + (FP + FN)} = \frac{95.14}{95.14 + 1.0} = 98.96\%$$

$$\text{Specificity} = \frac{TN}{TN + (FP + FN)} = \text{Undefined}$$

A normal or Gaussian curve showing values of Z (± 1.96), which includes the proportion which is .95 of the total area. The left and right tails of the distribution show probability values of .025 (one-tailed). The results of the cross-validation of 625 subjects showed a classification accuracy that was normally distributed with 2.28% of the Z-scores $> \pm 2$ standard deviations (SD) and 0.16% of the Z-scores $> \pm 3$ SD. The clinical evaluation of EEG measures rely upon such a normal distribution by estimating the probability of finding an observed EEG value in a given range of a normal population and then empirically testing the sensitivity of the database by cross-validation.



Bar graphs of percentage deviation of Z-scores from the ideal Gaussian cross-validation in eyes-closed linked ears, average reference and current source density (Laplacian) remontaging of the norms. The results of the validation tests show a good approximation to a Gaussian distribution in which the ideal or perfect Gaussian = 2.3%.



Bar graphs of the percentage deviation from the ideal Gaussian cross-validation in the eyes-open condition linked ears, average reference and current source density (Laplacian) re-montaging of the norms. The results of the validation tests show a good approximation to a Gaussian distribution in which the ideal or perfect Gaussian = 2.3%.

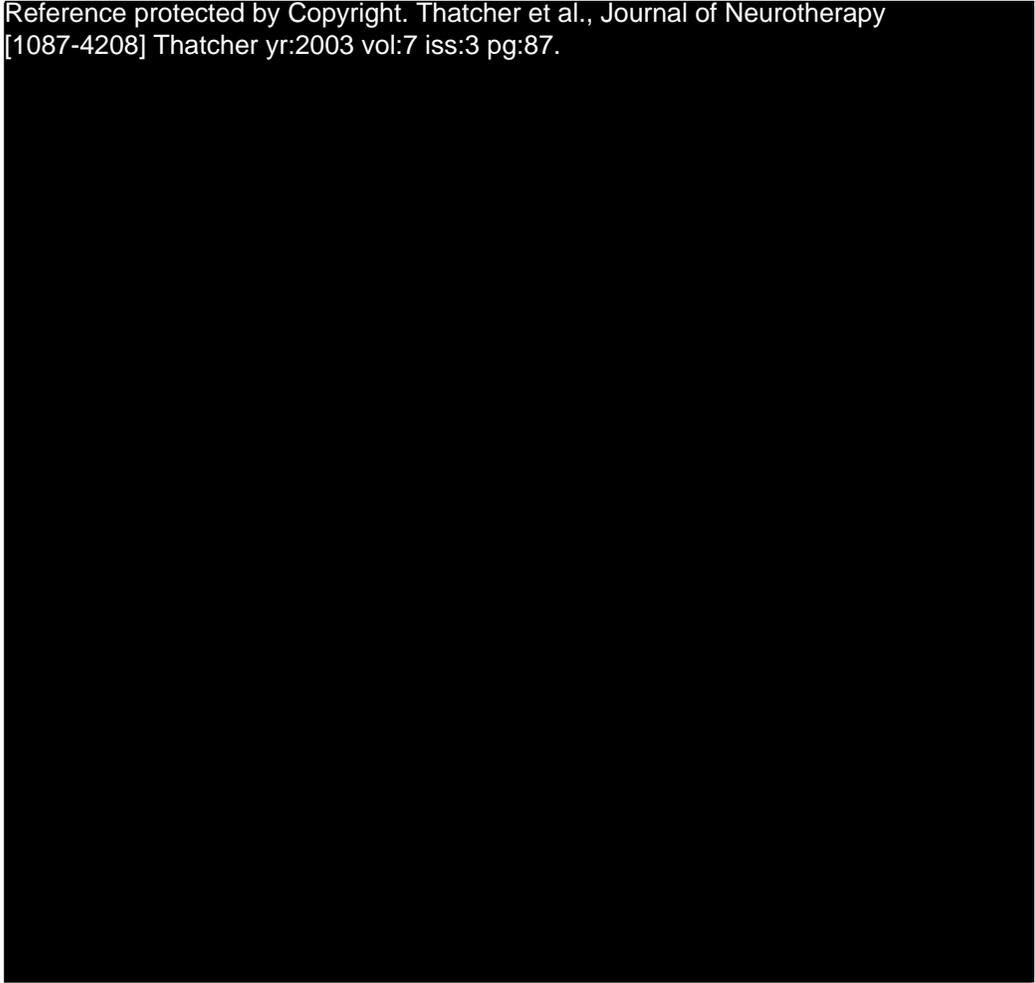
Example peer reviewed publications

Appendix - B

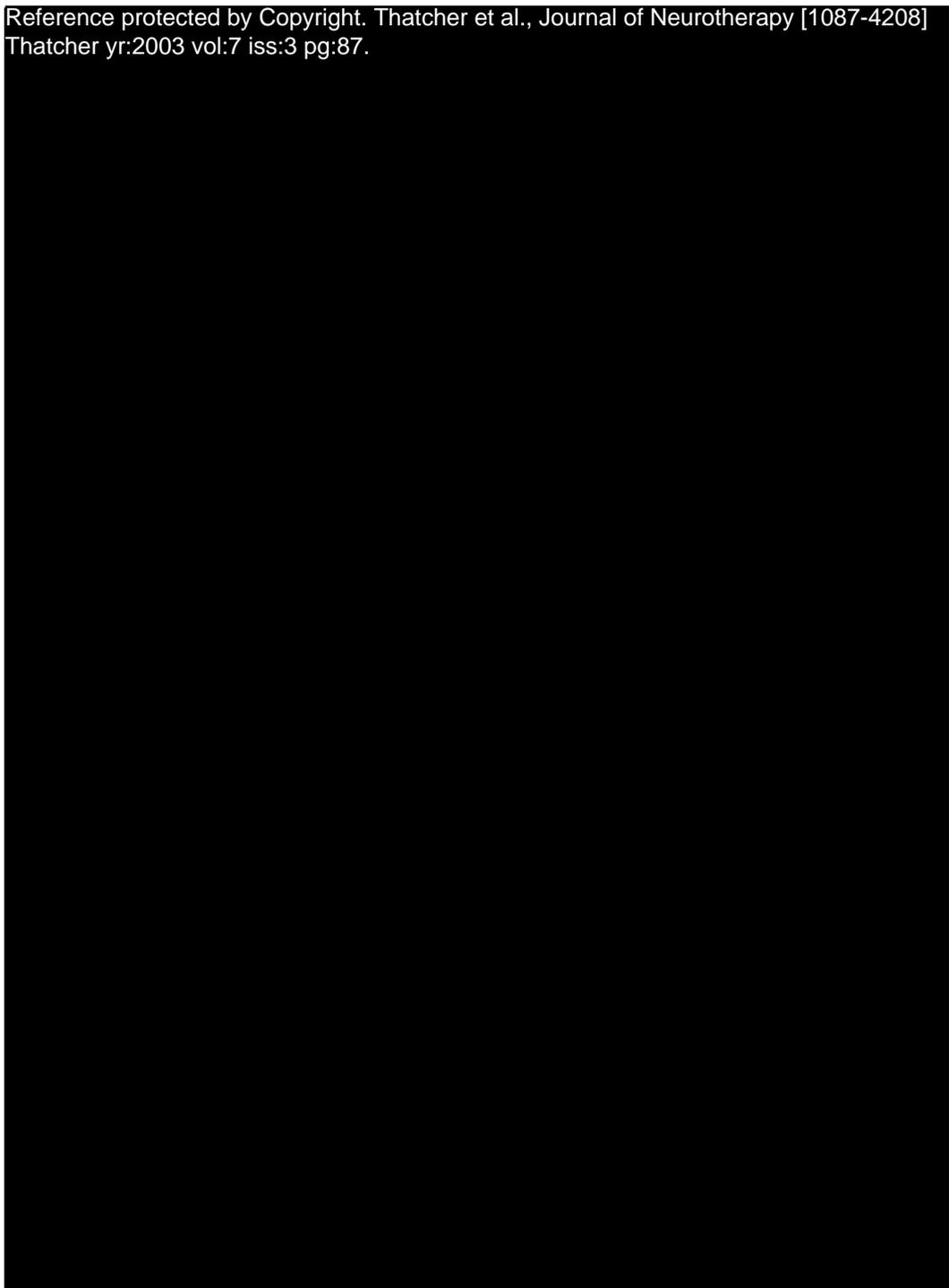
Quantitative EEG Normative Databases: Validation and Clinical Correlation

Robert W. Thatcher, PhD
Rebecca A. Walker, BS
Carl J. Biver, PhD
Duane N. North, MS
Richard Curtin, MA

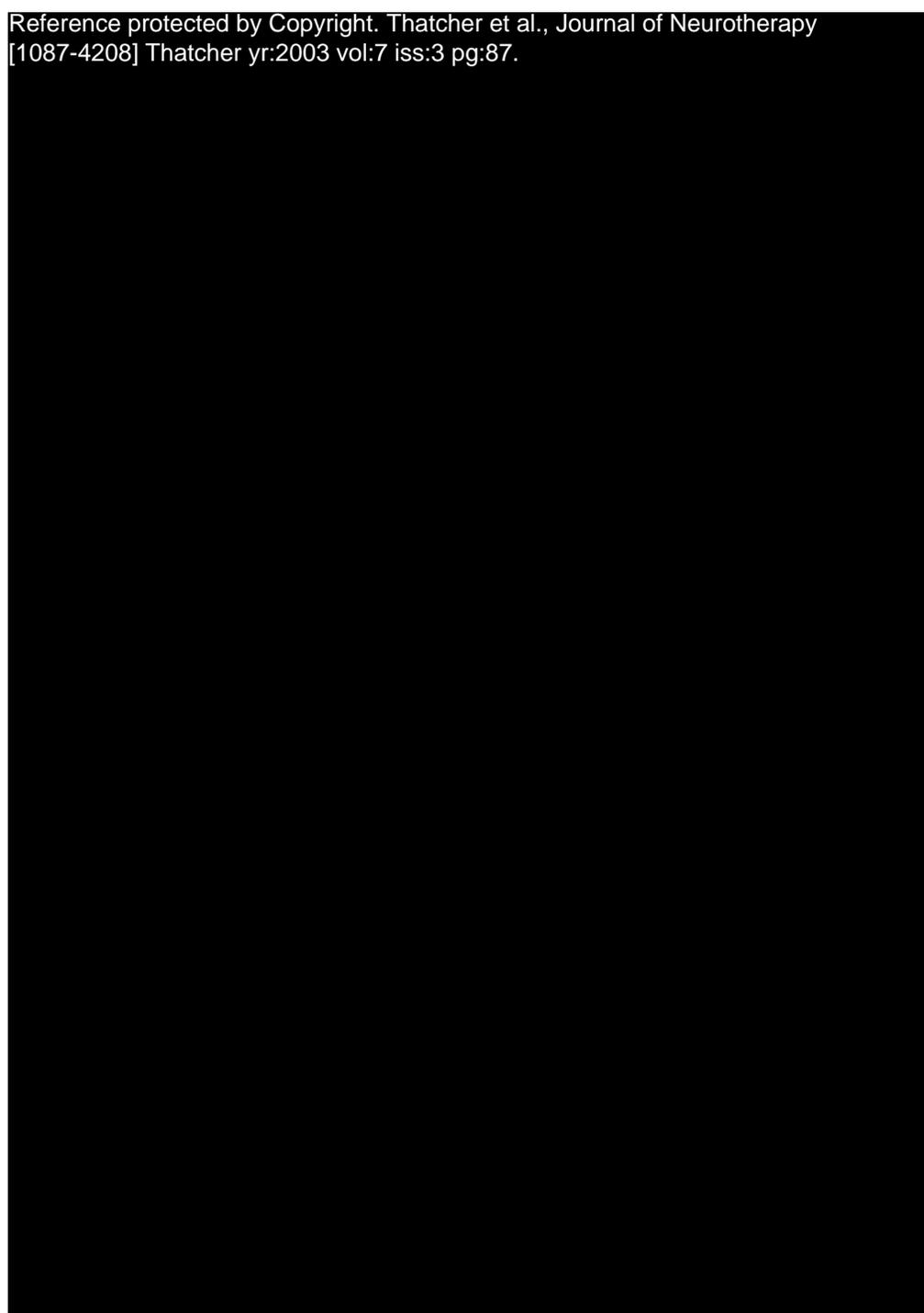
Reference protected by Copyright. Thatcher et al., Journal of Neurotherapy
[1087-4208] Thatcher yr:2003 vol:7 iss:3 pg:87.



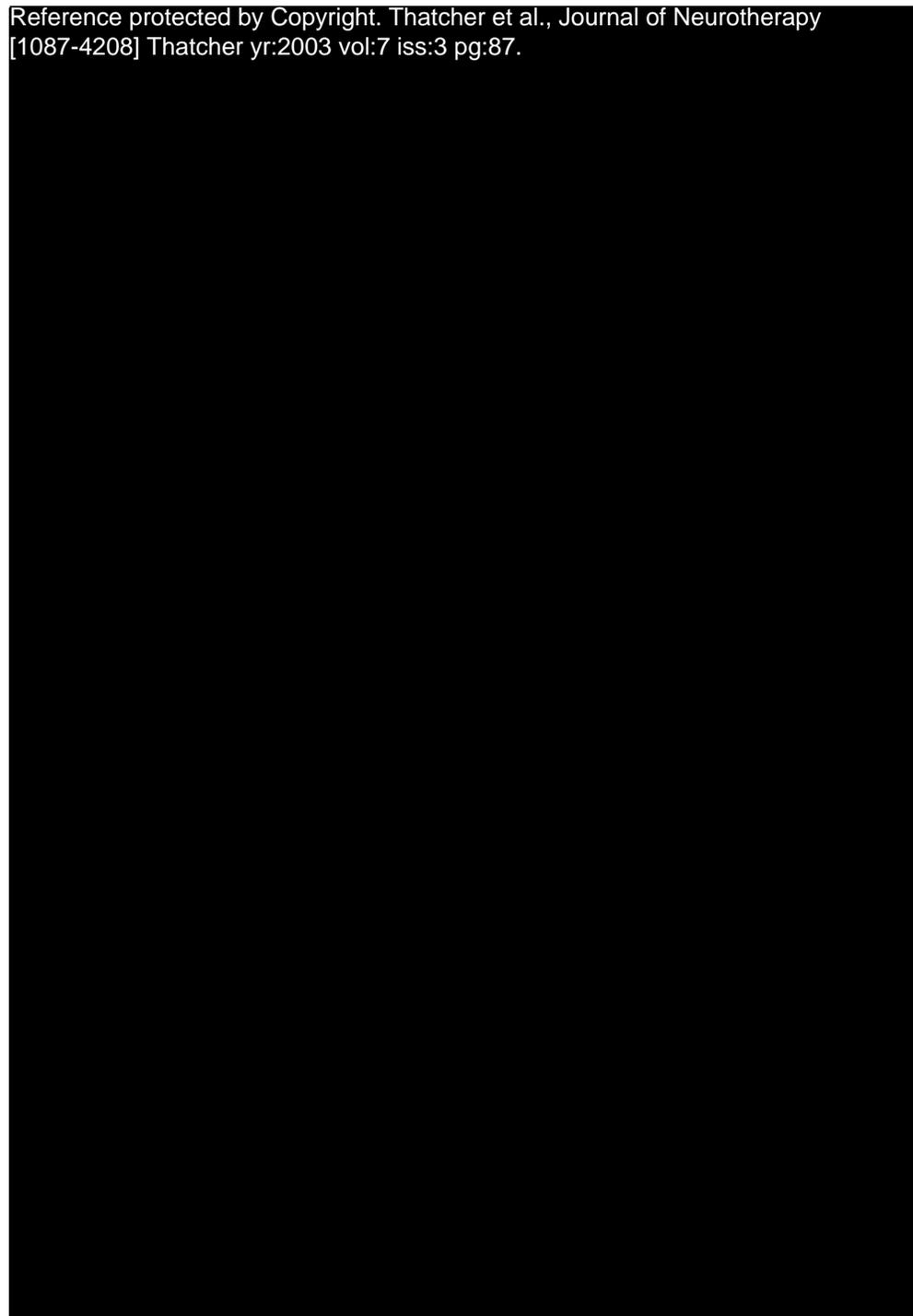
Reference protected by Copyright. Thatcher et al., Journal of Neurotherapy [1087-4208]
Thatcher yr:2003 vol:7 iss:3 pg:87.



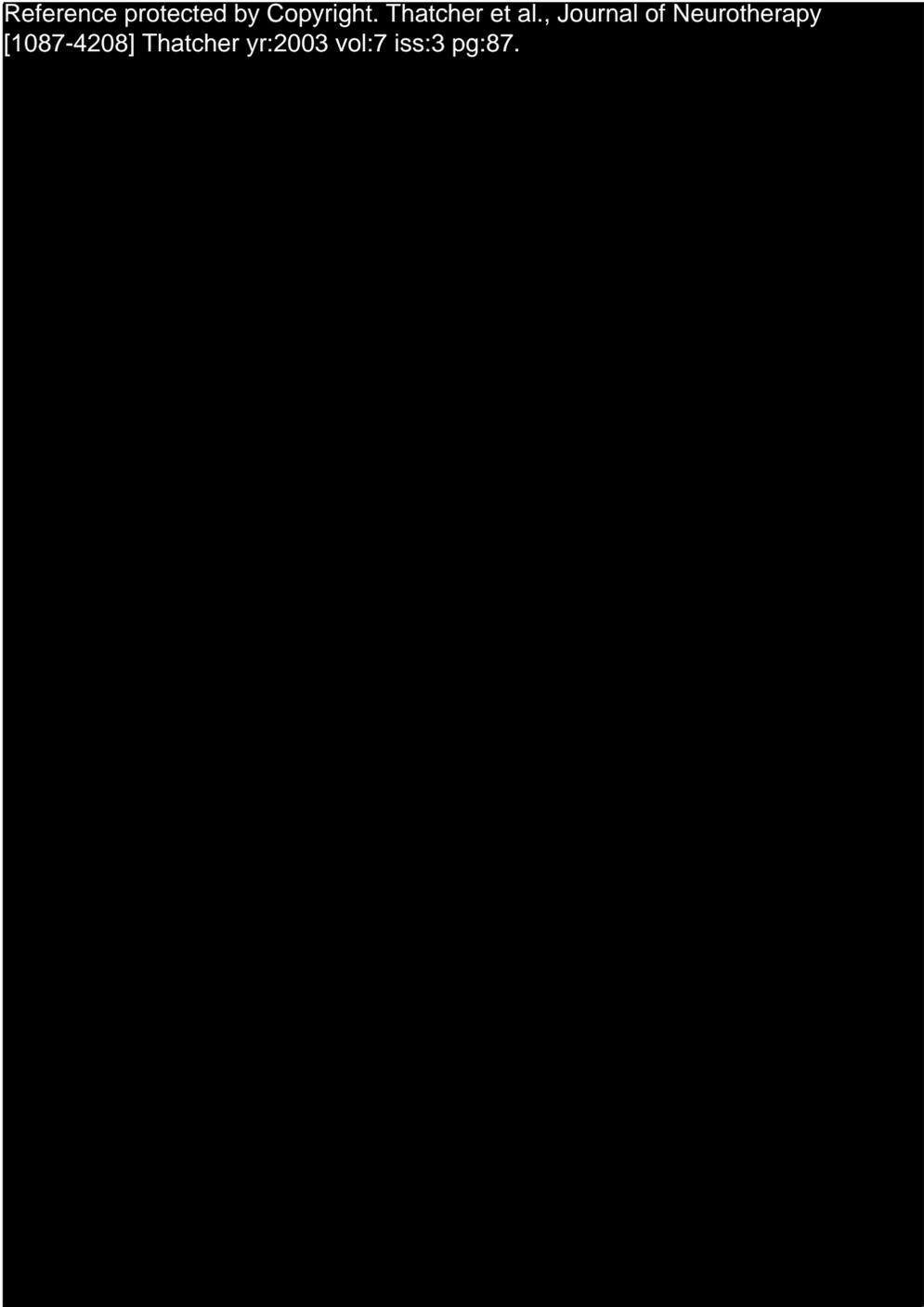
Reference protected by Copyright. Thatcher et al., Journal of Neurotherapy [1087-4208] Thatcher yr:2003 vol:7 iss:3 pg:87.



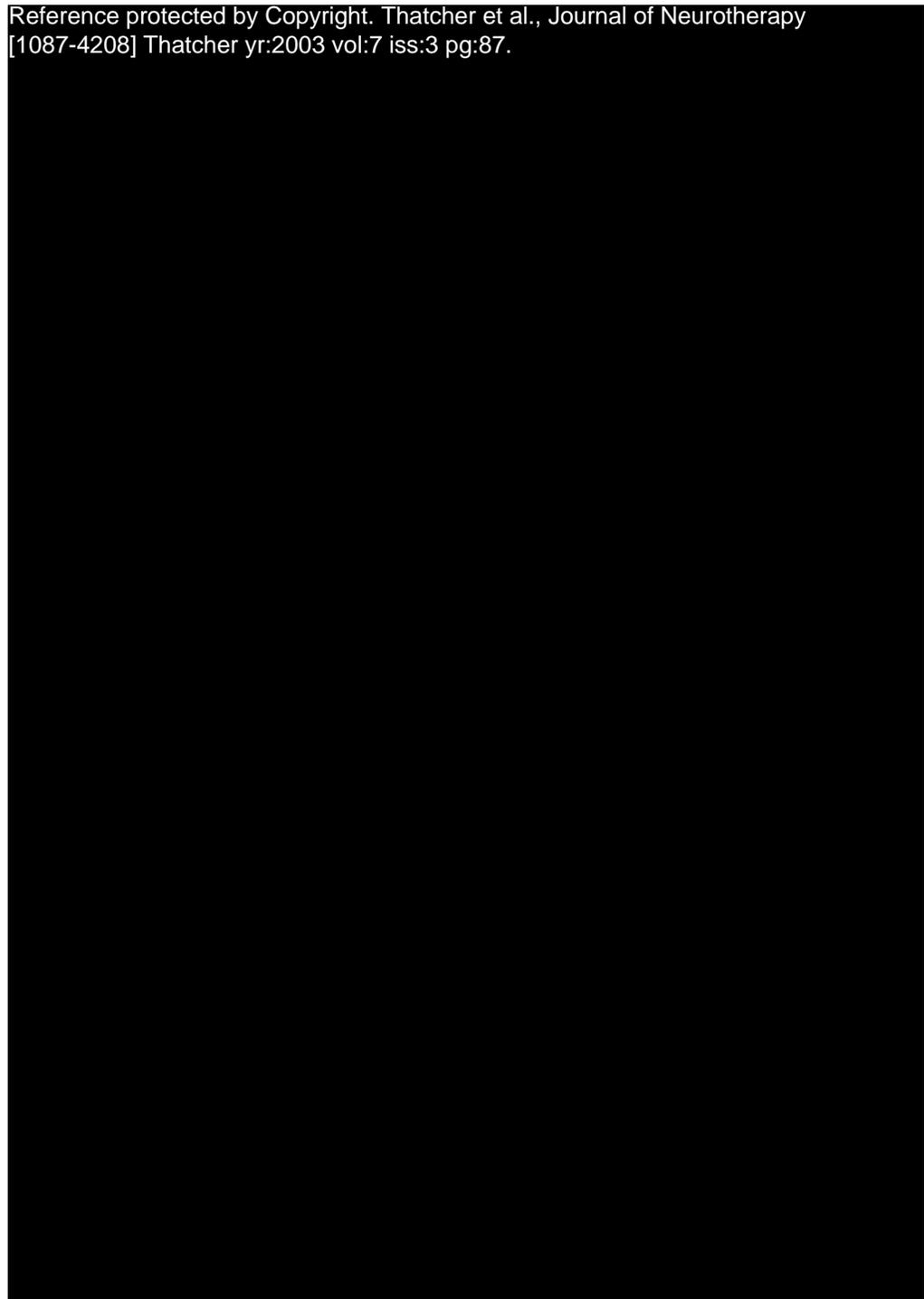
Reference protected by Copyright. Thatcher et al., Journal of Neurotherapy
[1087-4208] Thatcher yr:2003 vol:7 iss:3 pg:87.



Reference protected by Copyright. Thatcher et al., Journal of Neurotherapy [1087-4208] Thatcher yr:2003 vol:7 iss:3 pg:87.

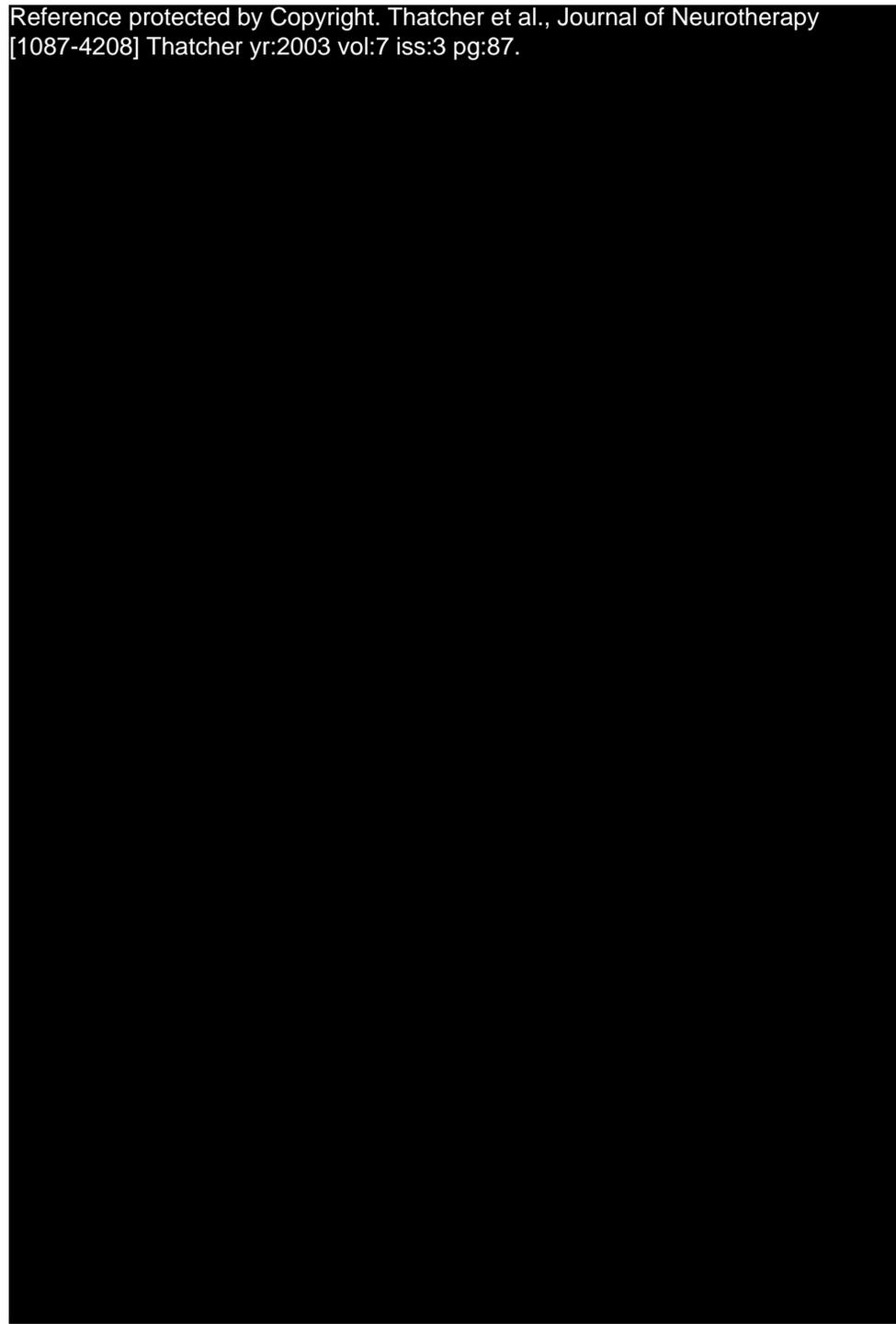


Reference protected by Copyright. Thatcher et al., Journal of Neurotherapy [1087-4208] Thatcher yr:2003 vol:7 iss:3 pg:87.

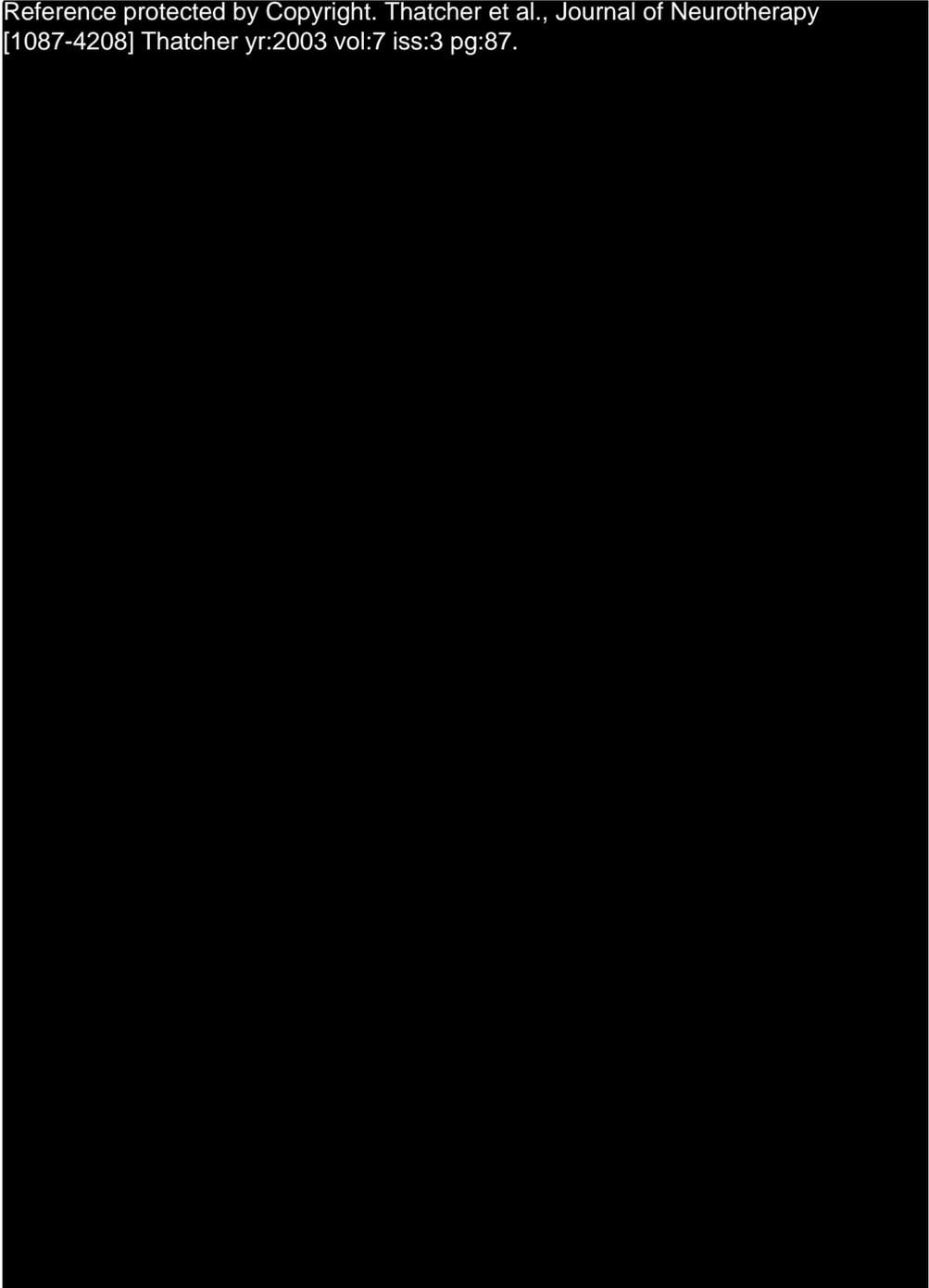


Reference protected by Copyright. Thatcher et al., Journal of Neurotherapy
[1087-4208] Thatcher yr:2003 vol:7 iss:3 pg:87.

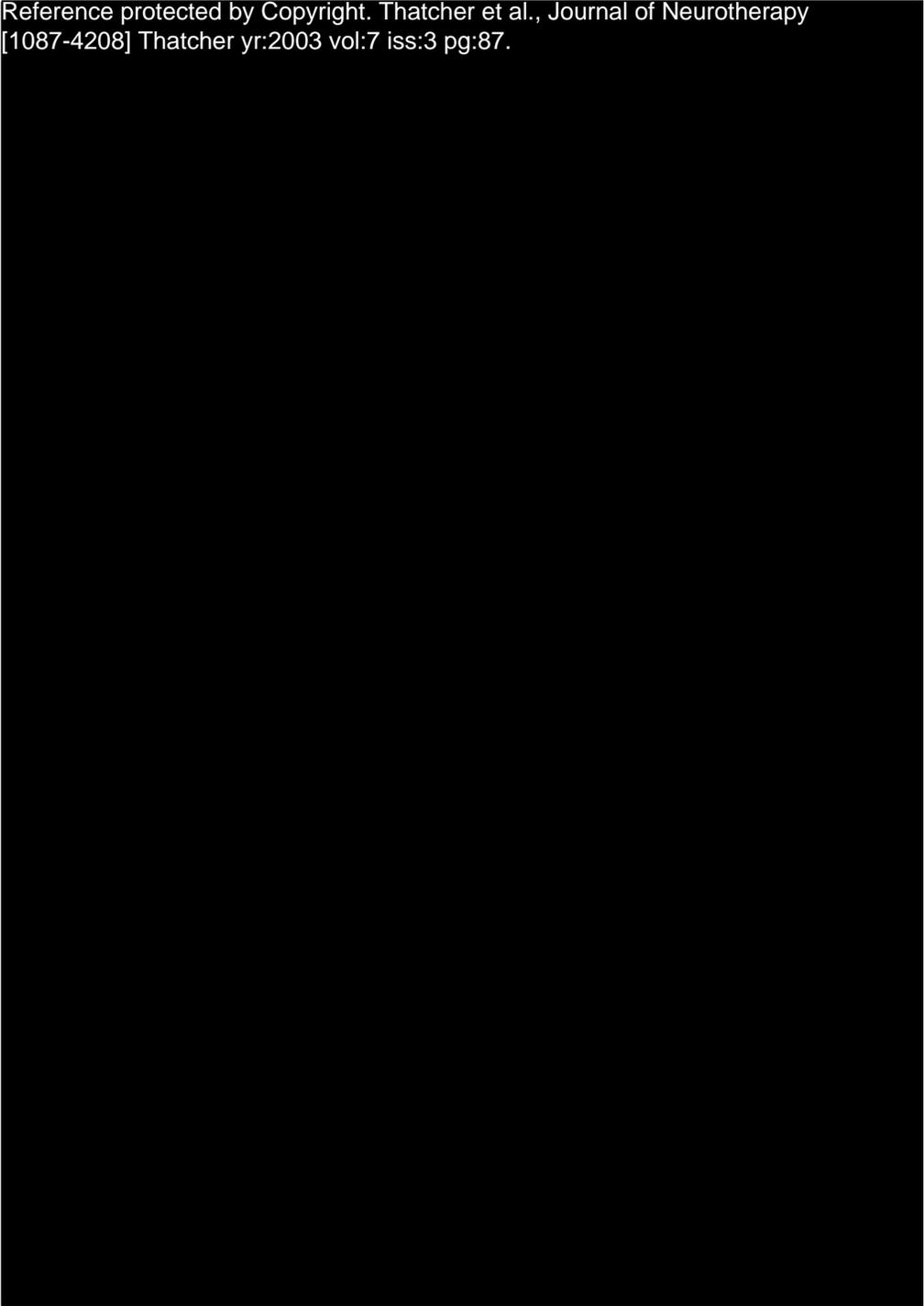
Reference protected by Copyright. Thatcher et al., Journal of Neurotherapy [1087-4208] Thatcher yr:2003 vol:7 iss:3 pg:87.



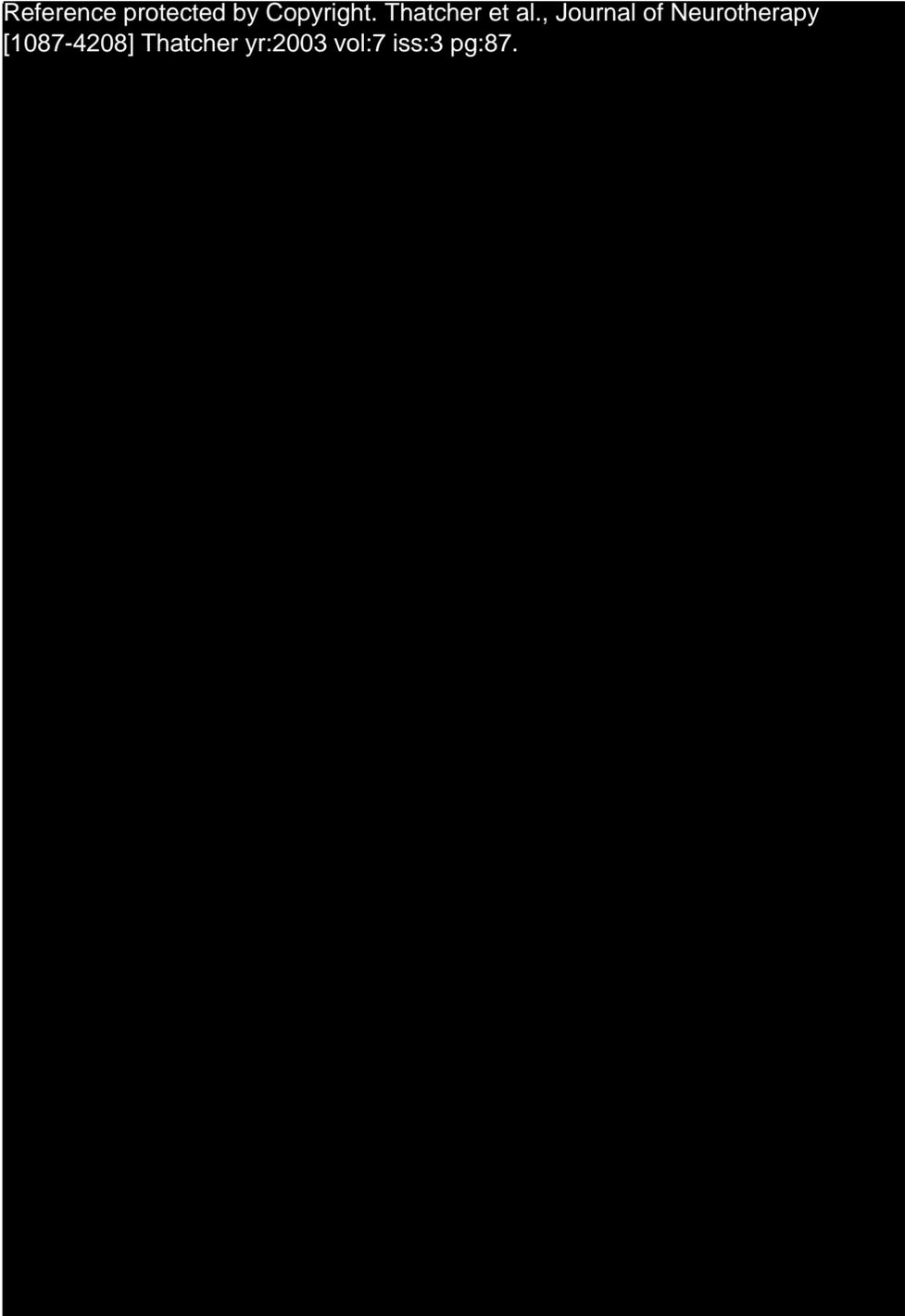
Reference protected by Copyright. Thatcher et al., Journal of Neurotherapy [1087-4208] Thatcher yr:2003 vol:7 iss:3 pg:87.



Reference protected by Copyright. Thatcher et al., Journal of Neurotherapy [1087-4208] Thatcher yr:2003 vol:7 iss:3 pg:87.



Reference protected by Copyright. Thatcher et al., Journal of Neurotherapy [1087-4208] Thatcher yr:2003 vol:7 iss:3 pg:87.



See

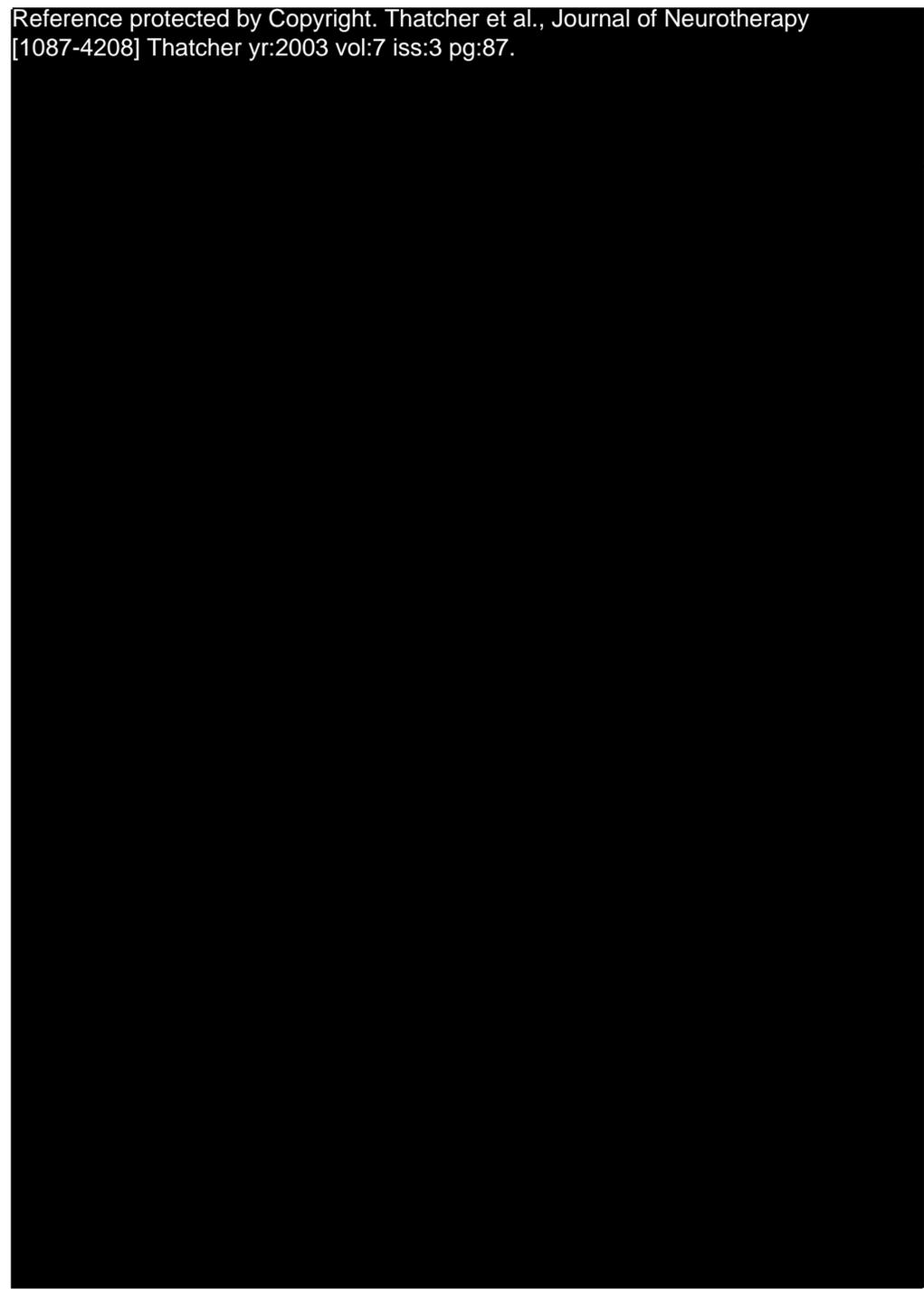
Reference protected by Copyright. Thatcher et al., Journal of Neurotherapy [1087-4208] Thatcher yr:2003 vol:7 iss:3 pg:87.



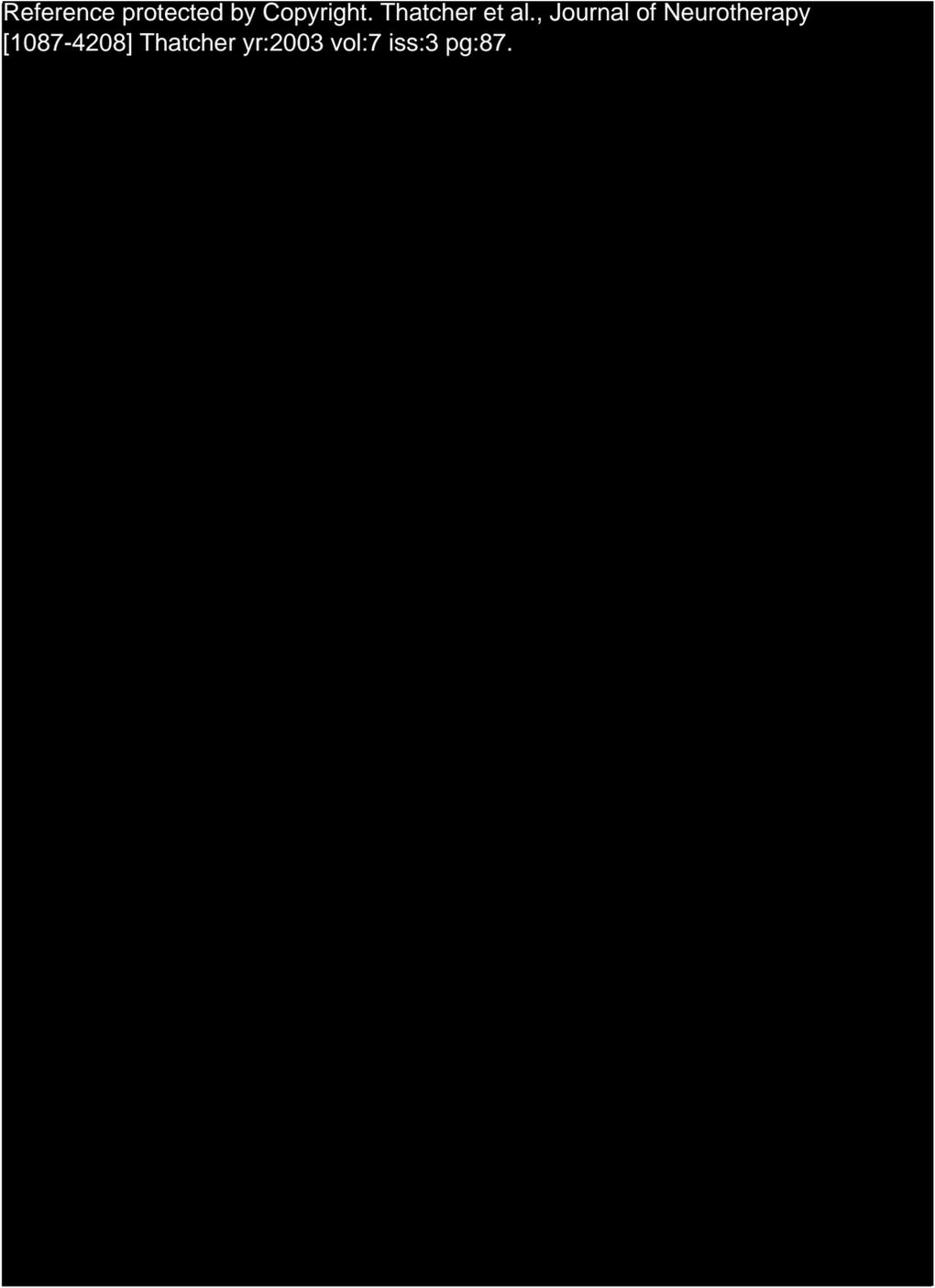
Reference protected by Copyright. Thatcher et al., Journal of Neurotherapy [1087-4208] Thatcher yr:2003 vol:7 iss:3 pg:87.



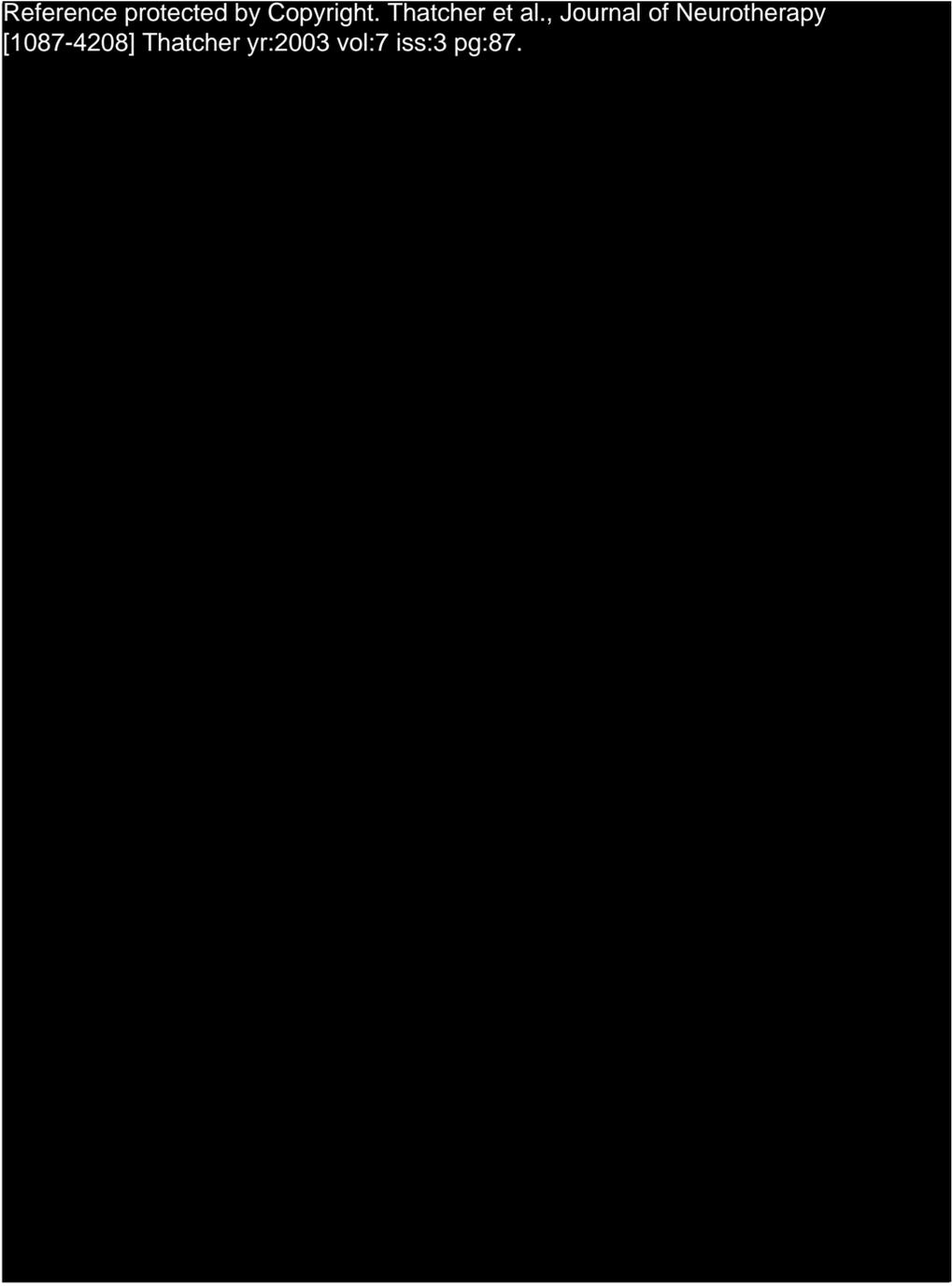
Reference protected by Copyright. Thatcher et al., Journal of Neurotherapy [1087-4208] Thatcher yr:2003 vol:7 iss:3 pg:87.



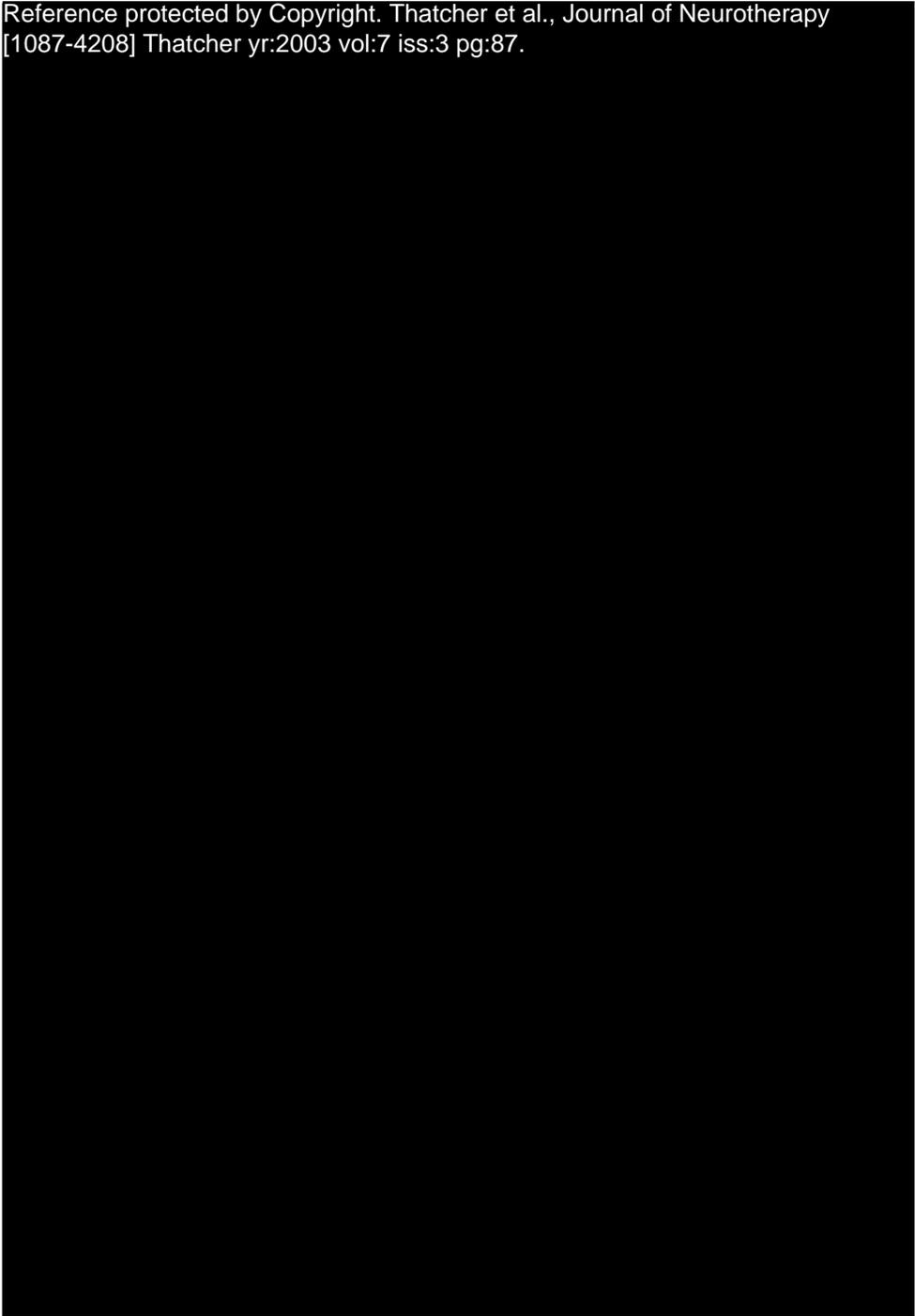
Reference protected by Copyright. Thatcher et al., Journal of Neurotherapy [1087-4208] Thatcher yr:2003 vol:7 iss:3 pg:87.



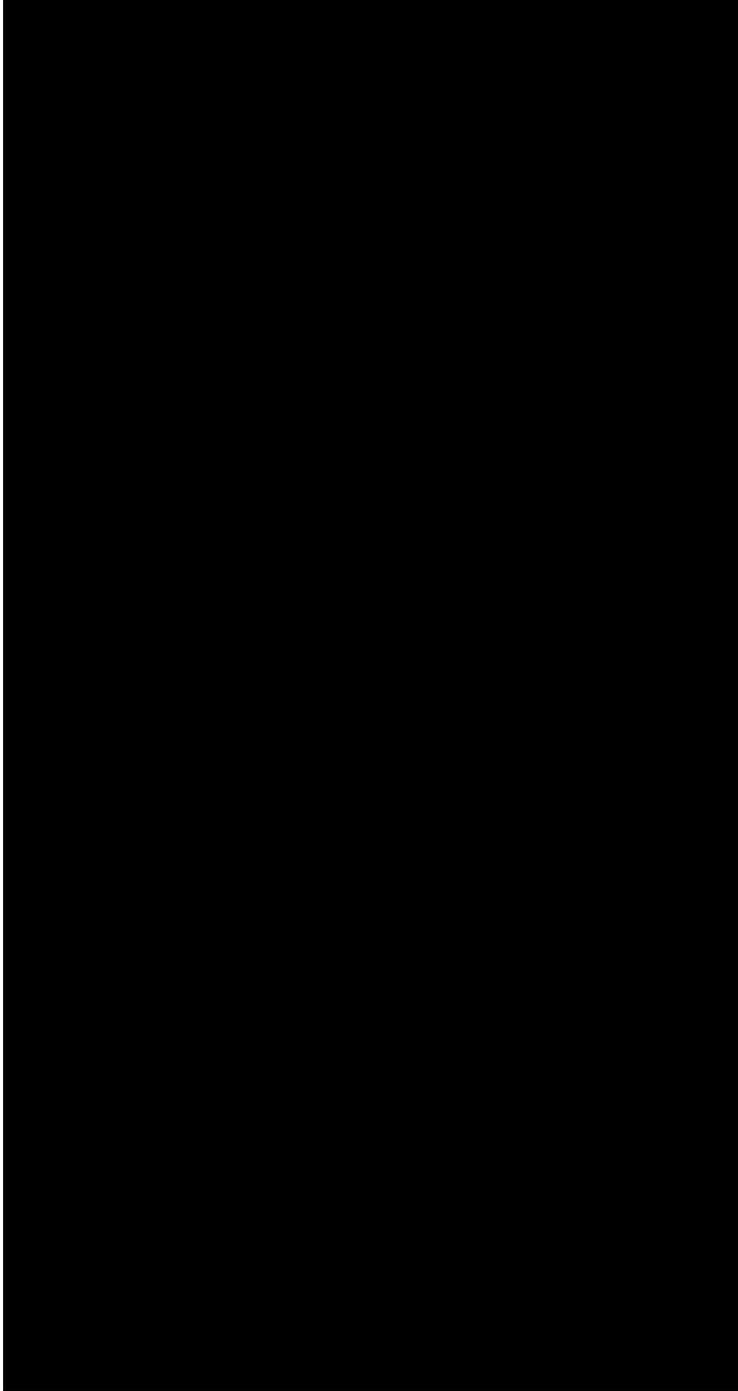
Reference protected by Copyright. Thatcher et al., Journal of Neurotherapy [1087-4208] Thatcher yr:2003 vol:7 iss:3 pg:87.



Reference protected by Copyright. Thatcher et al., Journal of Neurotherapy [1087-4208] Thatcher yr:2003 vol:7 iss:3 pg:87.

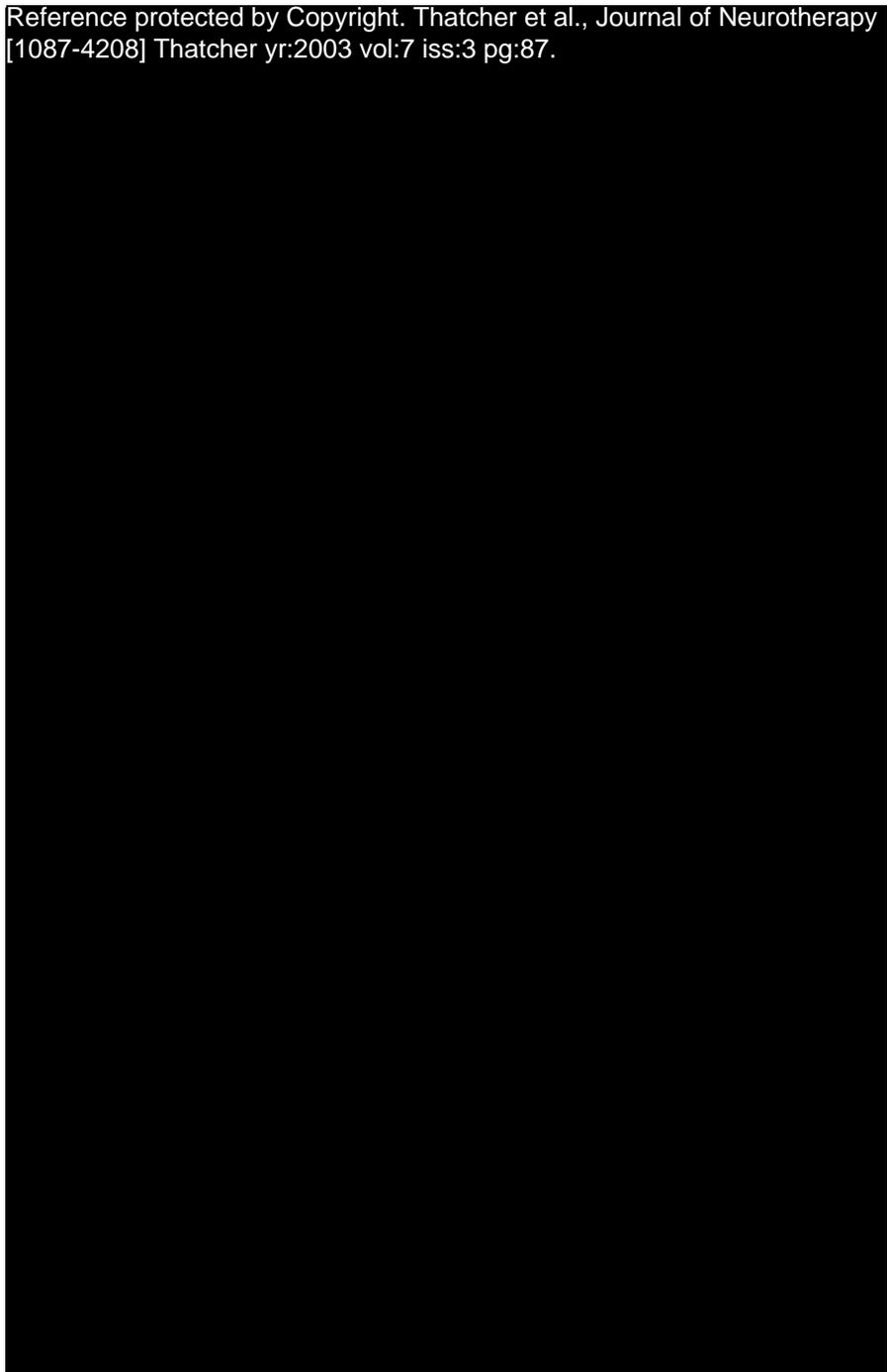


Reference protected by Copyright. Thatcher et al., Journal of Neurotherapy [1087-4208] Thatcher yr:2003 vol:7 iss:3 pg:87.

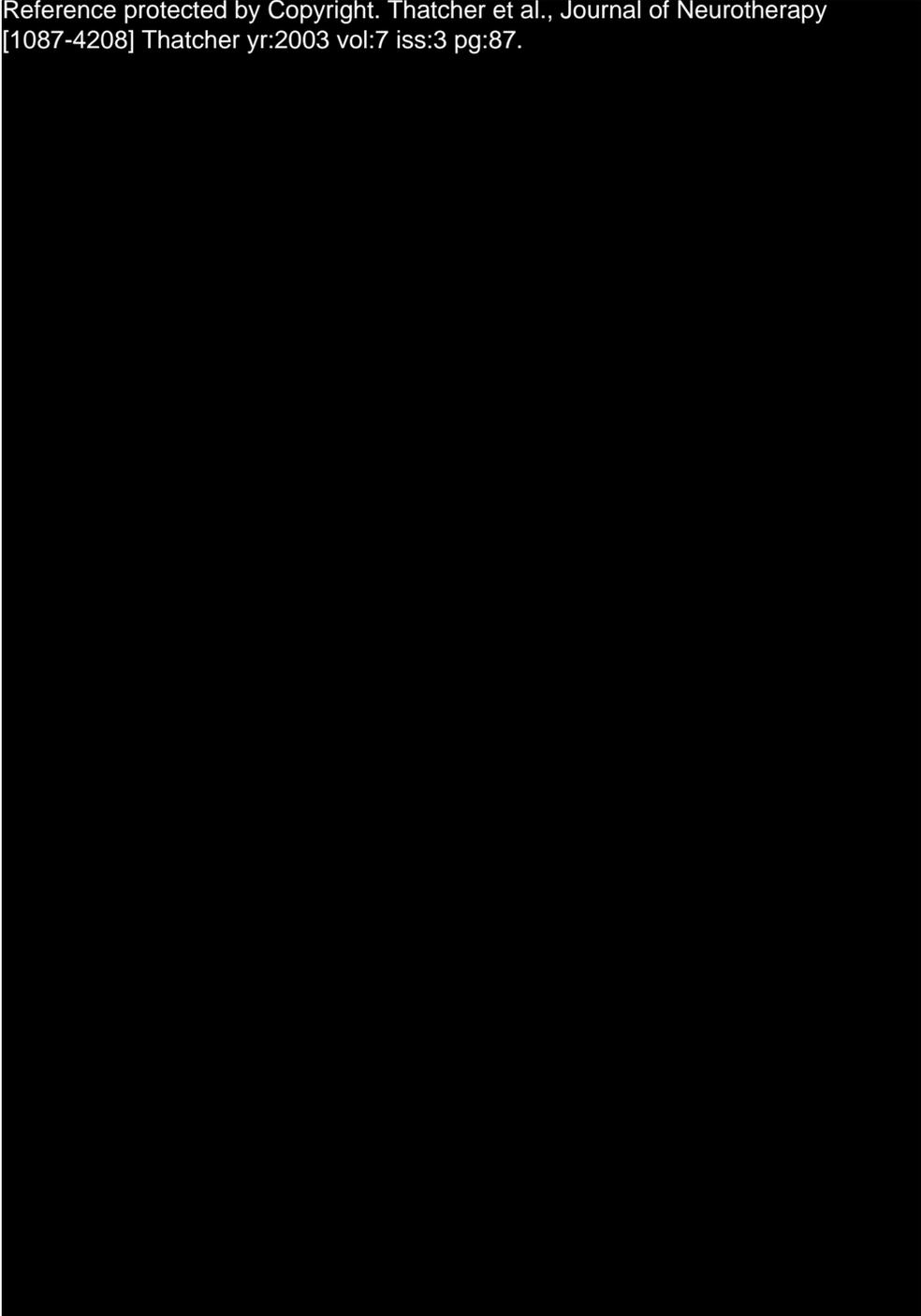


104

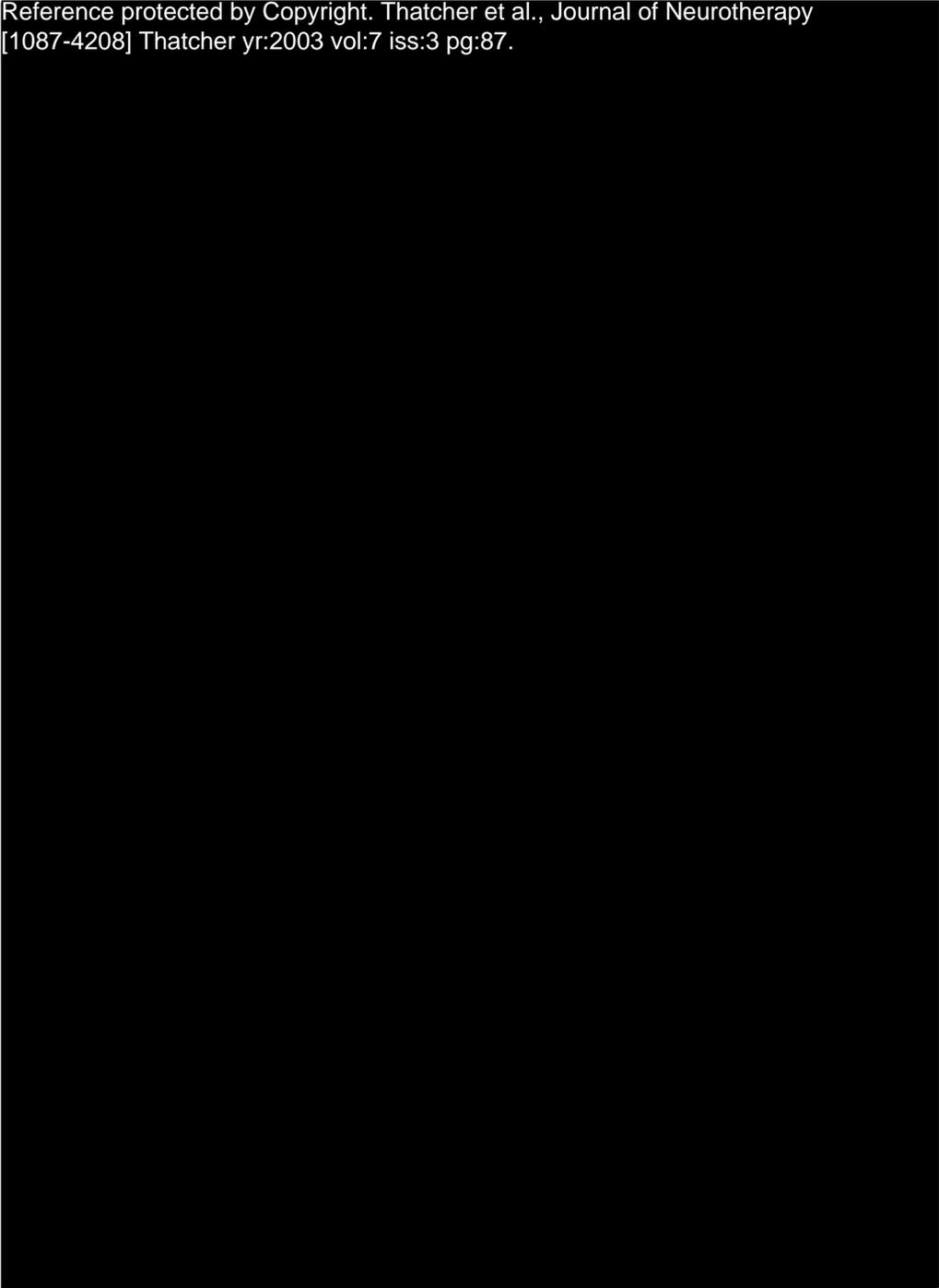
Reference protected by Copyright. Thatcher et al., Journal of Neurotherapy [1087-4208] Thatcher yr:2003 vol:7 iss:3 pg:87.



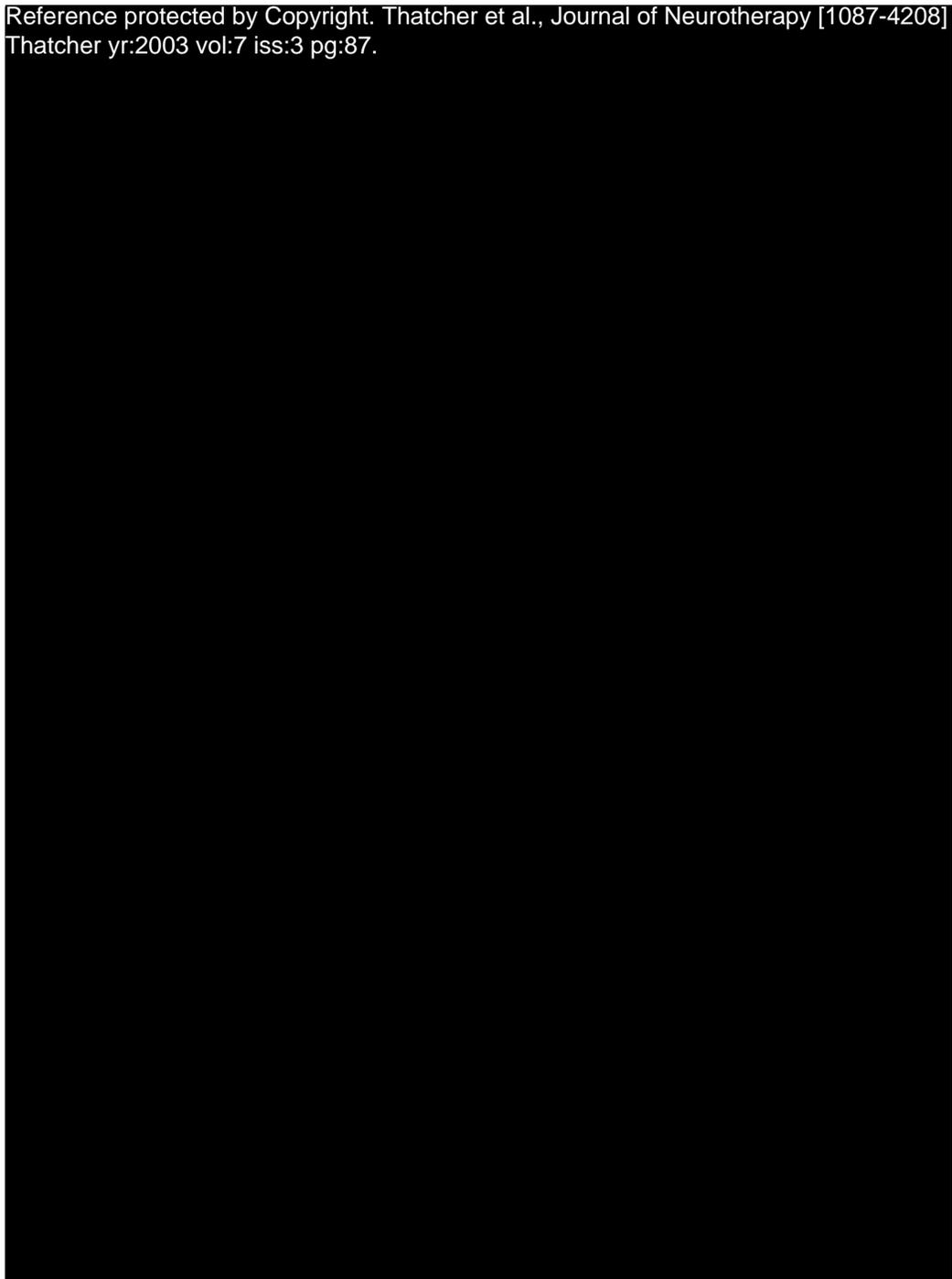
Reference protected by Copyright. Thatcher et al., Journal of Neurotherapy [1087-4208] Thatcher yr:2003 vol:7 iss:3 pg:87.



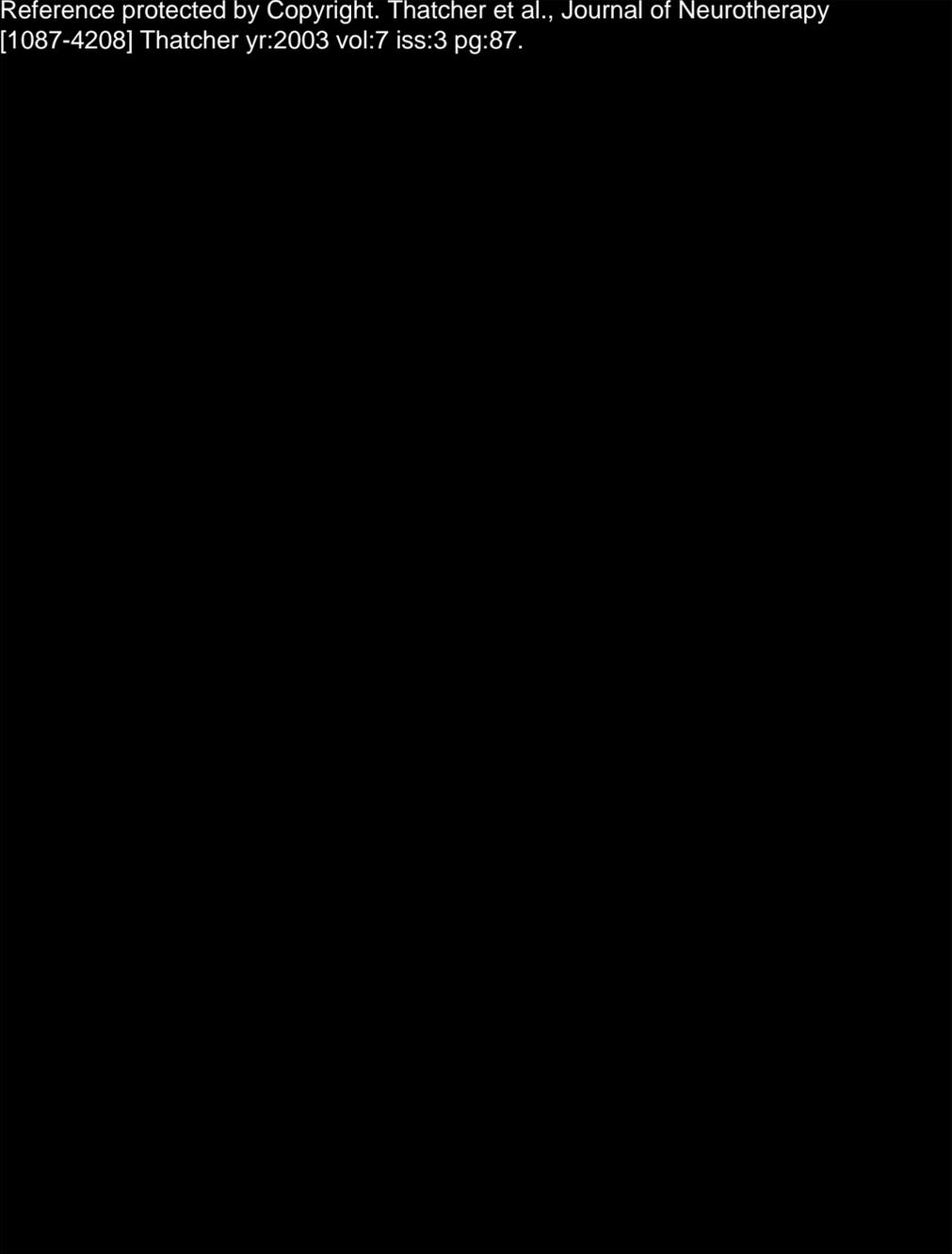
Reference protected by Copyright. Thatcher et al., Journal of Neurotherapy [1087-4208] Thatcher yr:2003 vol:7 iss:3 pg:87.



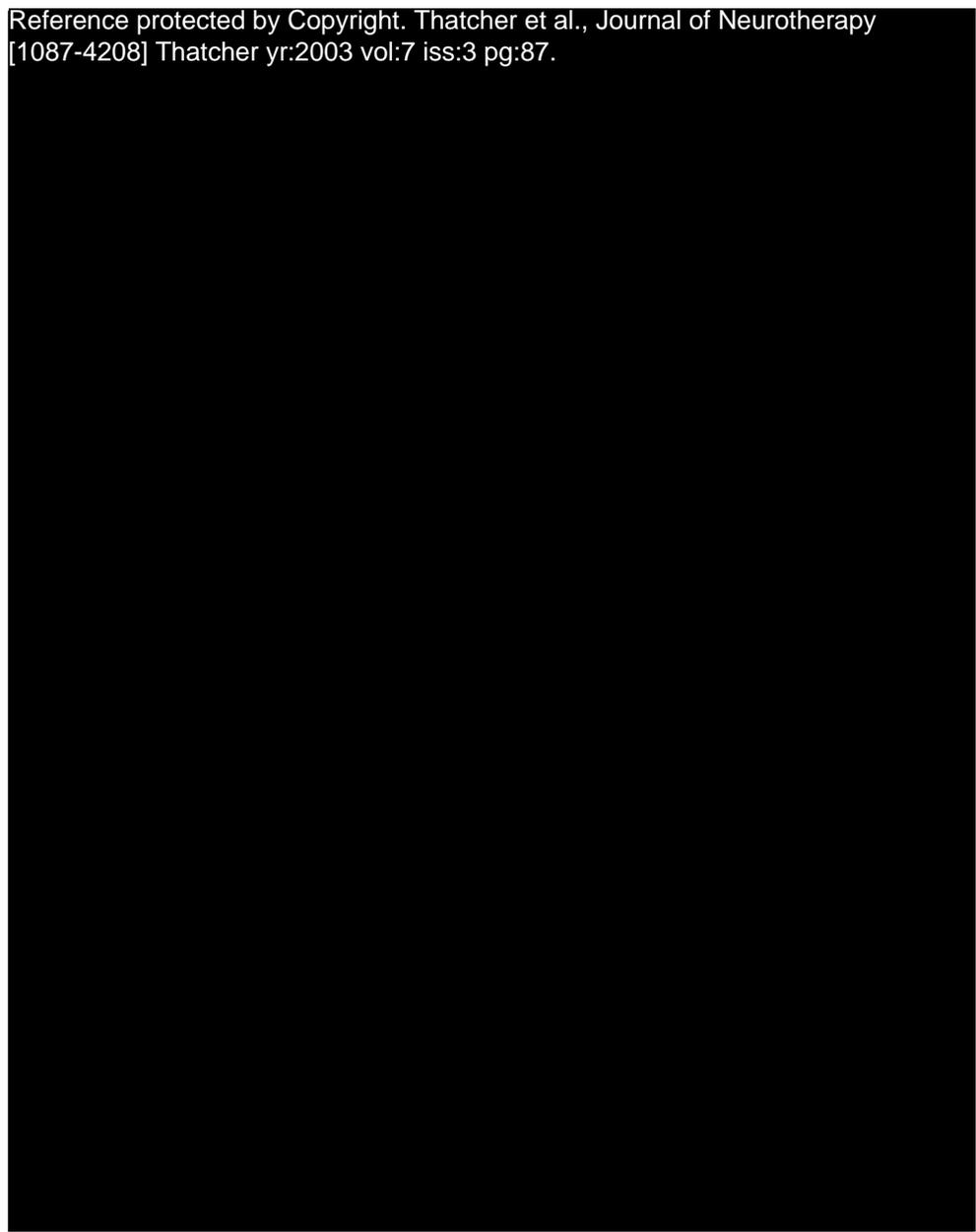
Reference protected by Copyright. Thatcher et al., Journal of Neurotherapy [1087-4208]
Thatcher yr:2003 vol:7 iss:3 pg:87.



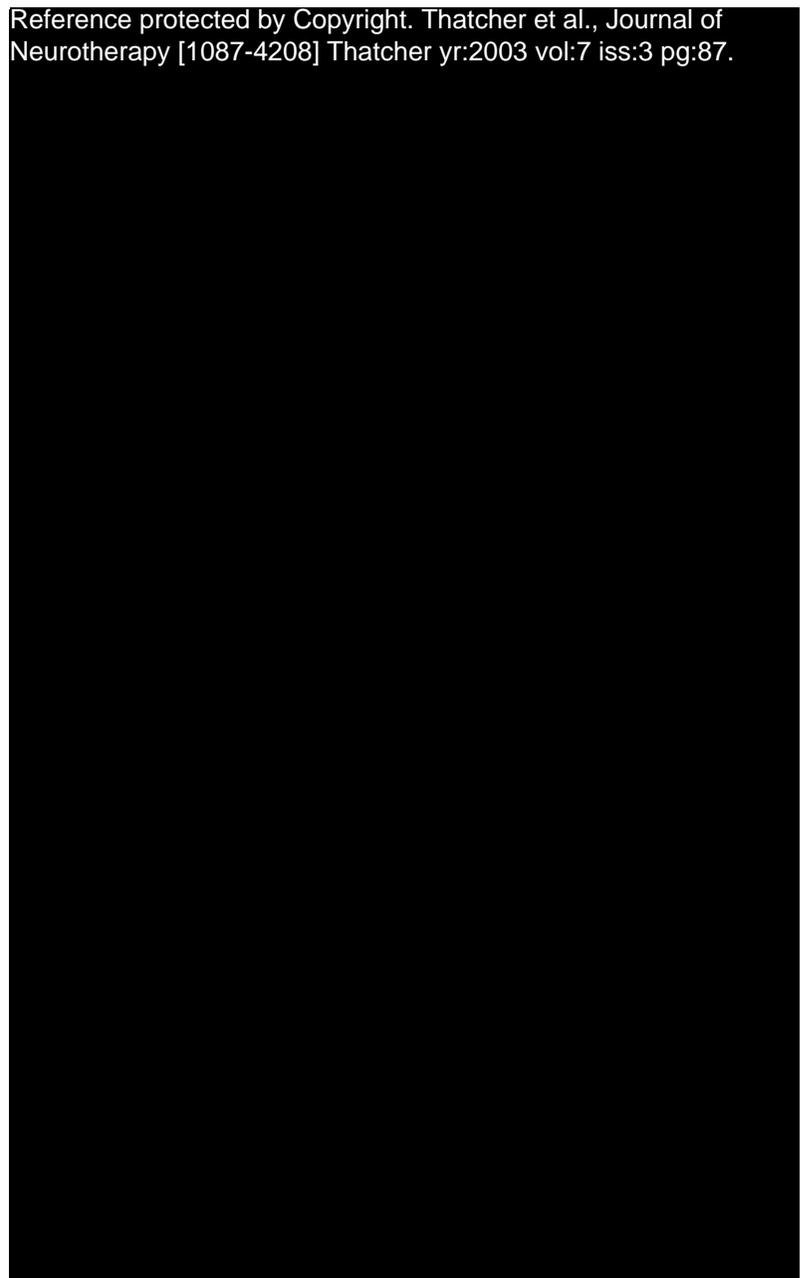
Reference protected by Copyright. Thatcher et al., Journal of Neurotherapy [1087-4208] Thatcher yr:2003 vol:7 iss:3 pg:87.



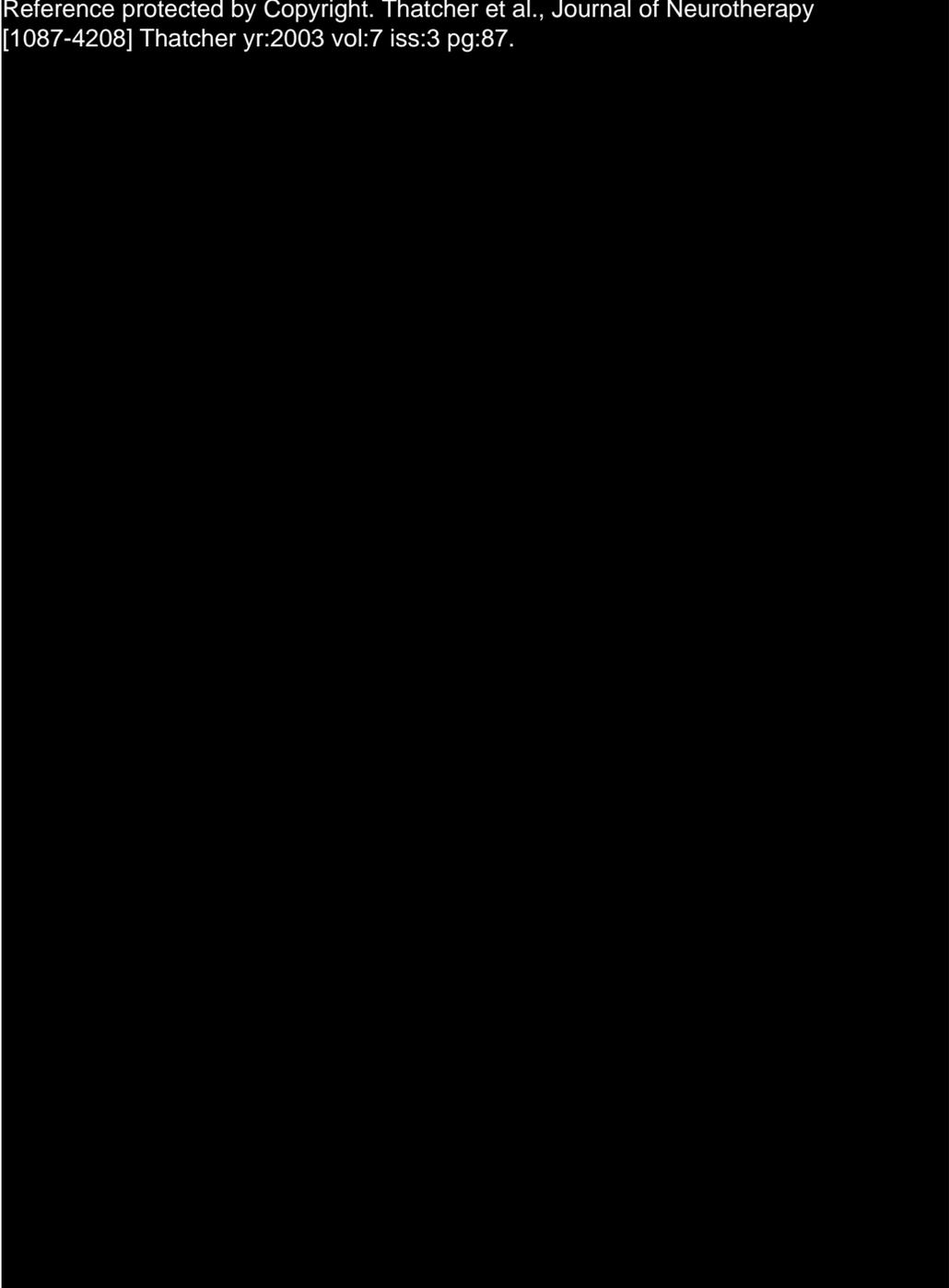
Reference protected by Copyright. Thatcher et al., Journal of Neurotherapy [1087-4208] Thatcher yr:2003 vol:7 iss:3 pg:87.



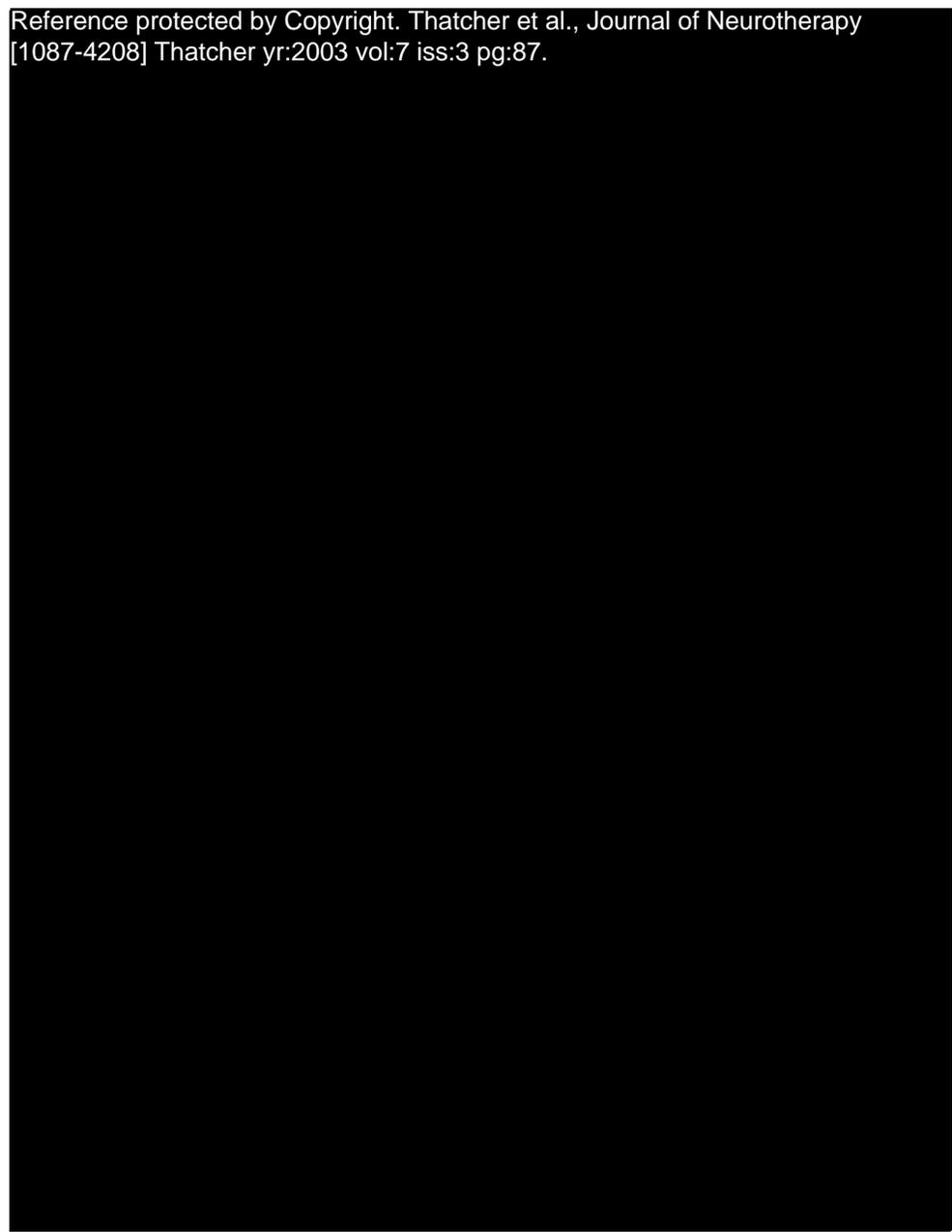
Reference protected by Copyright. Thatcher et al., Journal of Neurotherapy [1087-4208] Thatcher yr:2003 vol:7 iss:3 pg:87.



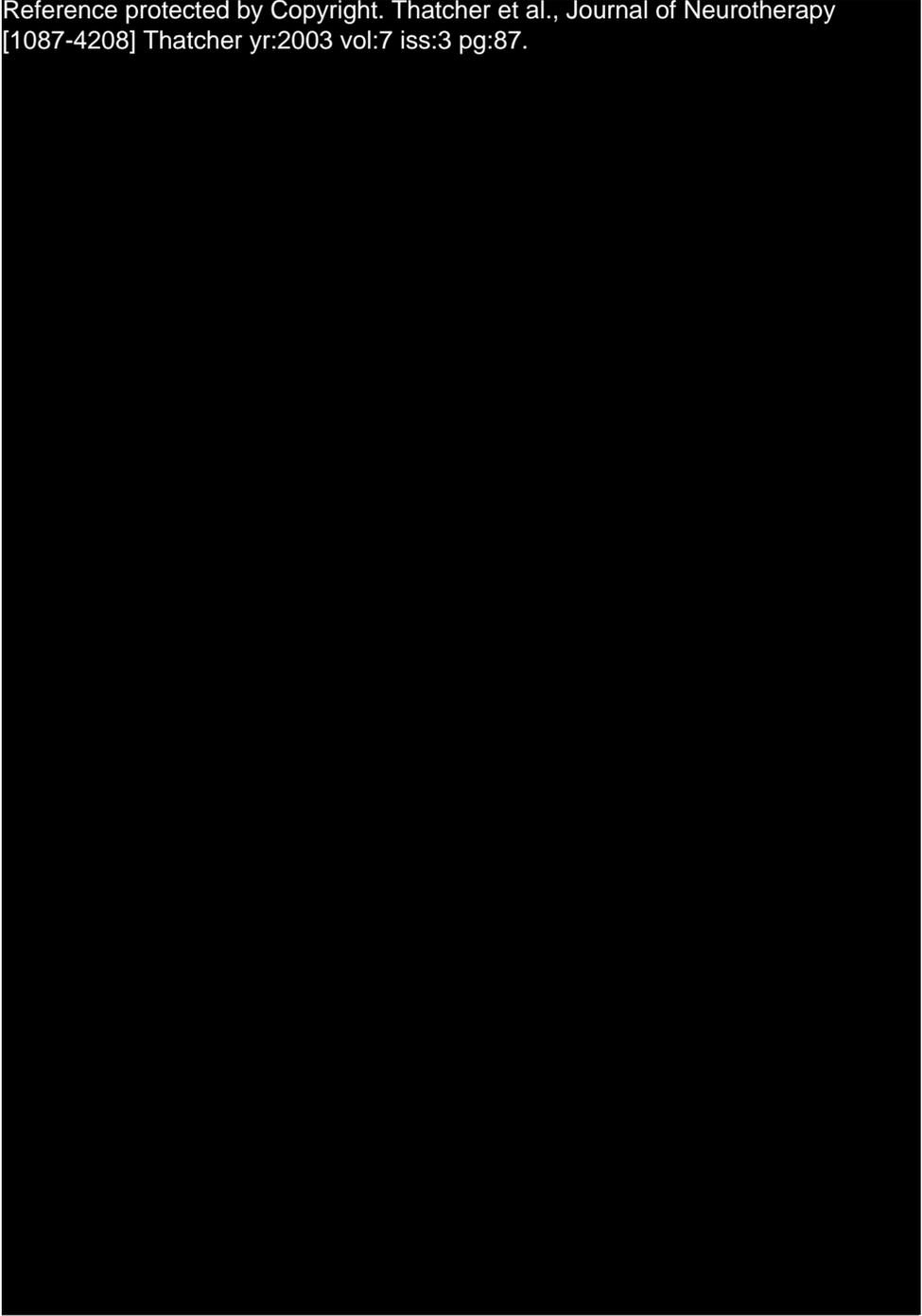
Reference protected by Copyright. Thatcher et al., Journal of Neurotherapy [1087-4208] Thatcher yr:2003 vol:7 iss:3 pg:87.



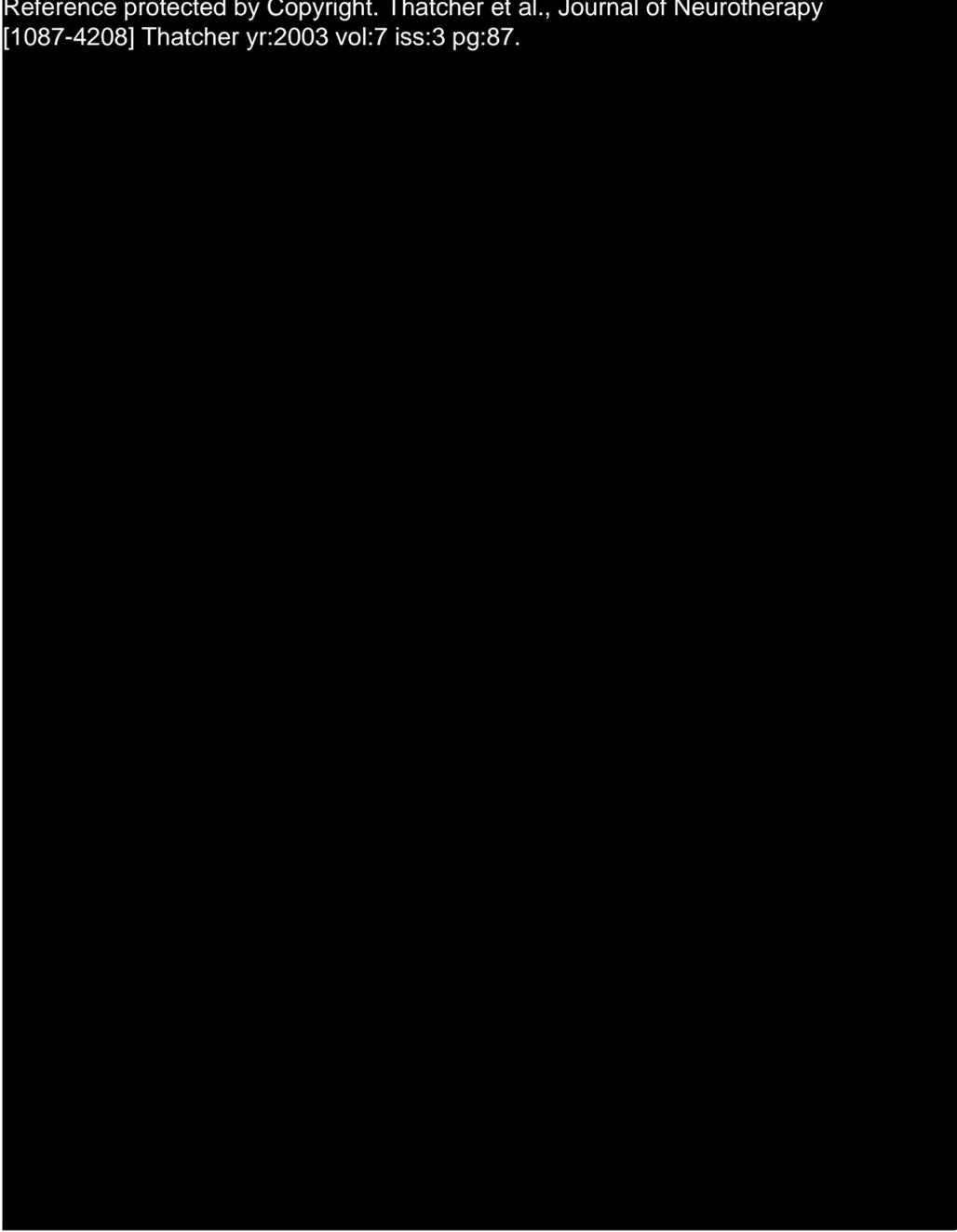
Reference protected by Copyright. Thatcher et al., Journal of Neurotherapy [1087-4208] Thatcher yr:2003 vol:7 iss:3 pg:87.



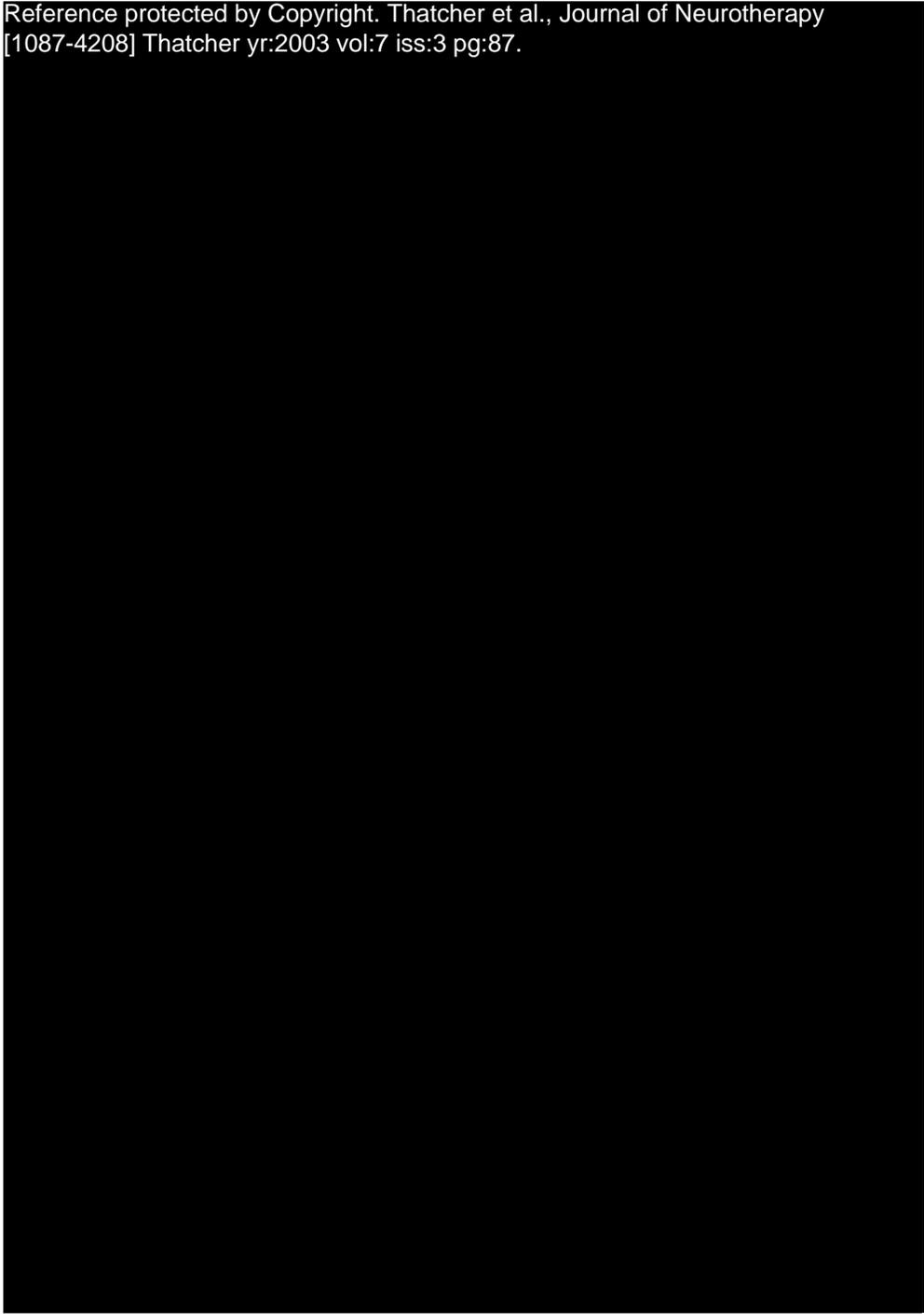
Reference protected by Copyright. Thatcher et al., Journal of Neurotherapy [1087-4208] Thatcher yr:2003 vol:7 iss:3 pg:87.



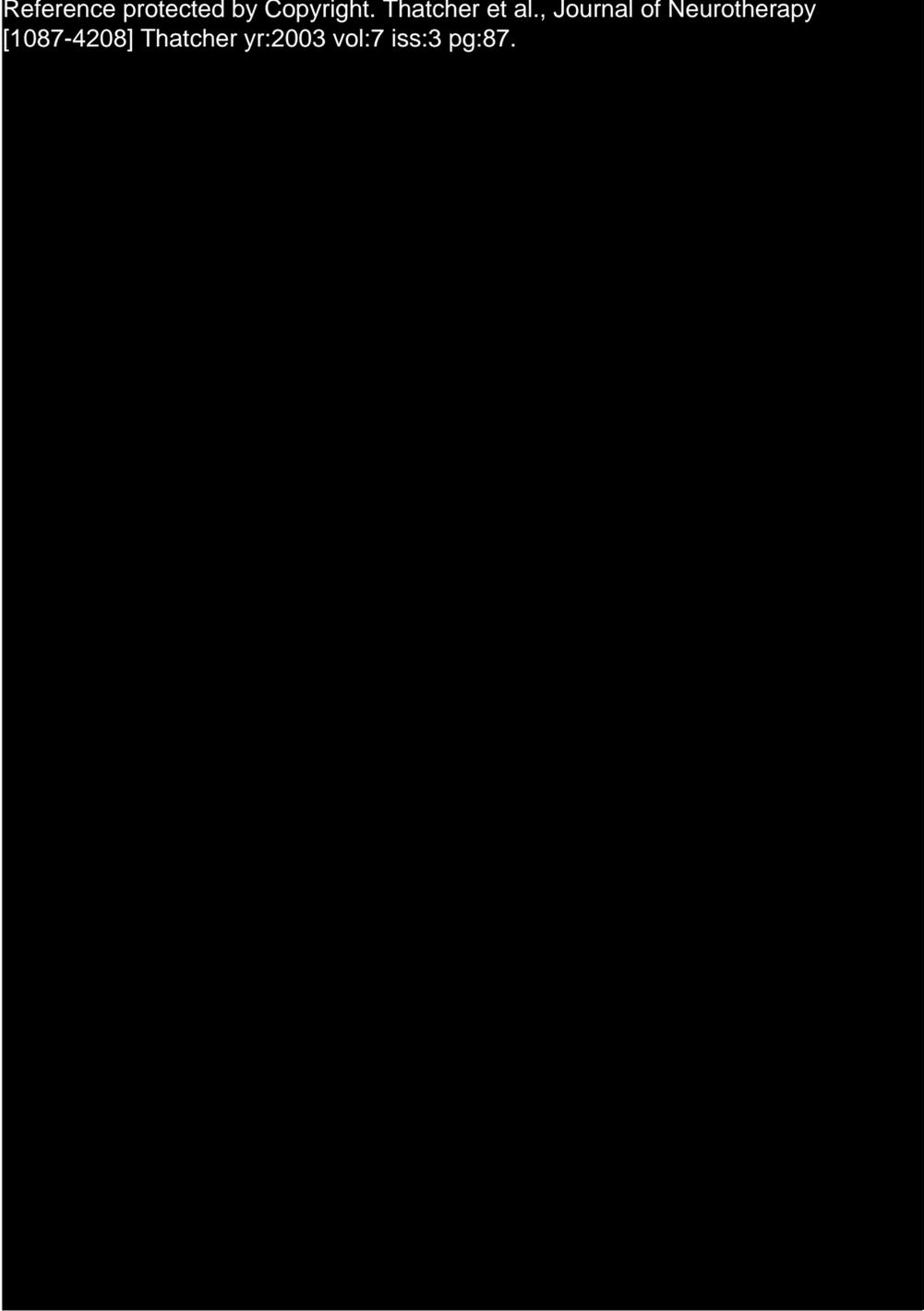
Reference protected by Copyright. Thatcher et al., Journal of Neurotherapy [1087-4208] Thatcher yr:2003 vol:7 iss:3 pg:87.



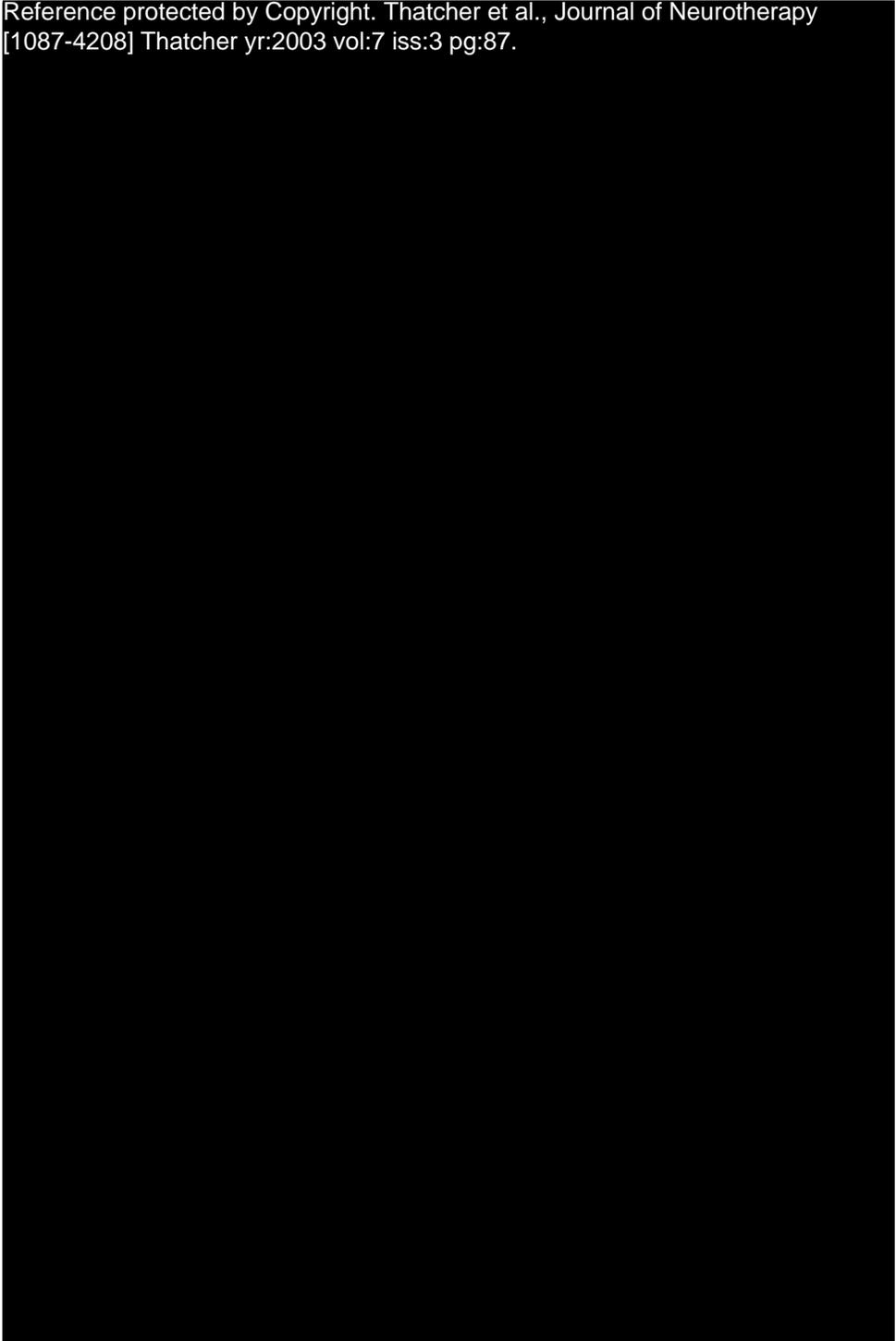
Reference protected by Copyright. Thatcher et al., Journal of Neurotherapy [1087-4208] Thatcher yr:2003 vol:7 iss:3 pg:87.



Reference protected by Copyright. Thatcher et al., Journal of Neurotherapy [1087-4208] Thatcher yr:2003 vol:7 iss:3 pg:87.



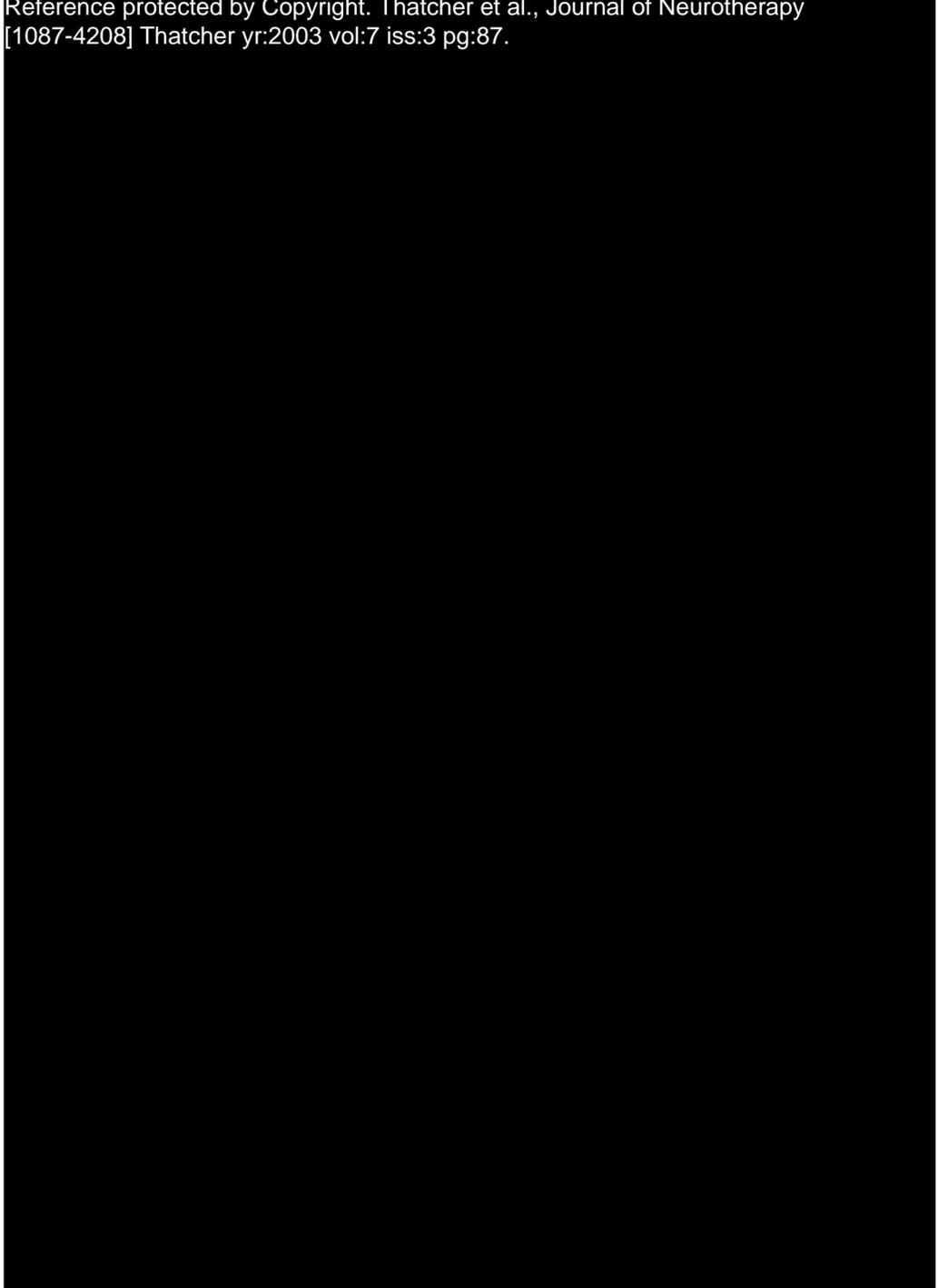
Reference protected by Copyright. Thatcher et al., Journal of Neurotherapy
[1087-4208] Thatcher yr:2003 vol:7 iss:3 pg:87.



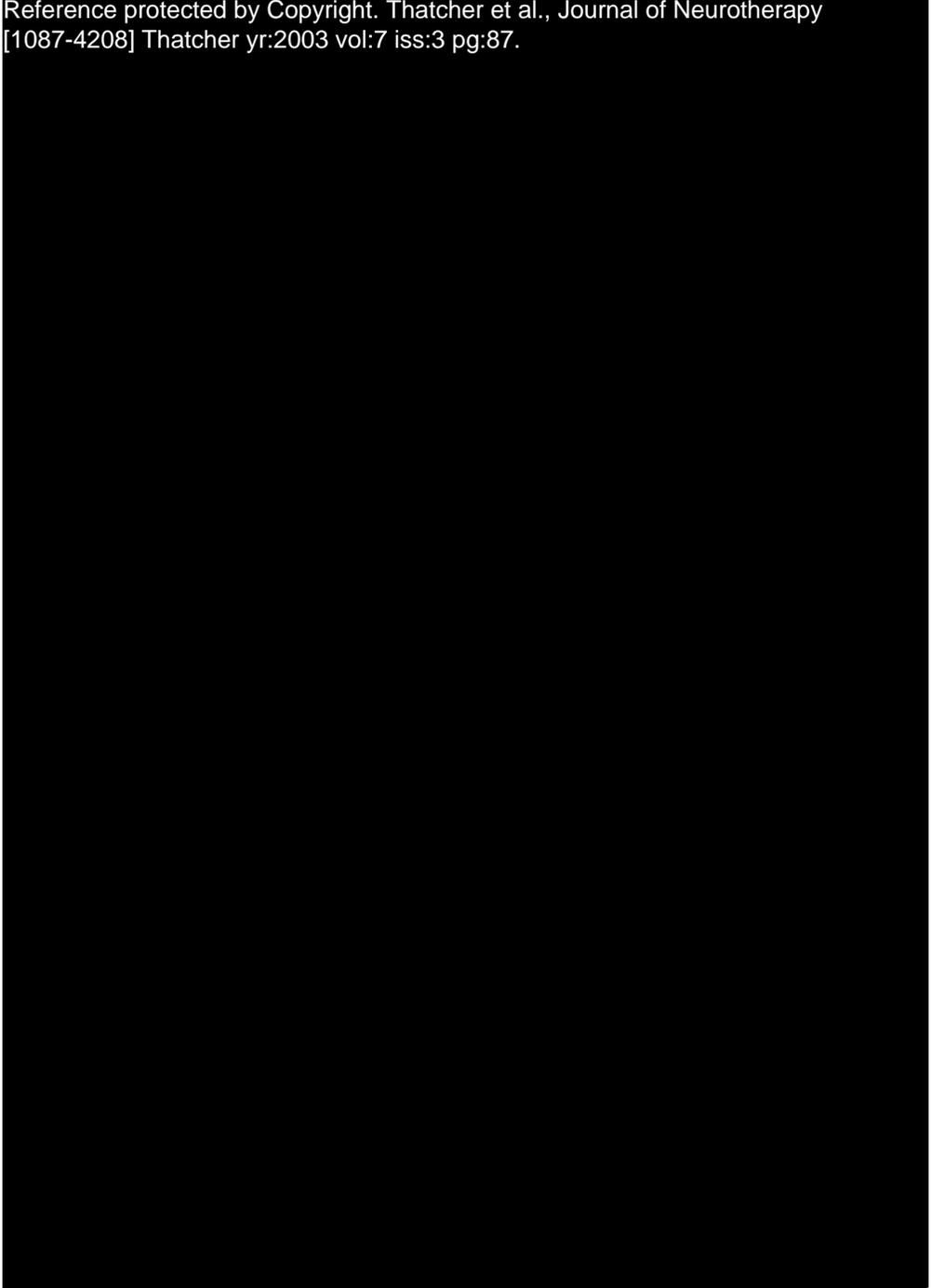
Reference protected by Copyright. Thatcher et al., Journal of Neurotherapy [1087-4208] Thatcher yr:2003 vol:7 iss:3 pg:87.



Reference protected by Copyright. Thatcher et al., Journal of Neurotherapy [1087-4208] Thatcher yr:2003 vol:7 iss:3 pg:87.



Reference protected by Copyright. Thatcher et al., Journal of Neurotherapy [1087-4208] Thatcher yr:2003 vol:7 iss:3 pg:87.

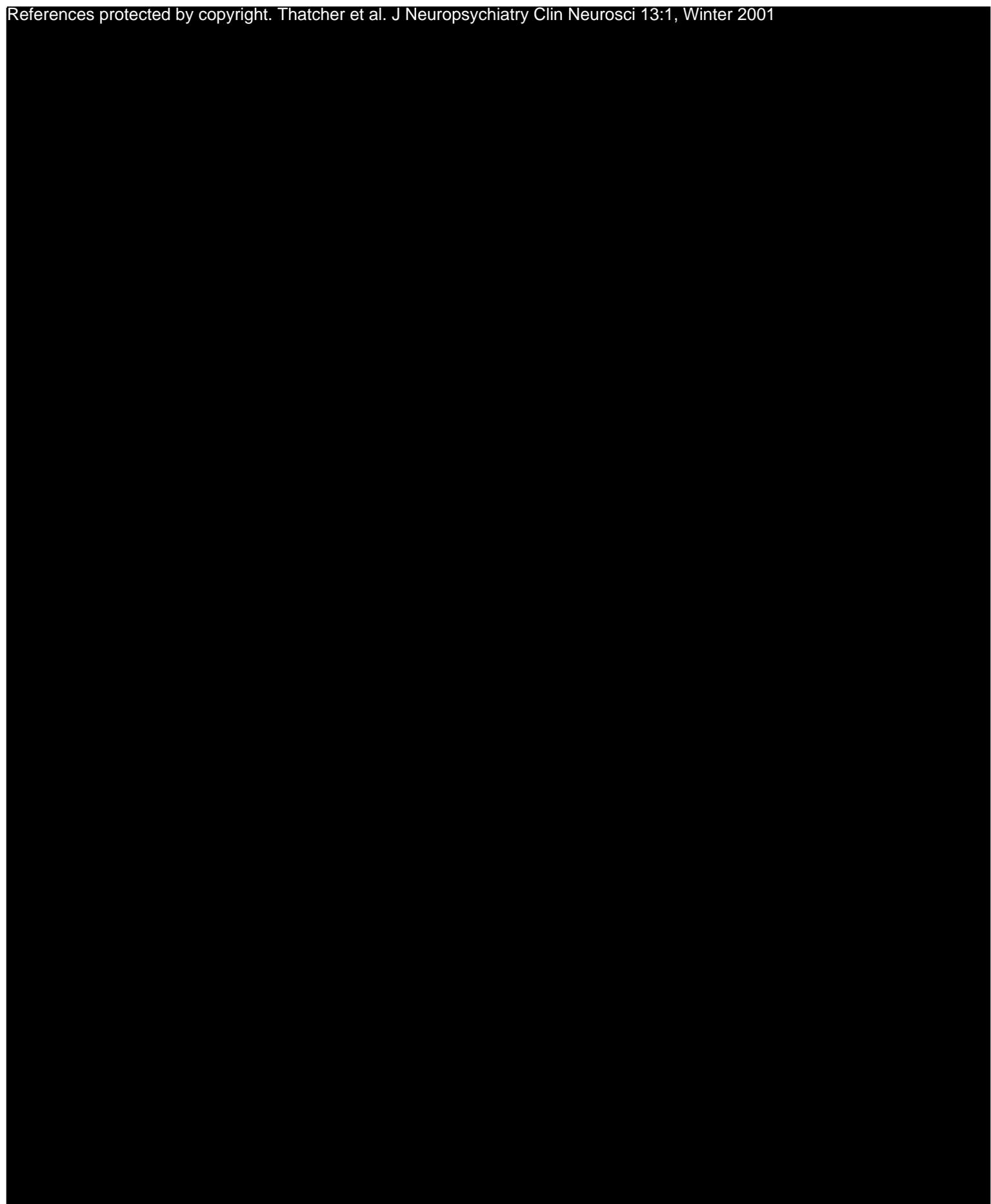


An EEG Severity Index of Traumatic Brain Injury

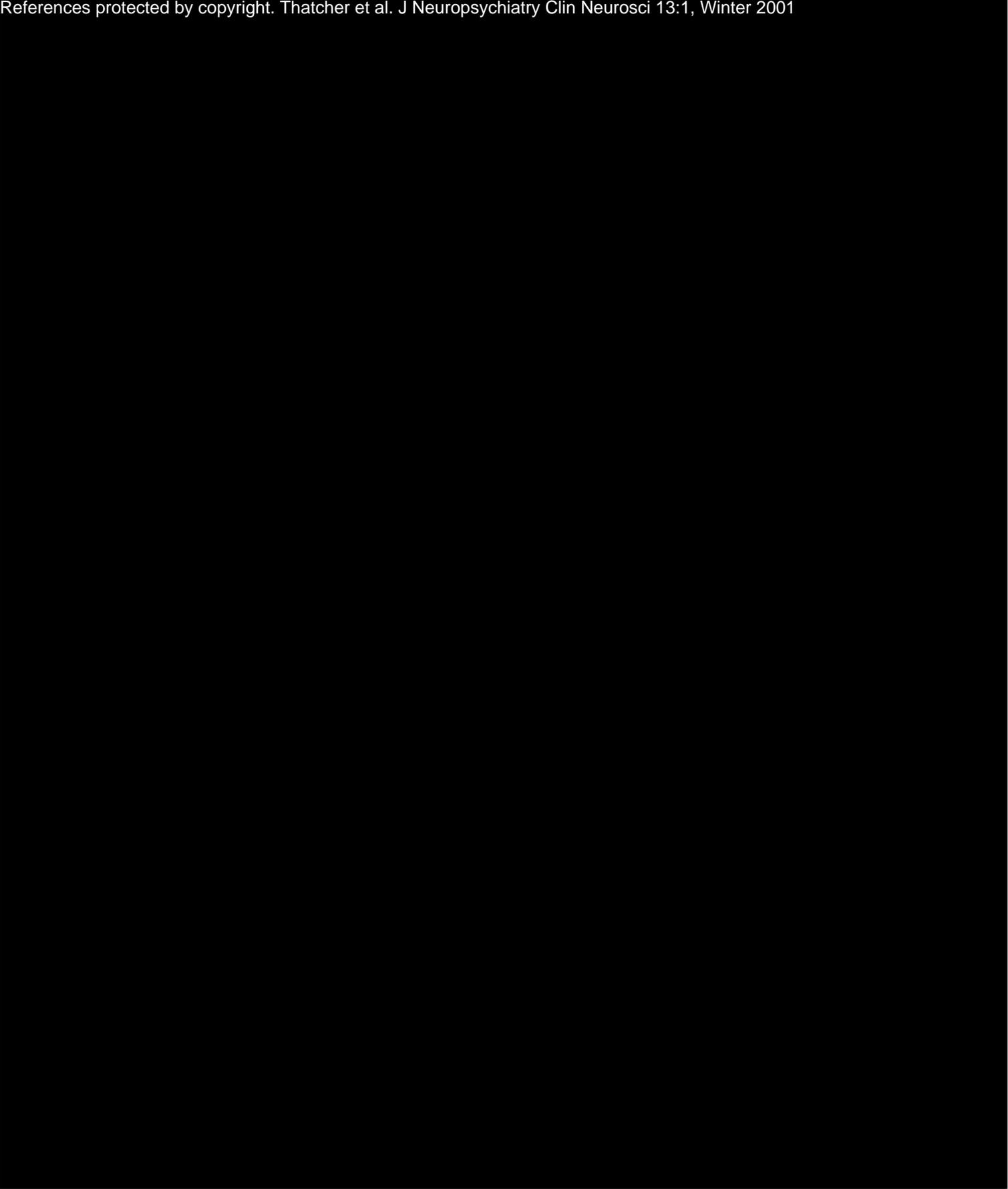
Robert W. Thatcher, Ph.D.
Duane M. North, M.S.
Richard T. Curtin, B.A.
Rebecca A. Walker, B.S.
Carl J. Biver, Ph.D.
Juan F. Gomez, B.A.
Andres M. Salazar, M.D.

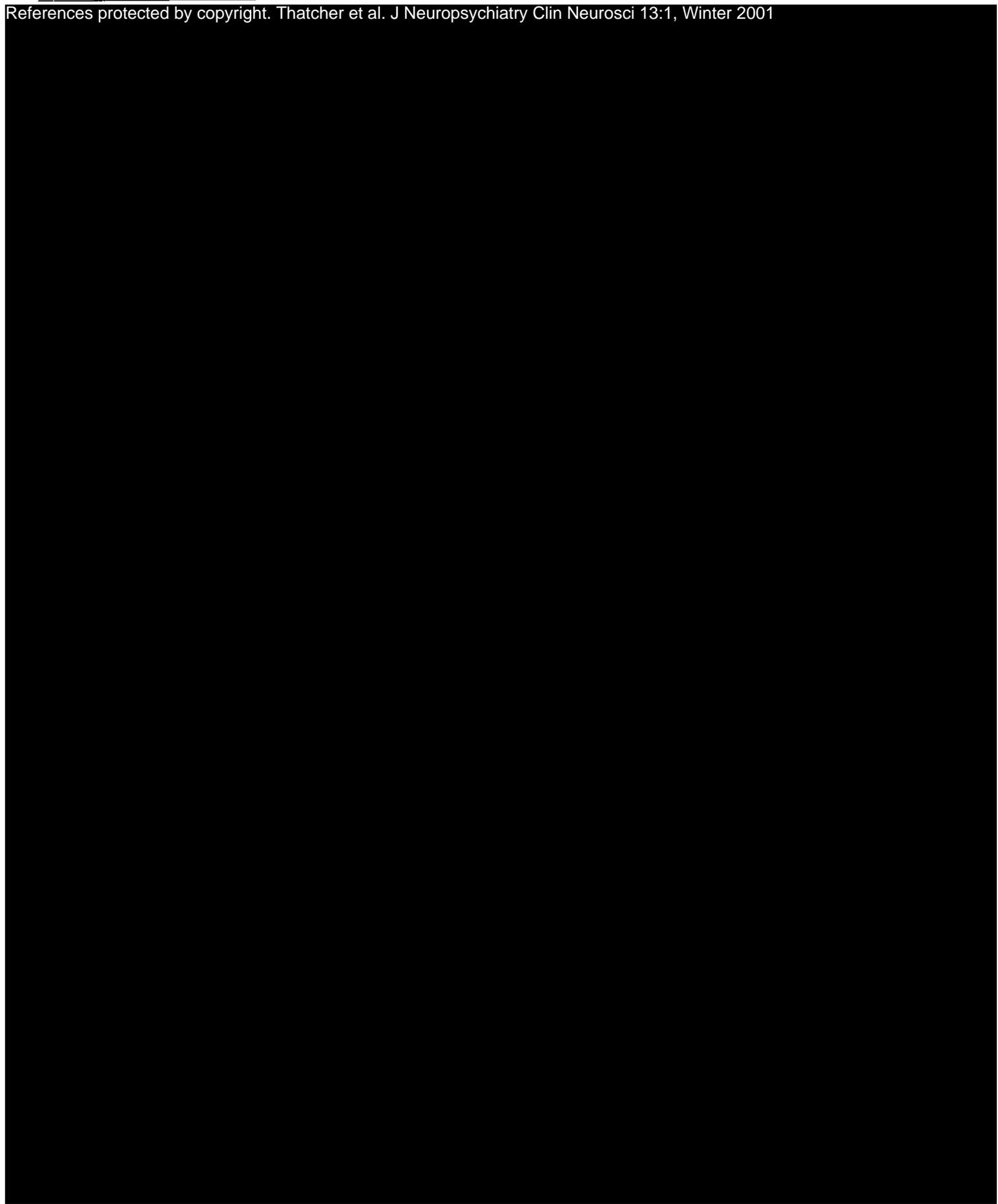
References protected by copyright. Thatcher et al. J Neuropsychiatry Clin Neurosci 13:1, Winter 2001



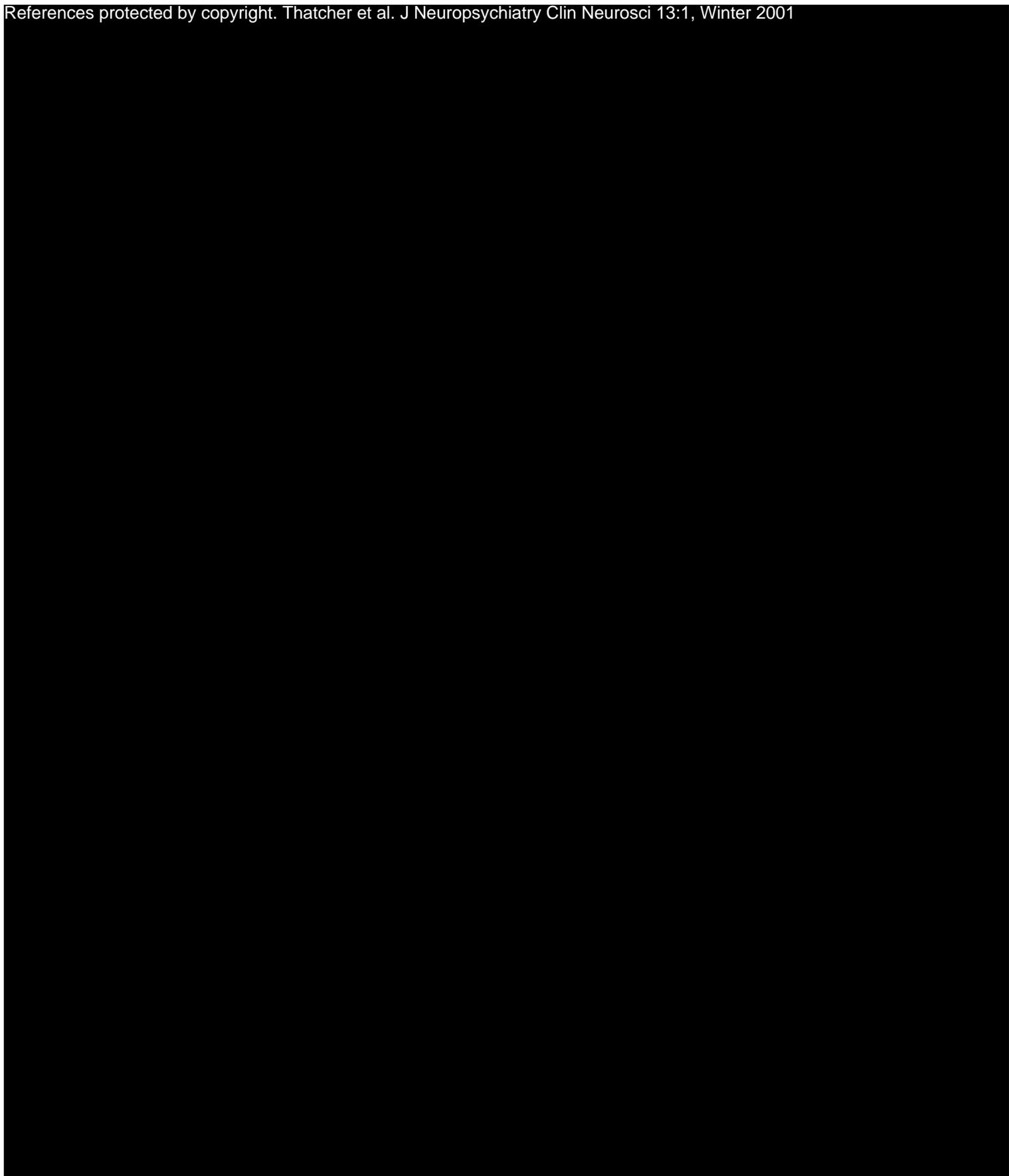


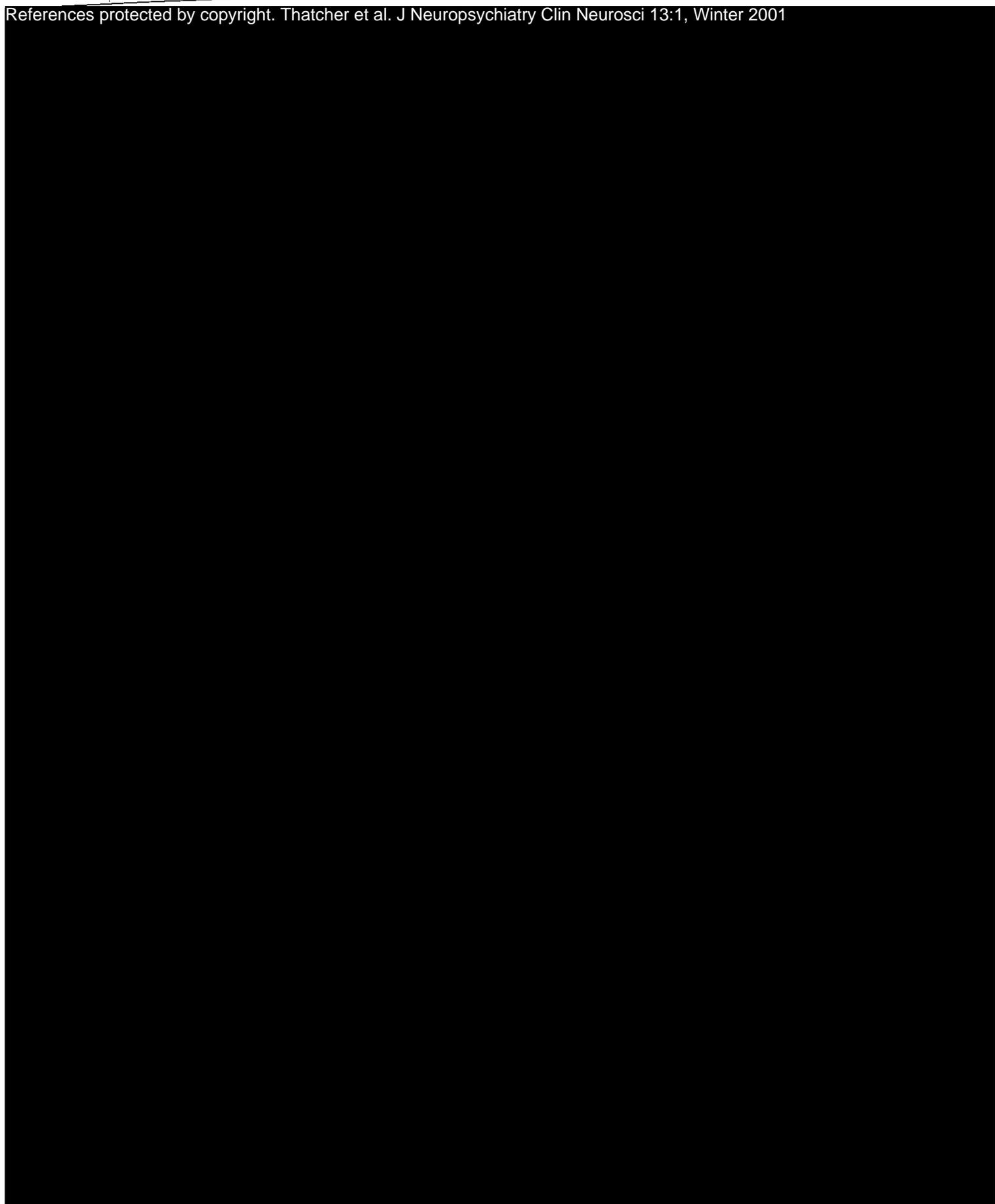
References protected by copyright. Thatcher et al. J Neuropsychiatry Clin Neurosci 13:1, Winter 2001



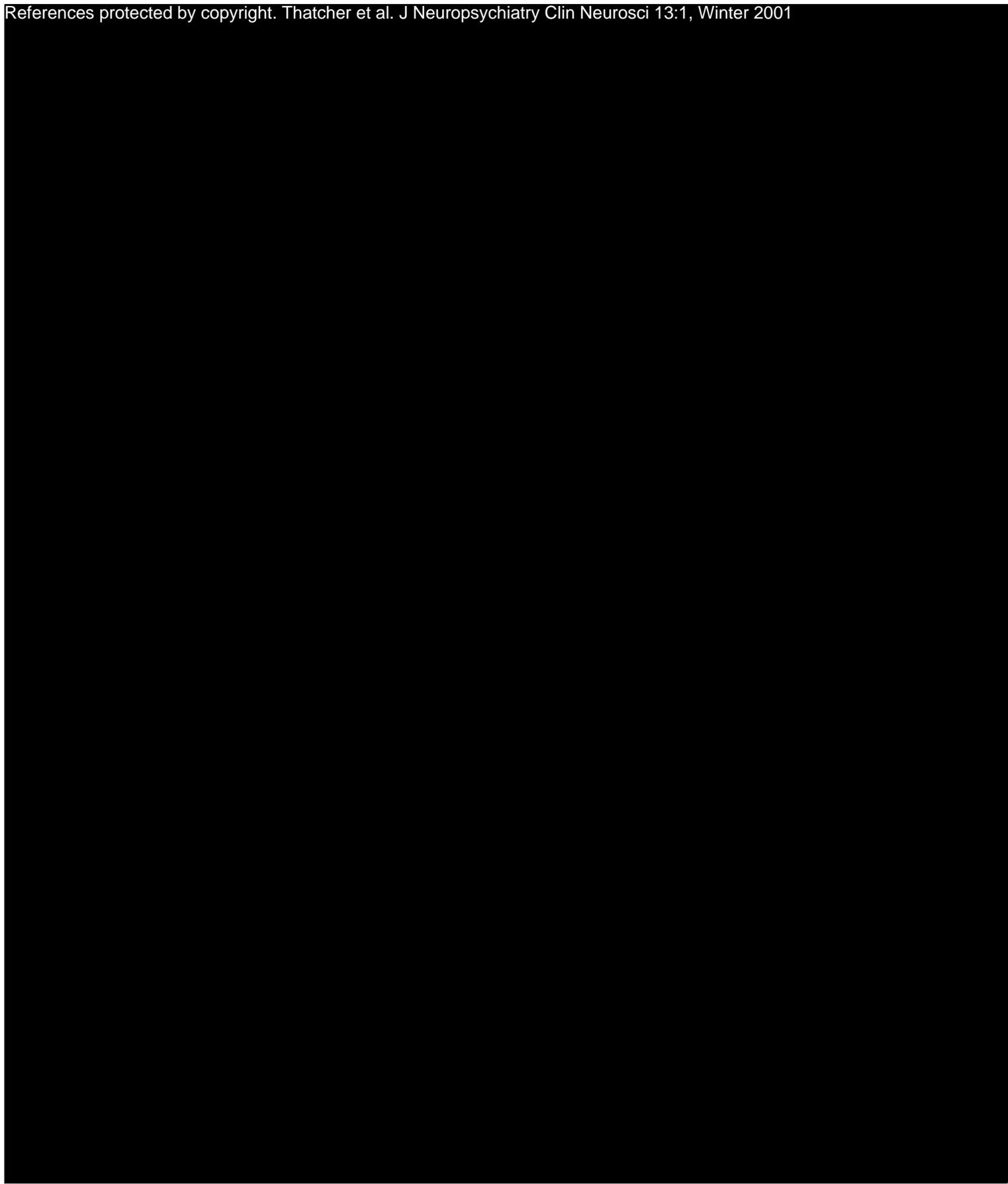


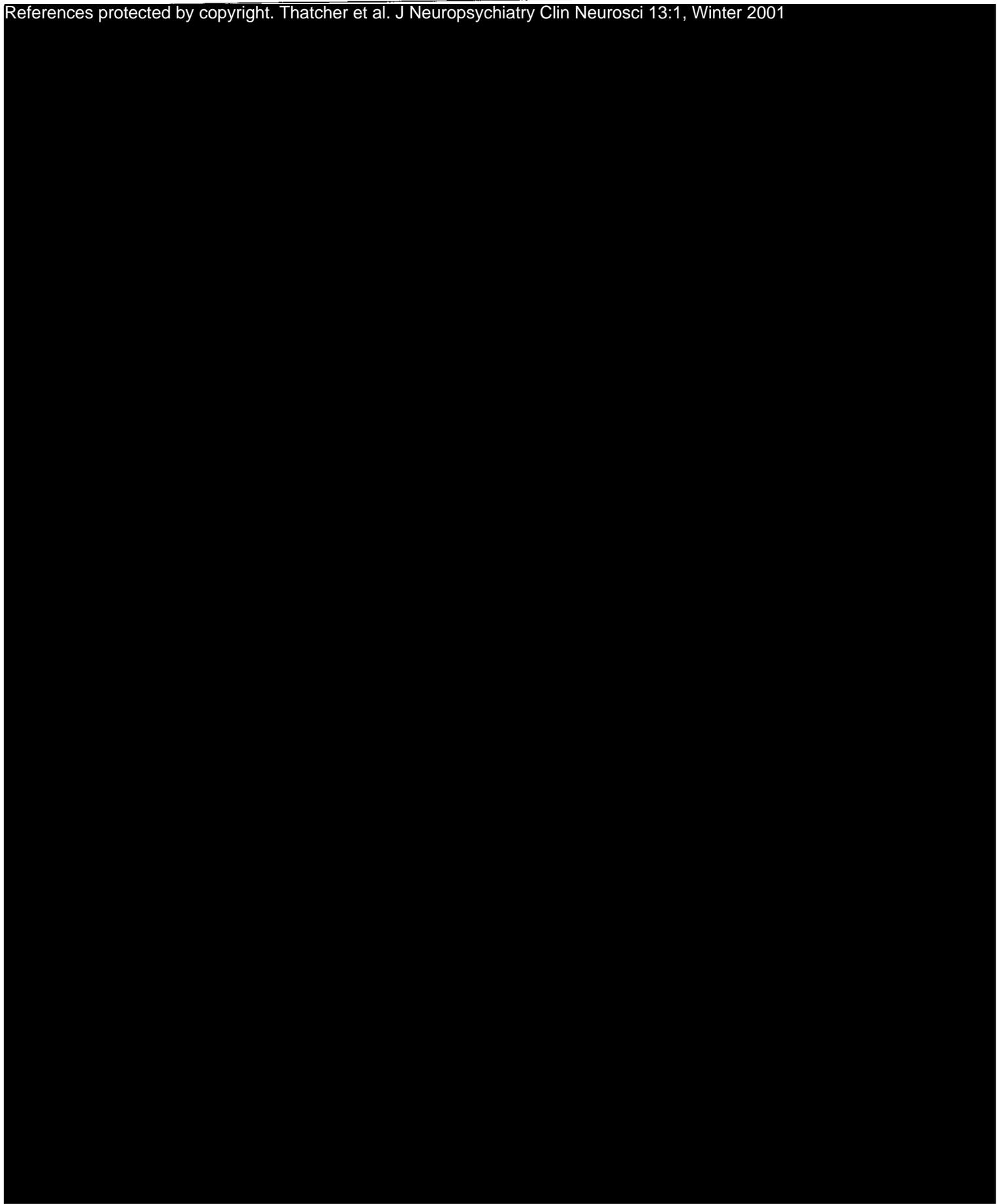
References protected by copyright. Thatcher et al. J Neuropsychiatry Clin Neurosci 13:1, Winter 2001



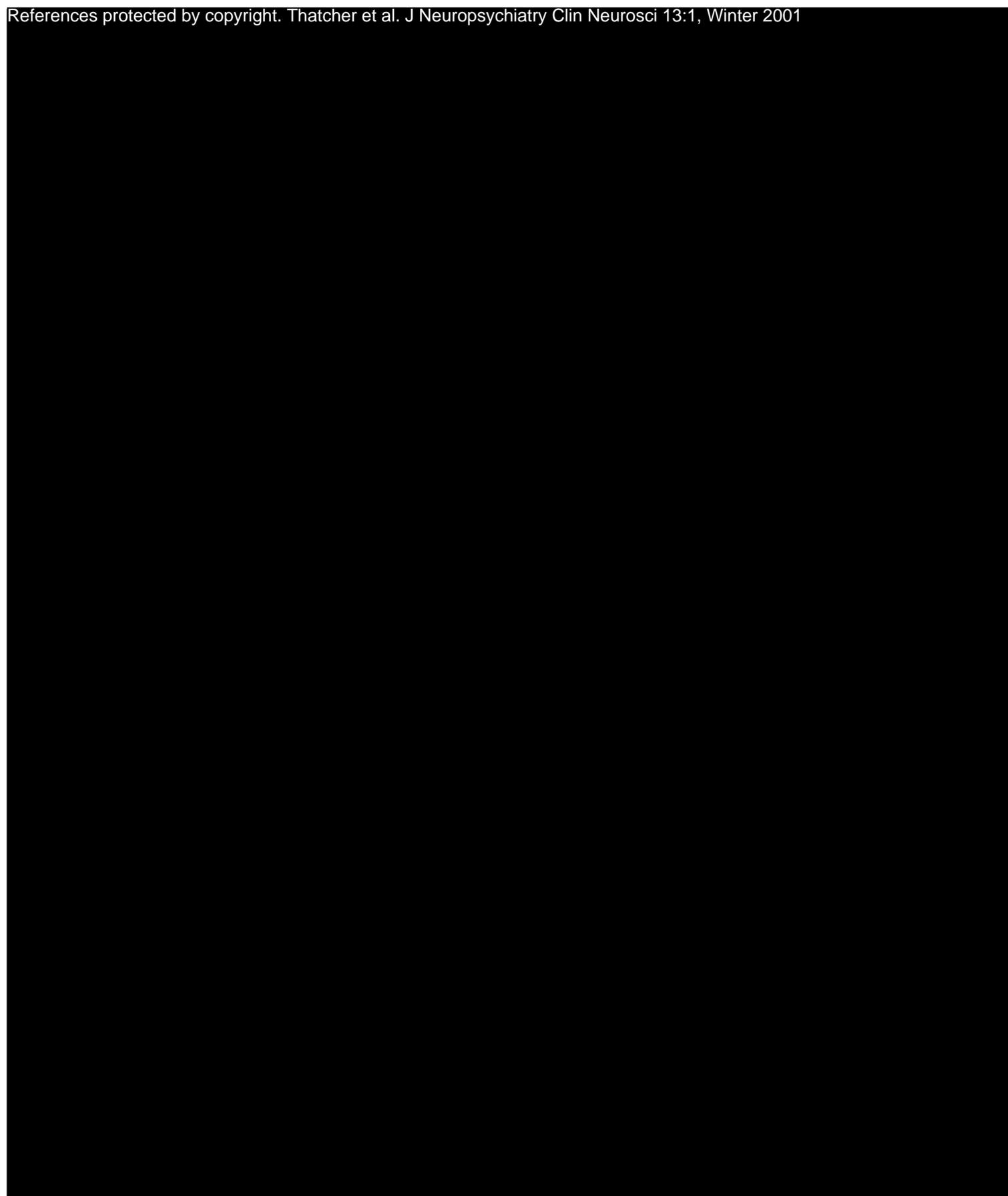


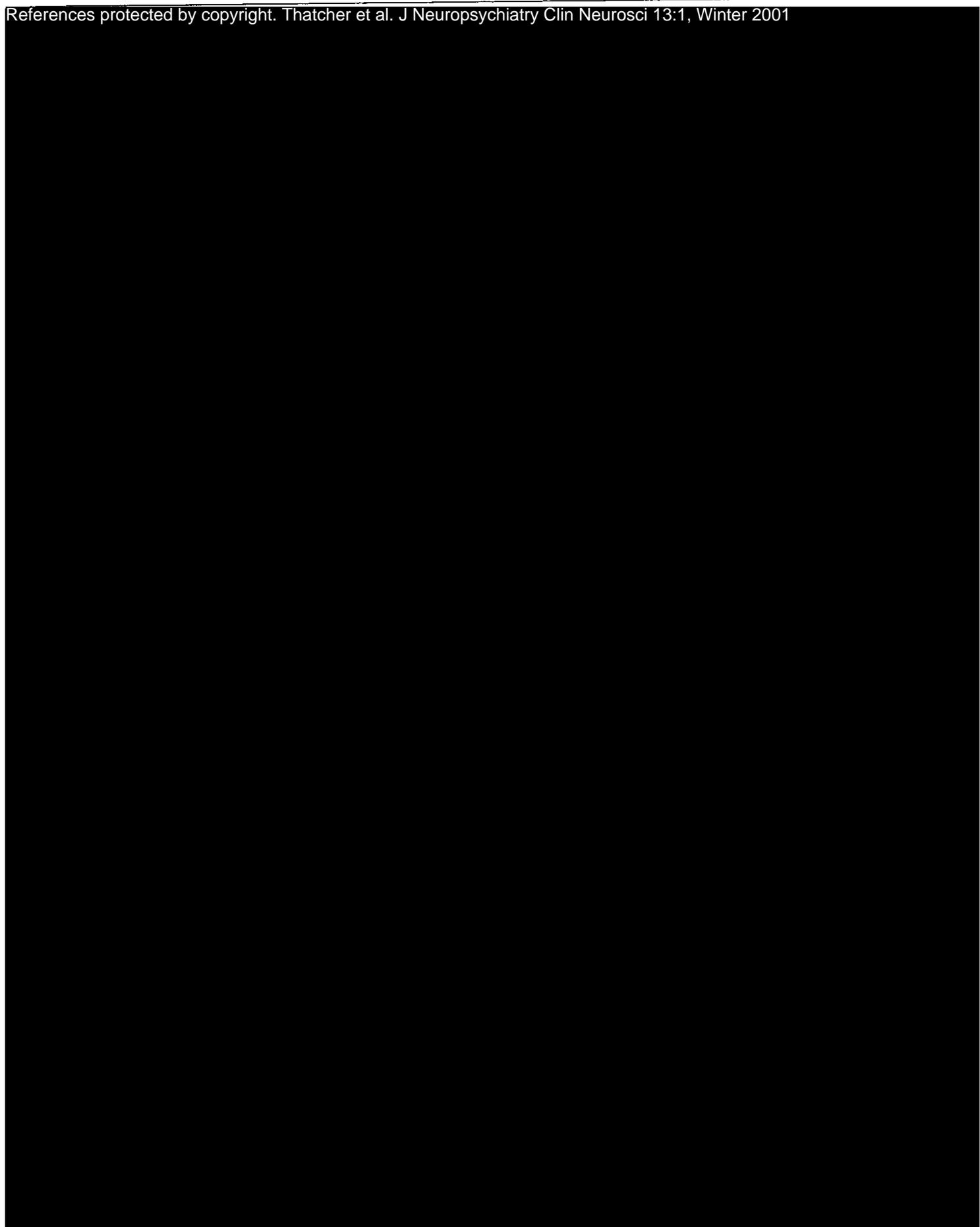
References protected by copyright. Thatcher et al. J Neuropsychiatry Clin Neurosci 13:1, Winter 2001



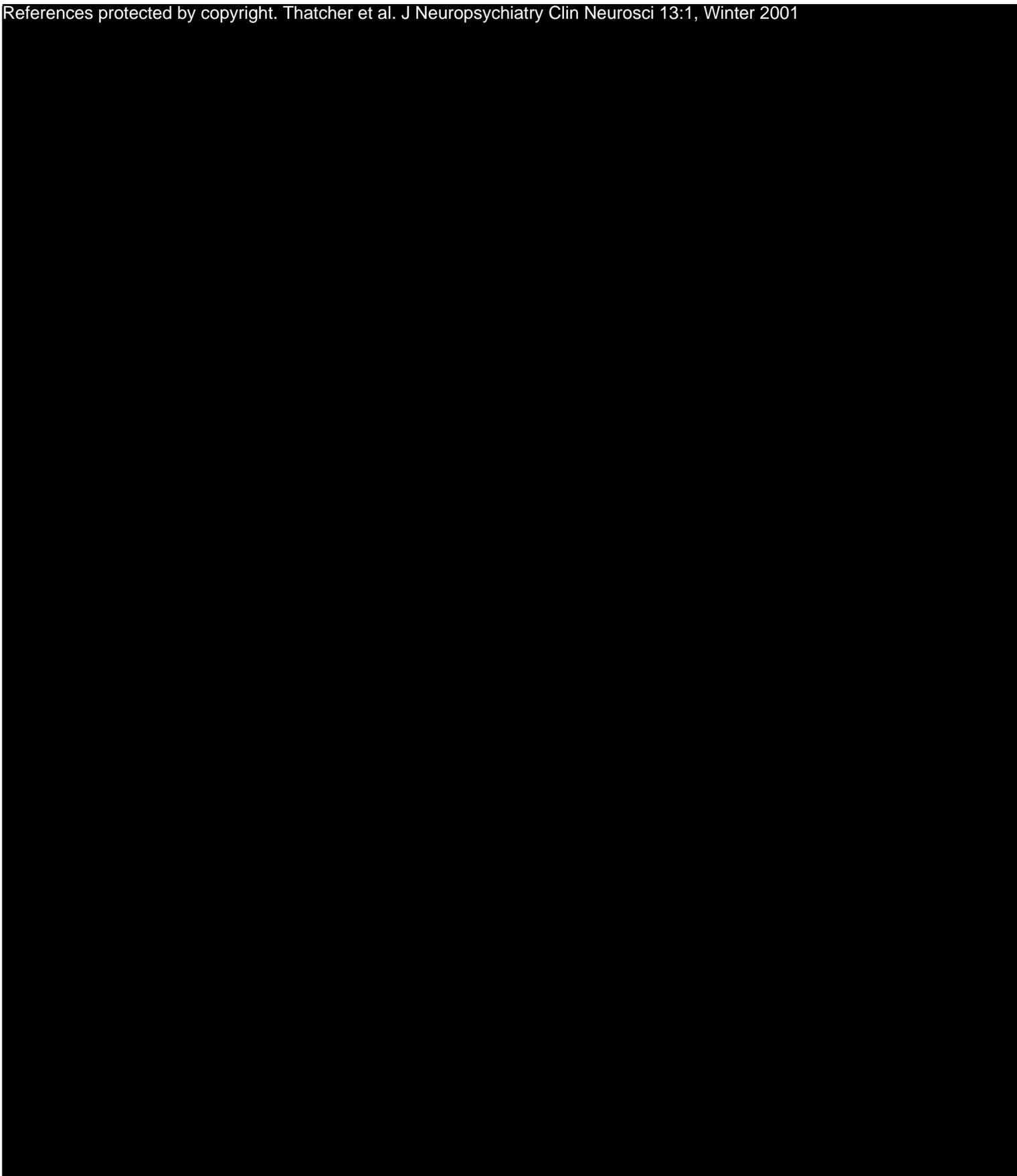


References protected by copyright. Thatcher et al. J Neuropsychiatry Clin Neurosci 13:1, Winter 2001





References protected by copyright. Thatcher et al. J Neuropsychiatry Clin Neurosci 13:1, Winter 2001



EEG 03703

EEG discriminant analyses of mild head trauma

R.W. Thatcher, R.A. Walker, I. Gerson and F.H. Geisler

Applied Neuroscience Laboratories, University of Maryland Eastern Shore, Princess Anne, MD (U.S.A.), Maryland Institute for Emergency Medical Services Systems, Baltimore, MD (U.S.A.), and University Services, Philadelphia, PA (U.S.A.)

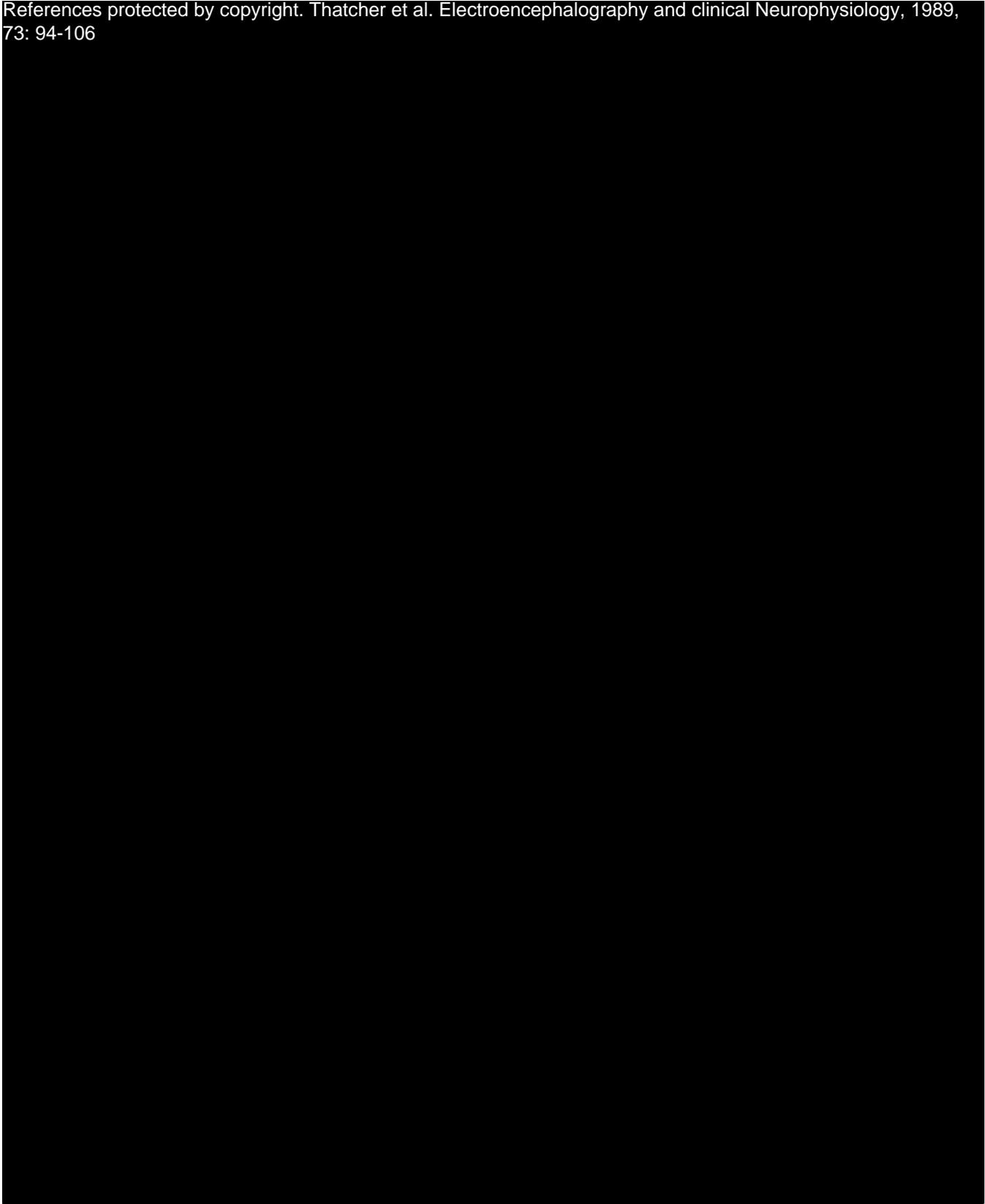
(Accepted for publication: 9 February 1989)

References protected by copyright. Thatcher et al. *Electroencephalography and clinical Neurophysiology*, 1989, 73: 94-106

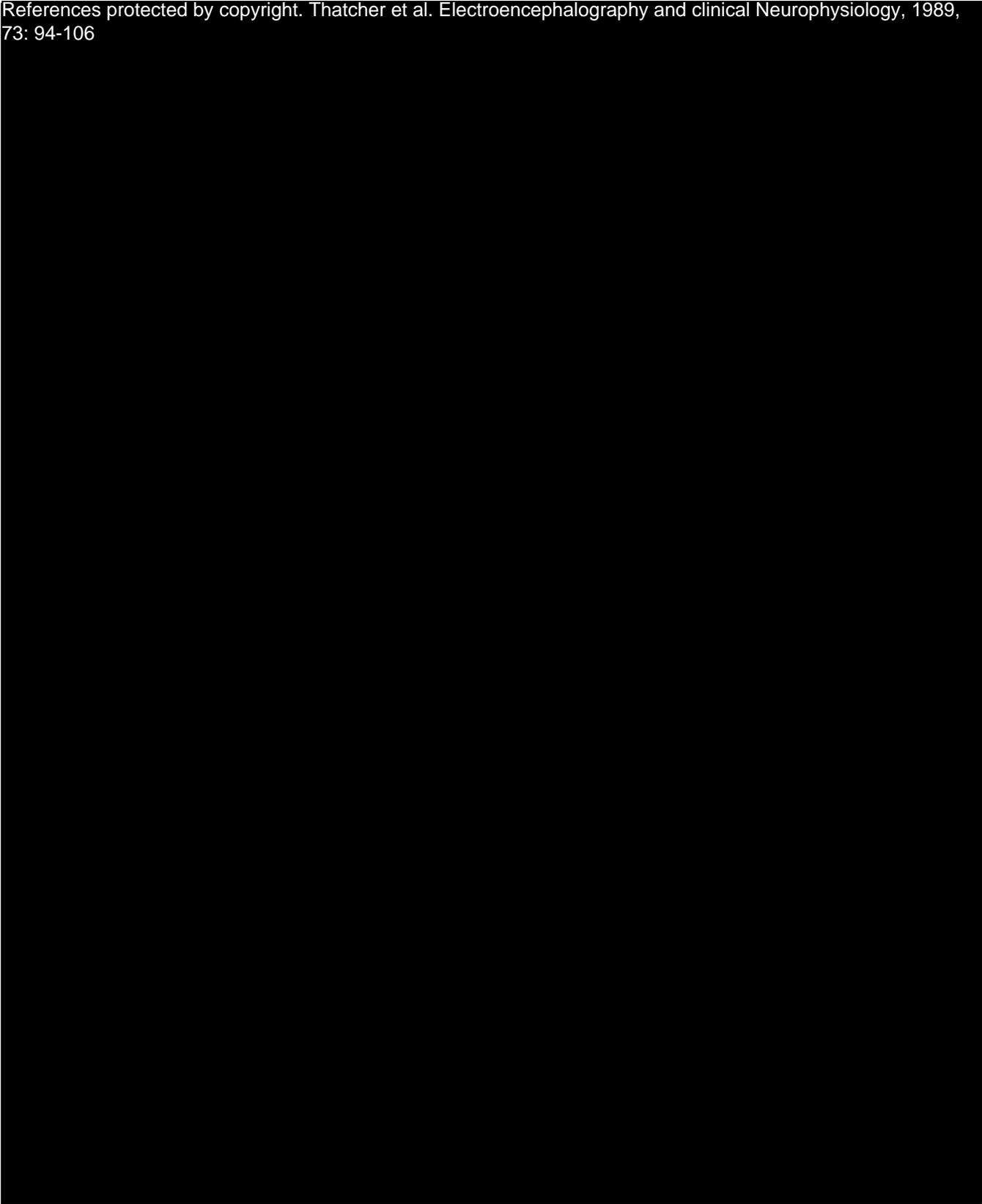


0013-4649/89/\$03.50 © 1989 Elsevier Scientific Publishers Ireland, Ltd.

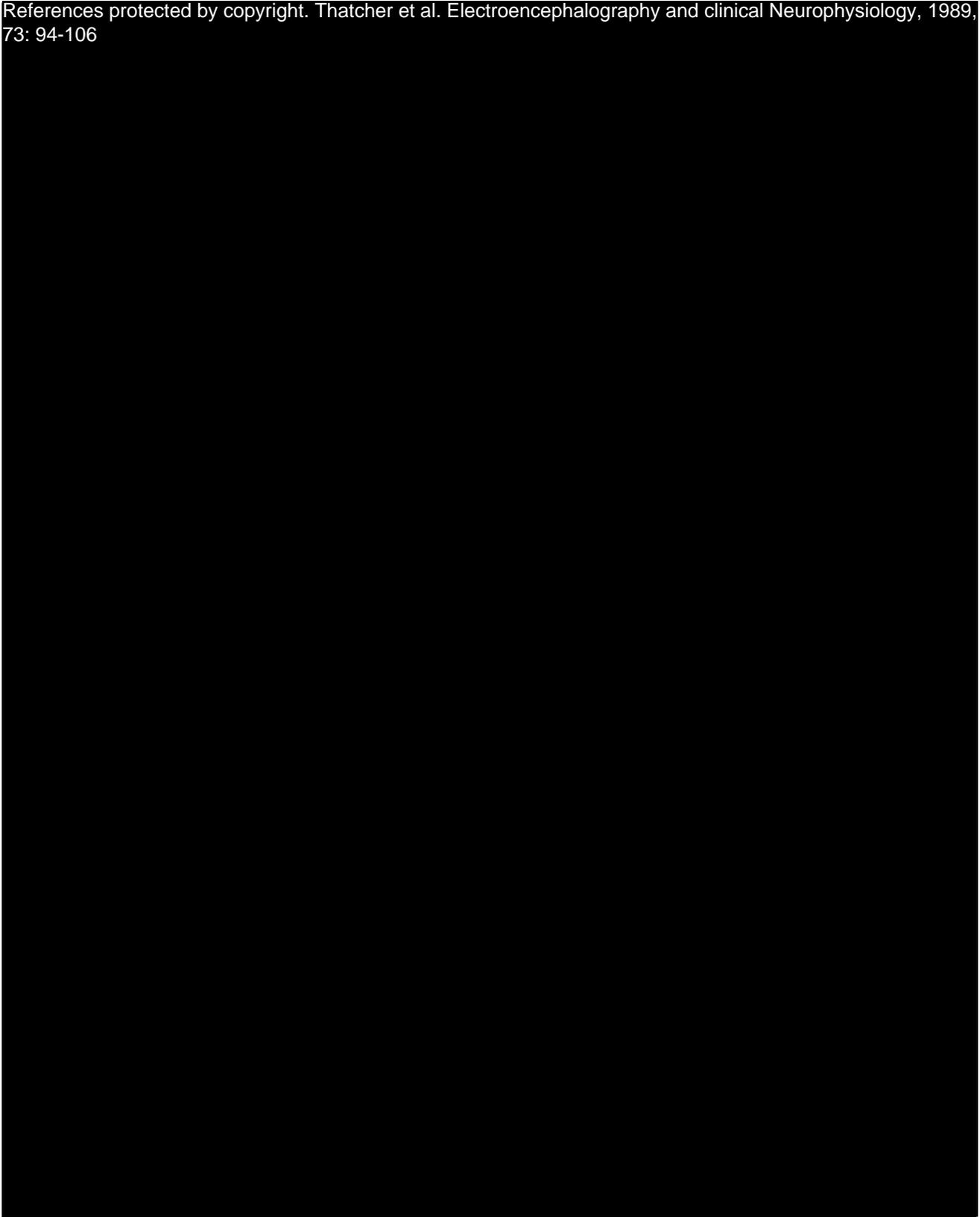
References protected by copyright. Thatcher et al. *Electroencephalography and clinical Neurophysiology*, 1989, 73: 94-106



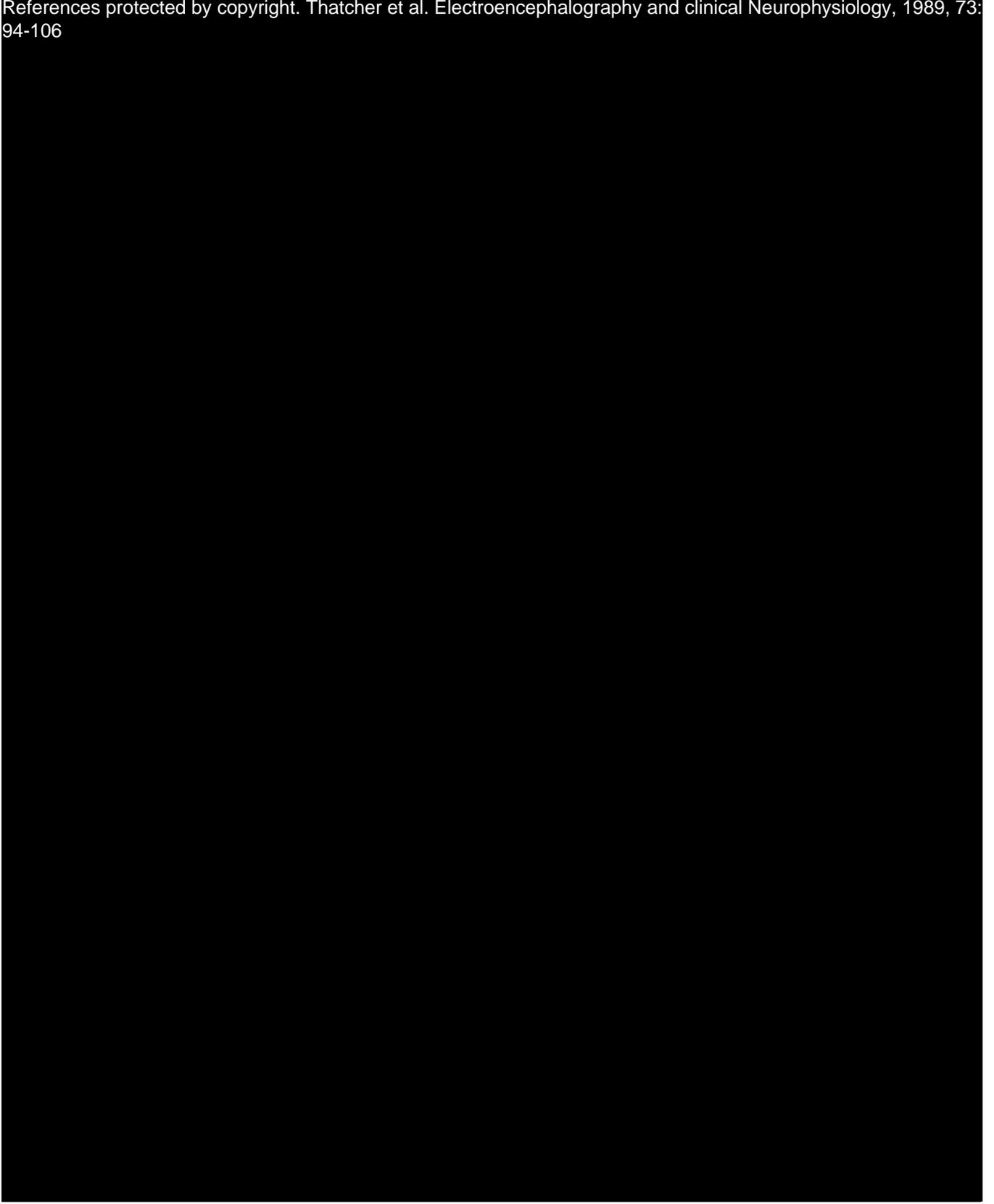
References protected by copyright. Thatcher et al. Electroencephalography and clinical Neurophysiology, 1989, 73: 94-106



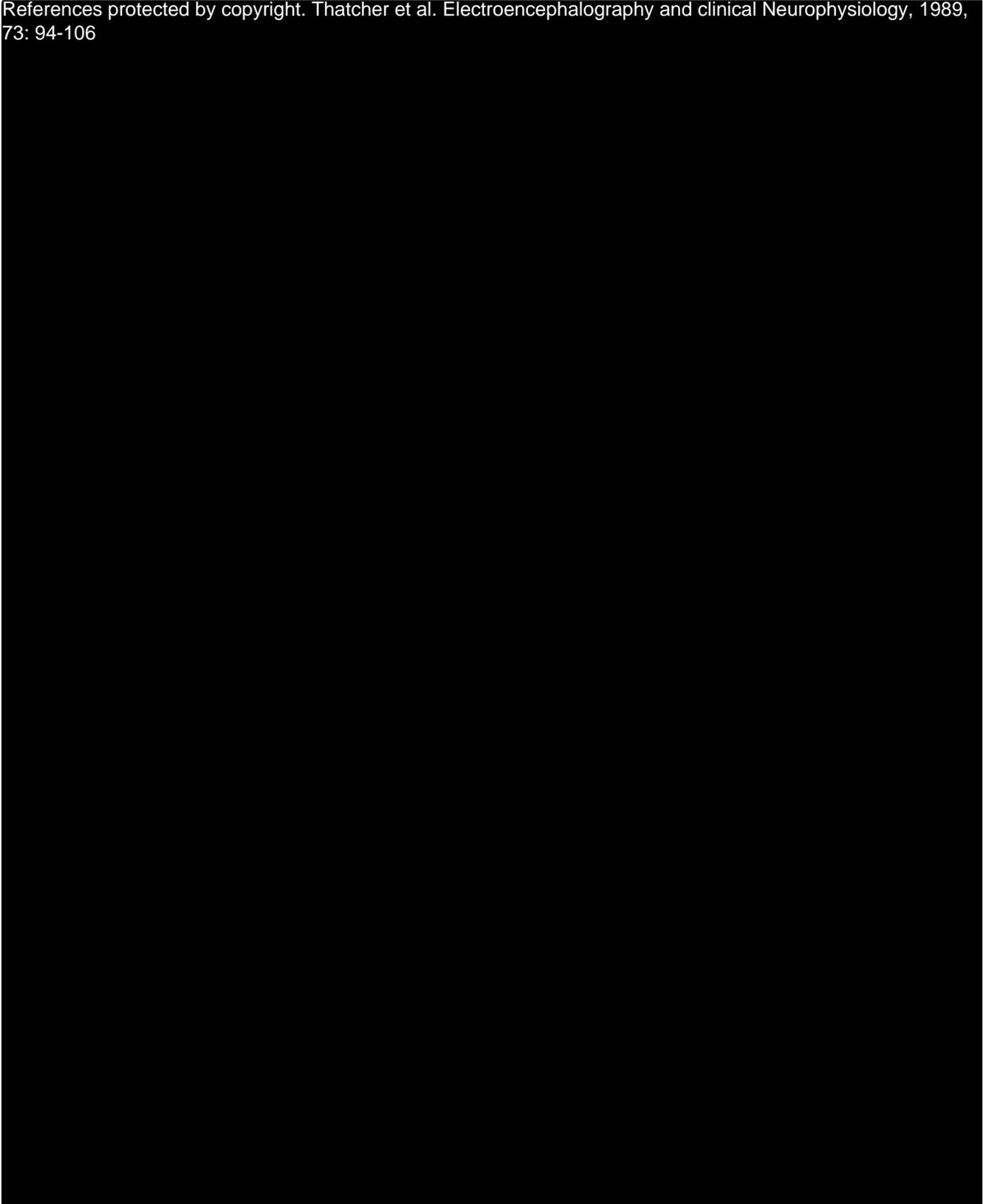
References protected by copyright. Thatcher et al. *Electroencephalography and clinical Neurophysiology*, 1989, 73: 94-106



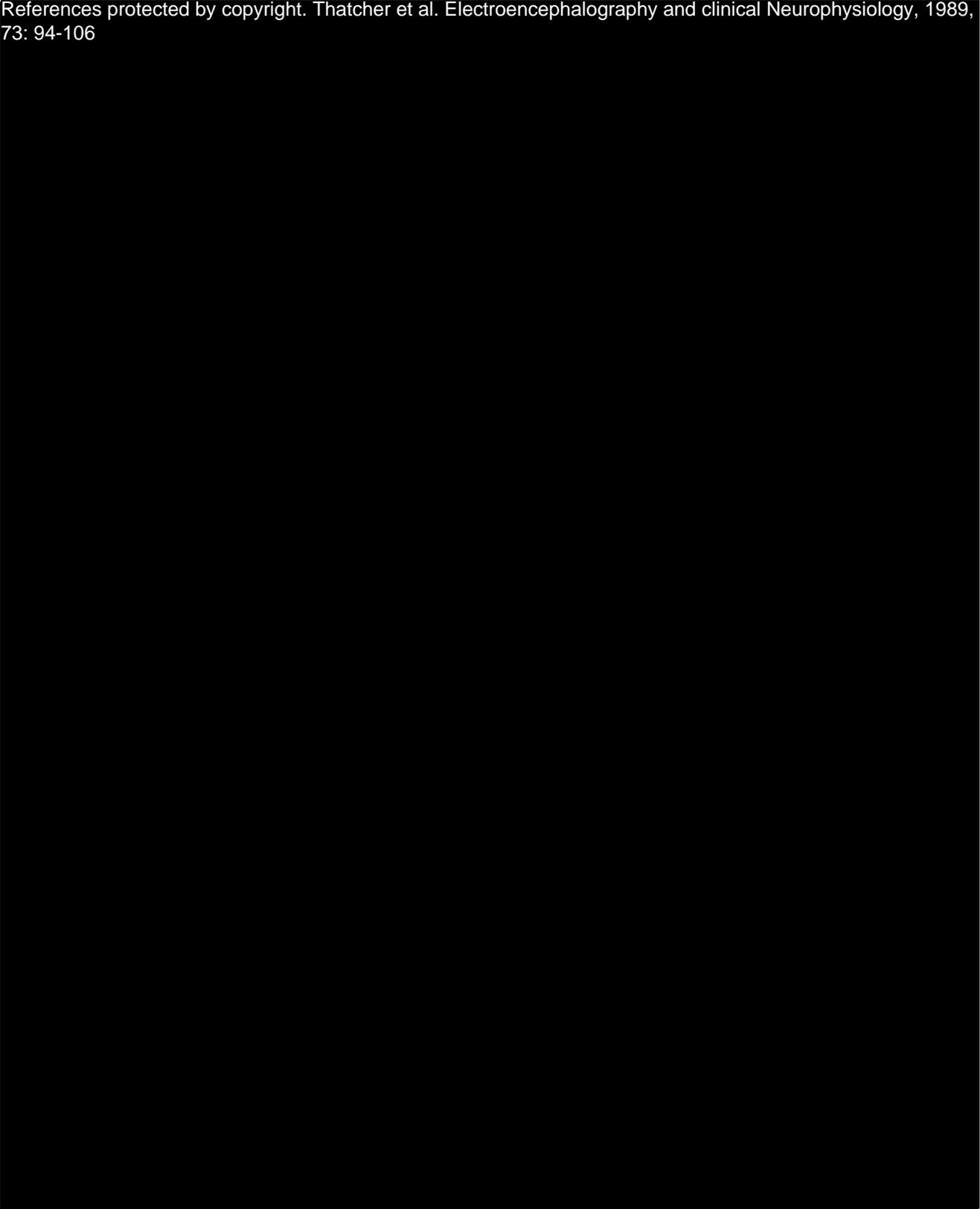
References protected by copyright. Thatcher et al. Electroencephalography and clinical Neurophysiology, 1989, 73: 94-106



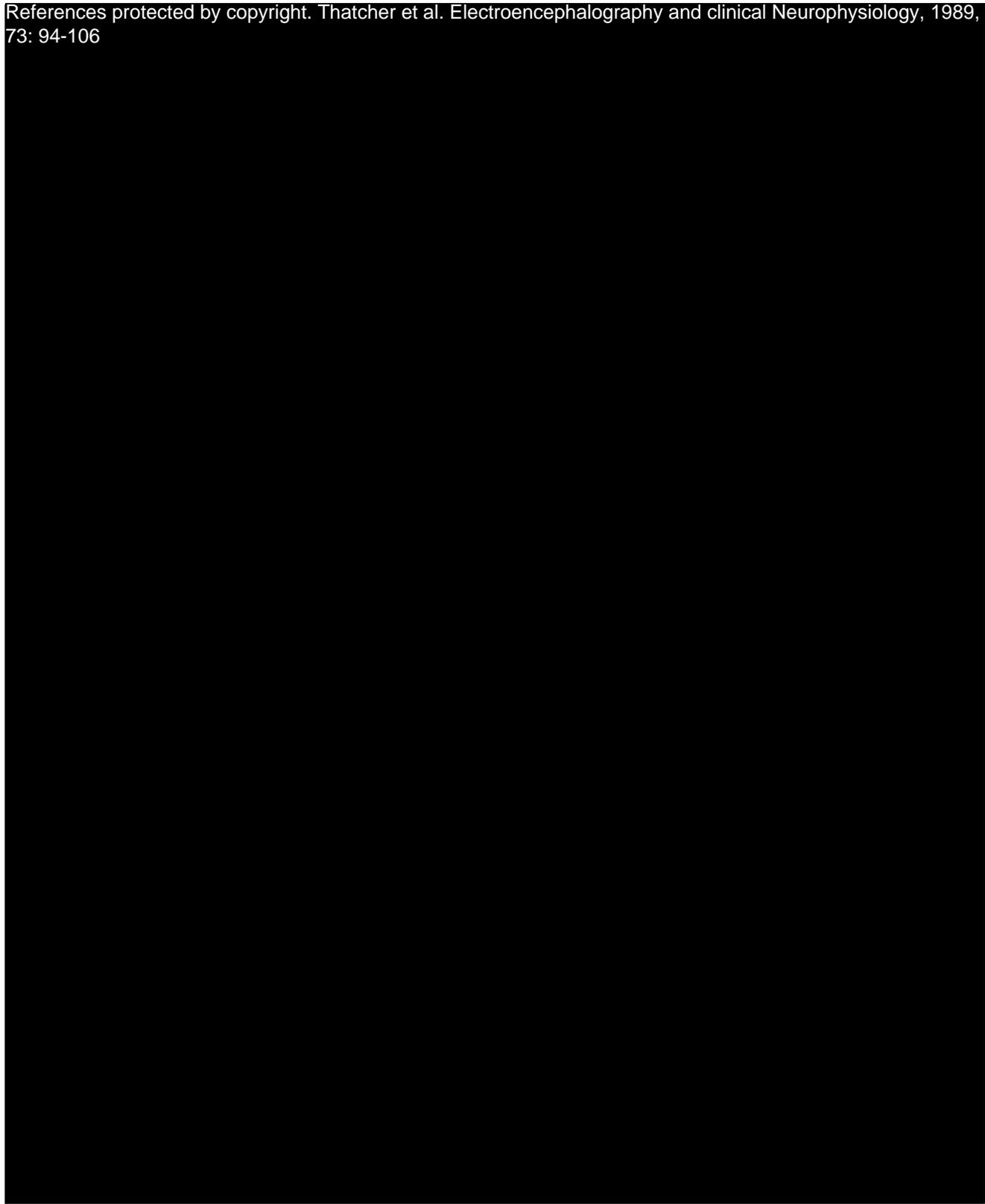
References protected by copyright. Thatcher et al. Electroencephalography and clinical Neurophysiology, 1989, 73: 94-106



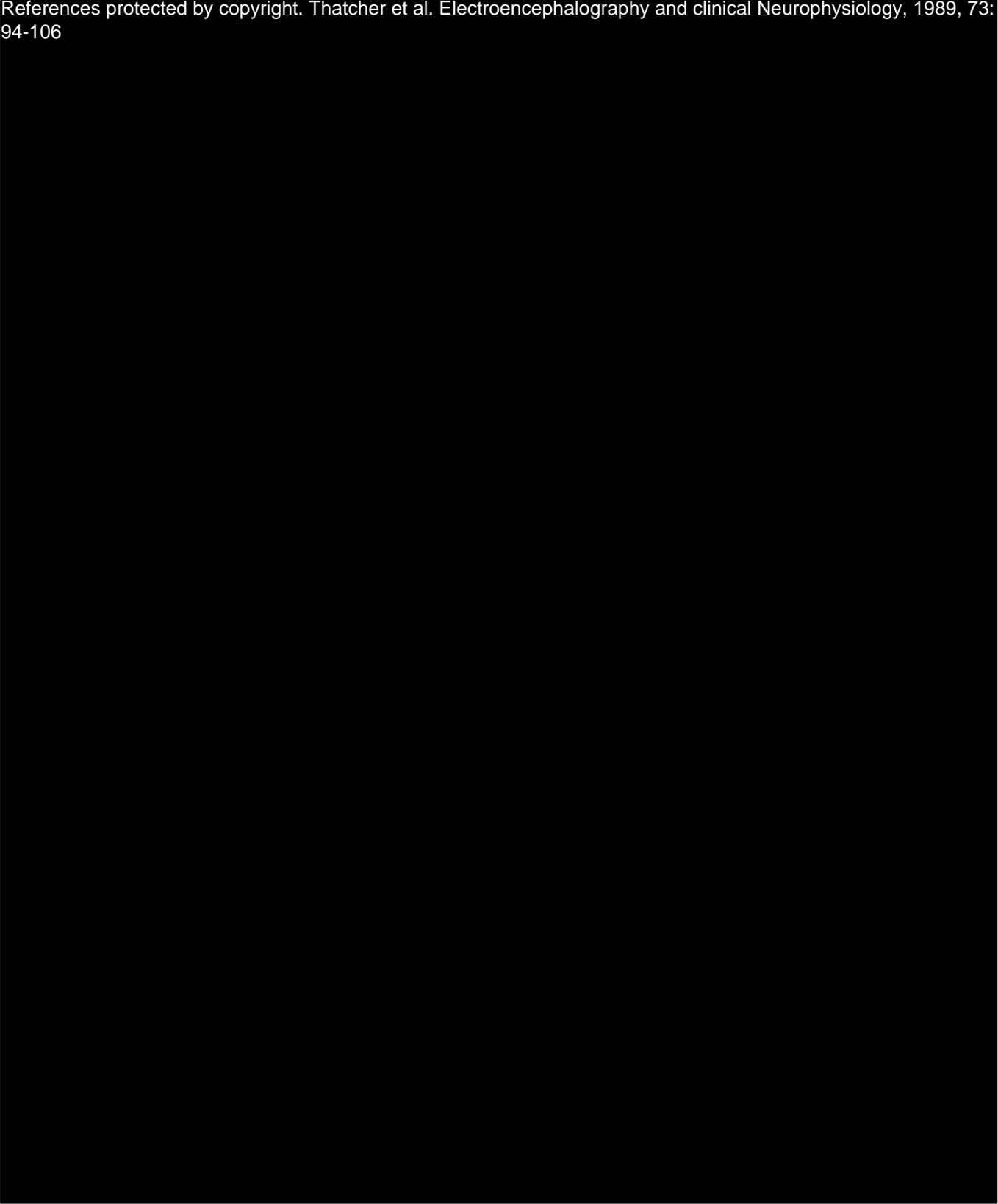
References protected by copyright. Thatcher et al. Electroencephalography and clinical Neurophysiology, 1989, 73: 94-106



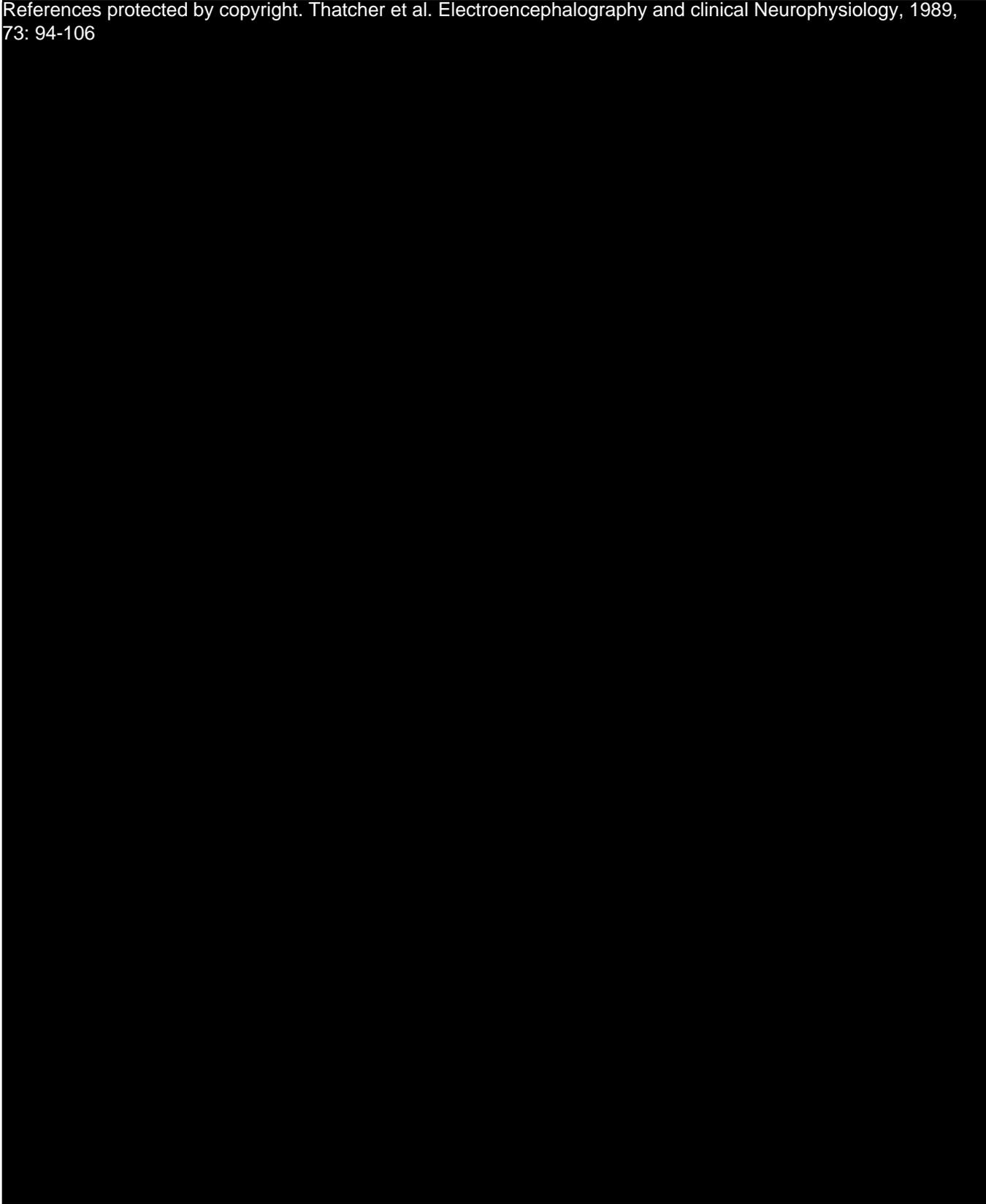
References protected by copyright. Thatcher et al. Electroencephalography and clinical Neurophysiology, 1989, 73: 94-106



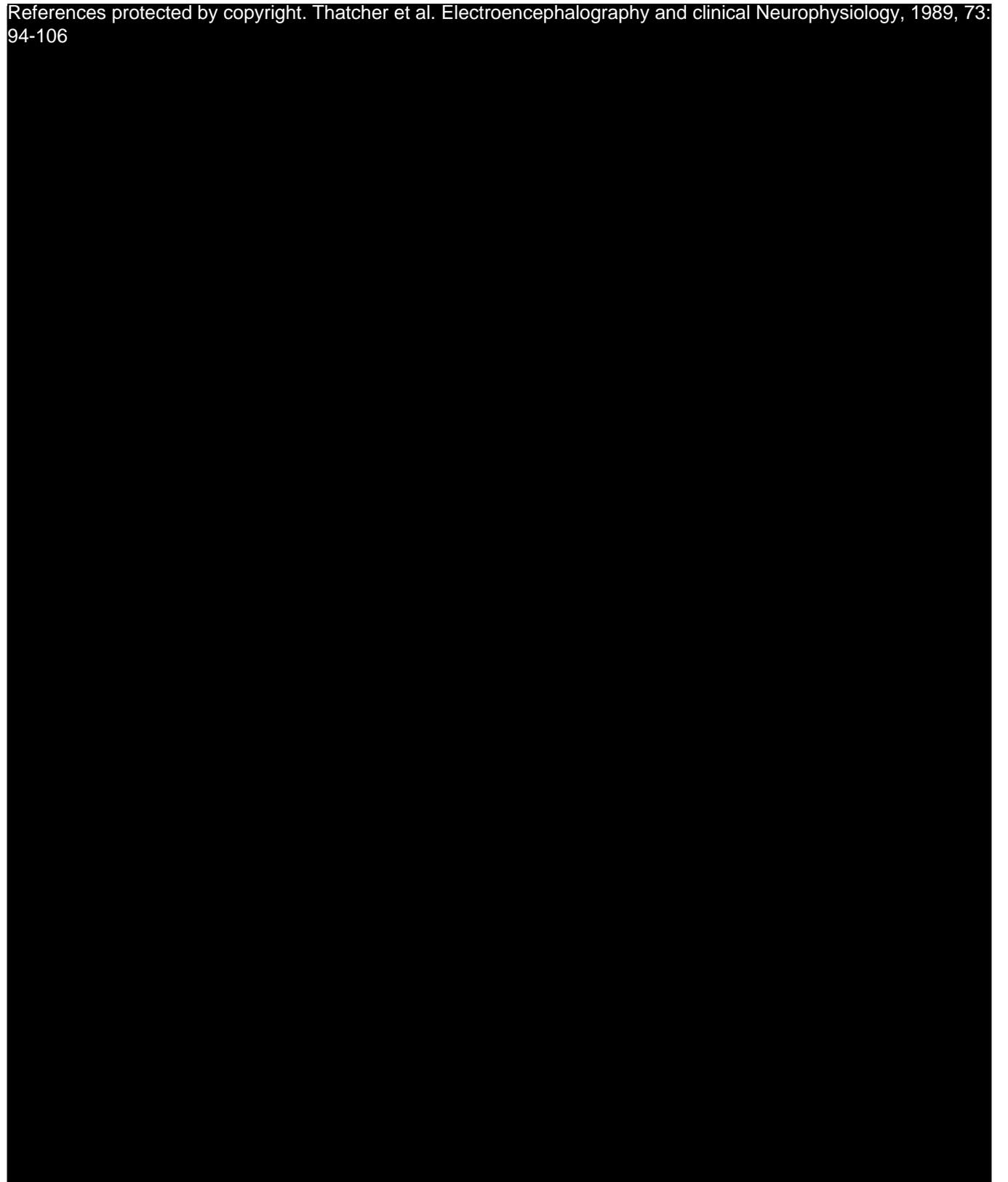
References protected by copyright. Thatcher et al. Electroencephalography and clinical Neurophysiology, 1989, 73: 94-106



References protected by copyright. Thatcher et al. Electroencephalography and clinical Neurophysiology, 1989, 73: 94-106

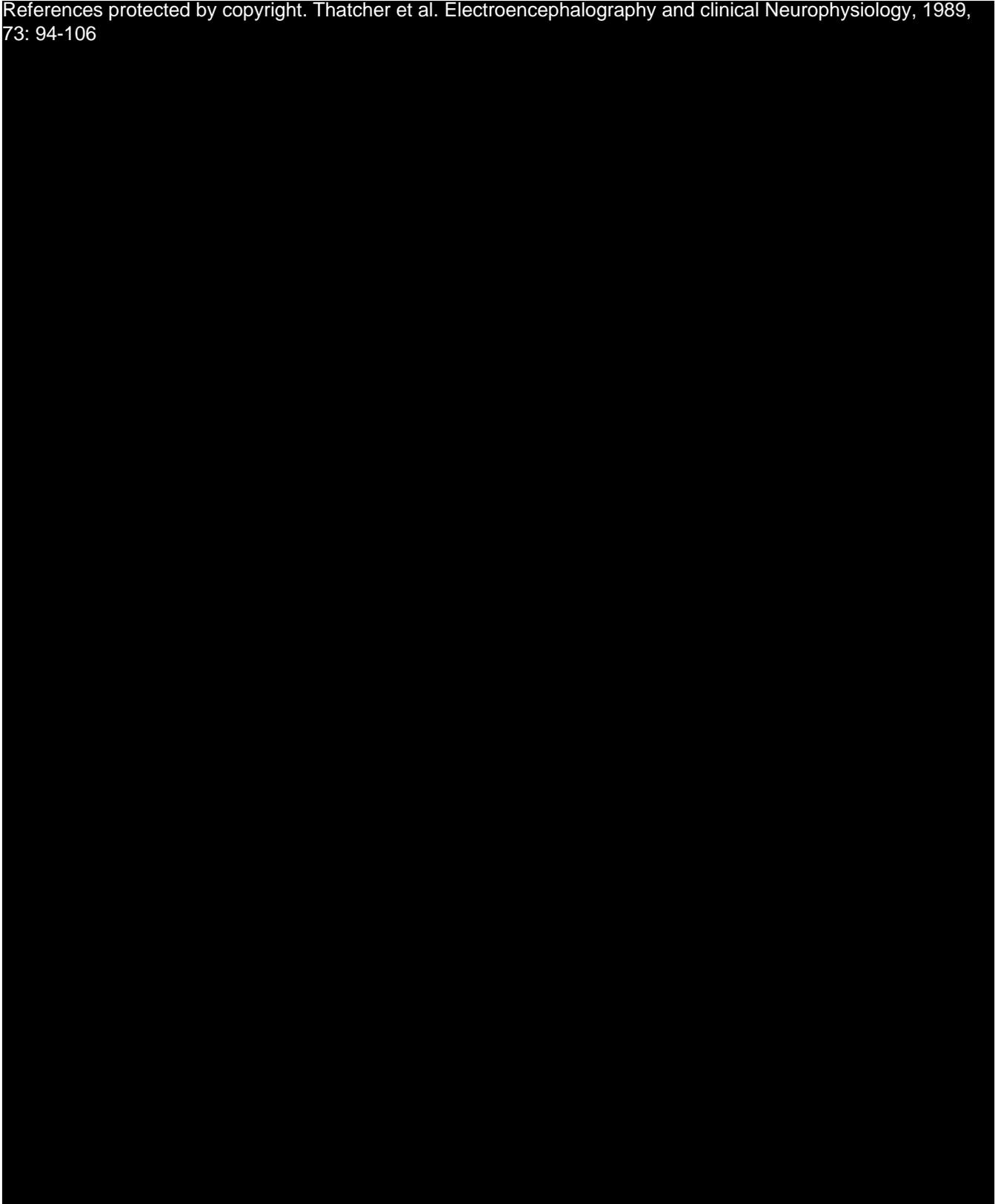


References protected by copyright. Thatcher et al. Electroencephalography and clinical Neurophysiology, 1989, 73: 94-106

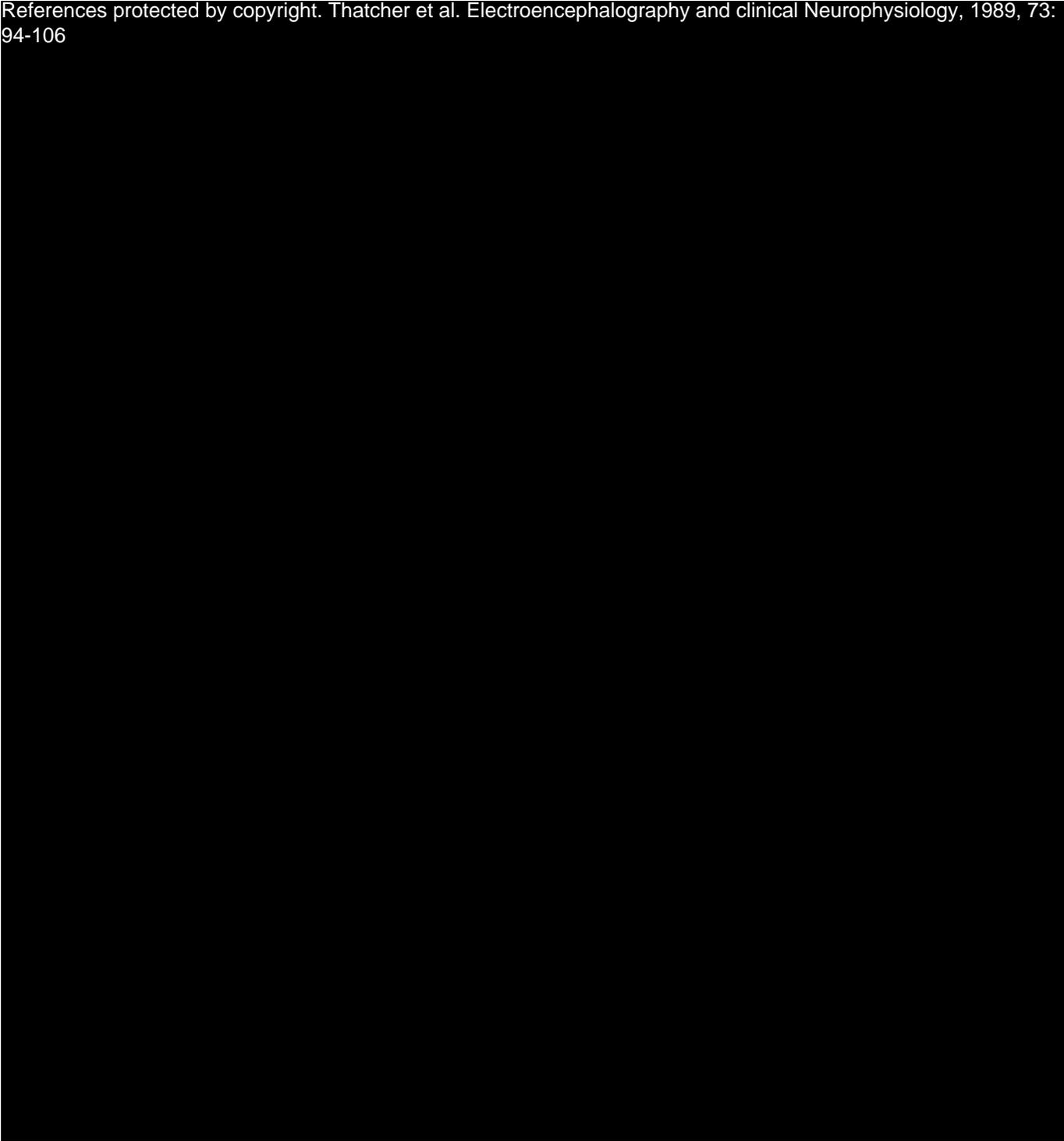


271

References protected by copyright. Thatcher et al. Electroencephalography and clinical Neurophysiology, 1989, 73: 94-106



References protected by copyright. Thatcher et al. Electroencephalography and clinical Neurophysiology, 1989, 73: 94-106



List of peer reviewed publications

Appendix - B

Normative Database Publications, Replications and Validations (see the National Library of Medicine database for more citations)

- Bell, M.A and Fox, N.A. (1992), The relations between frontal brain electrical activity and cognitive development during infancy. Child Dev. 63(5): 1142-63.**
- Boldyreva GN, Zhavoronkova LA. (1991). Interhemispheric asymmetry of EEG coherence as a reflection of different functional states of the human brain. Biomed Sci.; 2(3): 266-70.**
- Cantor DS, Thatcher RW, Hrybyk M, Kaye H. (1986). Computerized EEG analyses of autistic children. J. Autism Dev. Disord., 16(2):169-87.**
- Cantor, D.S., Thatcher, R.W. and Kaye, H. (1987). Computerized EEG Analyses of Autistic Children. Int. J. Autism, 114: 21-36.**
- Case, R. (1992). The role of the frontal lobes in the regulation of cognitive development. Brain Cogn. 20(1): 51-73.**
- Dawson G, Panagiotides H, Klinger LG, Hill D. (1992). The role of frontal lobe functioning in the development of infant self-regulatory behavior. Brain Cogn. 20(1): 152-75.**
- Fishbein, D. and Thatcher, R.W. (1986). New Diagnostic Methods in Criminology: Assessing Organic Sources of Behavioral Disorders. Research on Crime and Delinquency, 23 (3): 240 - 267.**
- Fisher, K.W. (1987), Relations between brain and cognitive development. Child Dev. 58(3): 623-32.**
- Hanlon, H. W. (1996). Topographically different regional networks impose structural limitations on both sexes in early postnatal development. In: K. Pribram & J. King (Eds.), Learning as self-organization (pp. 311-376). Mahwah, NJ: Lawrence Erlbaum Assoc., Inc.**
- Hanlon, H. W., Thatcher, R. W. & Cline, M. J. (1999). Gender differences in the development of EEG coherence in normal children. Developmental Neuropsychology, 16 (3), 479-506.**
- John, E.R. Karmel, B., Corning, W. Easton, P., Brown, D., Ahn, H., John, M., Harmony, T., Pritchep, L., Toro, A., Gerson, I., Bartlett, F., Thatcher, R., Kaye, H., Valdes, P., Schwartz, E. Neurometrics: Numerical taxonomy identifies different**

profiles of brain functions within groups of behaviorally similar people. *Science*, 196, :1393-1410, 1977.

John, E.R., Prichep, L.S. and Easton, P. Normative data banks and neurometrics: Basic concepts, methods and results of norm construction. In: Remond A. (ed.), *Handbook of Electroencephalography and Clinical Neurophysiology*, Vol. III, *Computer Analysis of the EEG and Other Neurophysiological Signals*. 1987, Amsterdam: Elsevier, pp. 449-495.

Ito Y, Teicher MH, Glod CA, Ackerman E. (1998). Preliminary evidence for aberrant cortical development in abused children: a quantitative EEG study. *J Neuropsychiatry Clin Neurosci*. 10(3): 298-307.

Kaiser J, Gruzelier JH. (1996). Timing of puberty and EEG coherence during photic stimulation. *Int J Psychophysiol*. 21(2-3): 135-49.

Matousek M. and Petersen, I. (1973). Automatic evaluation of EEG background activity by means of age-dependent EEG quotients. *EEG and Clin. Neurophysiology*, 35: 603-612.

Matousek M. and Petersen, I. (1973). Frequency analysis of the EEG in normal children and adolescents. In: P. Kellaway and I. Petersen (Eds.), *Automation of clinical electroencephalography*. New York, Raven Press, Pp. 45-53.

Matsuzawa J, Matsui M, Konishi T, Noguchi K, Gur RC, Bilker W, Miyawaki T. (2001). Age-related volumetric changes of brain gray and white matter in healthy infants and children. *Cereb Cortex*. 11(4): 335-42.

McAlaster, R. (1992). Postnatal cerebral maturation in Down's syndrome children: a developmental EEG coherence study. *Int J. Neurosci*. 65(1-4): 221-37.

Thatcher, R. W., McAlaster, R., Lester, M. L., Horst, R. L. & Cantor, D.S. (1983). Hemispheric EEG asymmetries related to cognitive functioning in children. In A. Perecuman (Ed.), *Cognitive processing in the right hemisphere* (pp. 125-145). New York: Academic Press.

Thatcher, R. W., Krause, P. and Hrybyk, M. (1986). Corticocortical association fibers and EEG coherence: A two compartmental model. *Electroencephalography and Clinical Neurophysiology*, 64, 123-143.

Thatcher, R. W., Walker, R. A. & Guidice, S. (1987). Human cerebral hemispheres develop at different rates and ages. *Science*, 236, 1110-1113.

Thatcher, R. W., Walker, R. A., Gerson, I. & Geisler, F. (1989). EEG discriminant analyses of mild head trauma. *Electroencephalography and Clinical Neurophysiology*, 73, 93-106.

- Thatcher, R. W. (1991). Maturation of the human frontal lobes: Physiological evidence for staging. *Developmental Neuropsychology*, 7 (3), 370-394.**
- Thatcher, R. W. (1992). Cyclic cortical reorganization during early childhood. *Brain and Cognition*, 20, 24-50.**
- Thatcher, R. W. (1994). Psychopathology of early frontal lobe damage: Dependence on cycles of postnatal development. *Developmental Pathology*, 6, 565-596.**
- Thatcher, R. W. (1998). EEG normative databases and EEG biofeedback. *Journal of Neurotherapy*, 2 (4), 8-39.**
- Thatcher, R.W. (1999). EEG database guided neurotherapy. In: J.R. Evans and A. Abarbanel Editors, *Introduction to Quantitative EEG and Neurofeedback*, Academic Press, San Diego.**
- Thatcher, R. W., Biver, C. & North, D. (2003) Quantitative EEG and the Frye and Daubert Standards of Admissibility. *Clinical Electroencephalography*., 34(2), 1 – 15.**
- Thatcher, R.W., Walker, R.A., Biver, C.J., North, D.M., and Curtin, R. Quantitative EEG Normative Databases: Validation and Clinical Correlation. *Journal of Neurotherapy* 7, 87-105, 2003.**
- Trudeau, D.L., Anderson, J., Hansen, L.M., Shagalov, D.N., Schmoller, J., Nugent, S. and Barton, S. (1998). Findings of mild traumatic brain injury in combat veterans with PTSD and a history of blast concussion”, *J. Neuropsychiatry Clin Neurosci*. 10(3):308-313.**
- Wolff, T. and Thatcher, R.W., (1990). Cortical reorganization in deaf children. *J. of Clinical and Experimental Neuropsychology*, 12: 209-221.**
- van Baal, G. C. (1997). A genetic perspective on the developing brain: EEG indices of neural functioning in five to seven year old twins. Organization for scientific research (NWO). The Netherlands: Vrije University Press.**
- van Baal, G. C., de Geus, E. J., & Boomsma, D.I. (1998). Genetic influences on EEG coherence in 5-year-old twins. *Behavioral Genetics*, 28 (1), 9-19.**
- van Beijsterveldt, C. E., Molenaar, P. C., de Geus, E. J., & Boomsma, D. I. (1996). Heritability of human brain functioning as assessed by electroencephalography. *American Journal of Human Genetics*, 58 (3), 562-573.**
- van Beijsterveldt, C. E., Molenaar, P. C., de Geus, E. J., & Boomsma, D. I. (1998). Genetic and environmental influences on EEG coherence. *Behavioral Genetics*, 28 (6), 443-453.**

From: Reviewer(s) - Name(s) Yung Pak
Subject: 510(k) Number K041263/S001
To: The Record - It is my recommendation that the subject 510(k) Notification:

- Refused to accept.
- Requires additional information (other than refuse to accept).
- Is substantially equivalent to marketed devices.
- NOT substantially equivalent to marketed devices.
- Other (e.g., exempt by regulation, not a device, duplicate, etc.)

Is this device subject to Section 522 Postmarket Surveillance? YES NO
 Is this device subject to the Tracking Regulation? YES NO
 Was clinical data necessary to support the review of this 510(k)? YES NO
 Is this a prescription device? YES NO
 Was this 510(k) reviewed by a Third Party? YES NO
 Special 510(k)? YES NO
 Abbreviated 510(k)? Please fill out form on H Drive 510k/boilers YES NO

Truthful and Accurate Statement Requested Enclosed
 A 510(k) summary OR A 510(k) statement
 The required certification and summary for class III devices NA
 The indication for use form

Combination Product Category (Please see algorithm on H drive 510k/Boilers) N

Animal Tissue Source YES NO Material of Biological Origin YES NO

The submitter requests under 21 CFR 807.95 (doesn't apply for SEs):
 No Confidentiality Confidentiality for 90 days Continued Confidentiality exceeding 90 days

Predicate Product Code with class: 84GWQ, II, 882.1400 - Electroencephalograph
 Additional Product Code(s) with panel (optional):
84GWS, I, 882.1420 - Electroencephalograph signal spectrum (EEG) analyzer

Review: Carla Peña 45240 07-29-04
 (Branch Chief) (Branch Code) (Date)

Final Review: Miriam C. Provost 8/2/04
 (Division Director) (Date)

K041263

Reviewer: Yung Pak
Mechanical Engineer

General Surgical Devices Branch:
(HFZ-410)

Proprietary Trade Name: NeuroGuide Analysis System

Common Name: EEG, EEG signal spectrum analyzer

Product to which compared: NxLink (K974748)

Applicant: Applied NeuroScience

Contact: Robert W. Thatcher, Ph.D.

Phone (727)392-7851

CLP
07.29.04
SETXELION
CEN

Intended Use

The NeuroGuide Analysis System is to be used by qualified medical or qualified clinical professionals for the statistical evaluation of the human electroencephalogram (EEG). (Flowchart #3)

Device Description

The NeuroGuide Analysis System (NAS) is a software program for the post-hoc analysis of the human electroencephalogram (EEG). EEG is recorded on a separate device is transferred to the NAS for display and user-review. Analysis consists of the Fast-Fourier Transformation (FFT) of the data to extract the spectral power for each of the four primary frequency bands (delta, theta, alpha, and beta), and frequency information from the EEG. The results of this analysis then converted to statistical values in the table. The similar software program was cleared for the similar mathematical function and statistical values.

The table below compares the similarities between proposed device and predicate device:

<i>Device Characteristics</i>	<i>Predicate device (K974748)</i>	<i>Proposed Device</i>
Input host digital EEG	Yes	Yes
Frequency	0.5 – 3.0 Hz	0.5 – 27 Hz
Spectral Analysis	FFT	FFT
Coherence analysis	Yes	Yes
Phase delay analysis	Yes	Yes
Amplitude asymmetry	Yes	Yes
Ratio of power	Yes	Yes
Multivariate statistics	Yes	Yes
Topographic color maps	Yes	Yes
Normative database	Sample size = 470	Sample size =625
Gaussian distribution	Yes	Yes
Z scores	Yes	Yes

Operating system	DOS	Windows
Visual display of EEG	Yes	Yes

The new device is very similar to predicate device but with faster operating system and with larger database population. Therefore, the new device is able to display/calculate functions efficiently due to faster operating system.
(Flowchart #5)

Clinical Consult

Dr. Mike Schlosser reviewed the submission and stated that he does not see any safety or effectiveness issues since the new device is doing same functions as the predicate device. See his review – attached.

Software

The software requirements specification, architectural design chart, hazard analysis and software verification, validation and testing are provided and adequate for this type of device.

Biocompatibility

Not applicable since the device is software and does not come in contact with patients.

Sterilization

Not applicable since the device is software program.

Labeling

The users manual contain information labeling contains installation instruction for the software which is comparable to the predicate labeling. This is adequate.

Administrative

Indications for Use Statement – enclosed
Truthful and Accurate Statement – enclosed
510(k) Summary – enclosed

Substantial Equivalence (SE) Decision Making Documentation

	<u>YES</u>	<u>NO</u>	
1. IS PRODUCT A DEVICE?	<u>X</u>	—	IF NO, STOP
2. DEVICE SUBJECT TO 510(k)?	<u>X</u>	—	IF NO, STOP
3. SAME INDICATION STATEMENT?	<u>X</u>	—	IF YES, GO TO 5
4. DO DIFFERENCES ALTER THE EFFECT OR RAISE NEW ISSUES OF SAFETY OR EFFECTIVENESS?	—	—	IF YES, STOP -> NE
5. SAME TECHNOLOGICAL CHARACTERISTICS?	<u>X</u>	—	IF YES, GO TO 7
6. COULD THE NEW CHARACTERISTICS AFFECT SAFETY OR EFFECTIVENESS?	—	—	IF YES, GO TO 8
7. DESCRIPTIVE CHARACTERISTICS PRECISE ENOUGH?	—	<u>X</u>	IF YES, STOP -> SE
10. PERFORMANCE DATA AVAILABLE TO SUPPORT EQUIVALANCE?	<u>X</u>	—	IF NO, REQUEST DATA
11. PERFORMANCE DATA DEMONSTRATES EQUIVALANCE?	<u>X</u>	—	IF NO, STOP -> NSE

10. The software documentation has been provided.

11. The provided software documentation demonstrated equivalence the predicate.

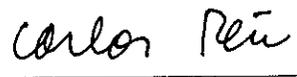
Reviewer Recommendation:

Substantially equivalent.

ProCode: 84GWQ, 84GWS
Class: II
CFR #: 21 CFR §882.1400, 882.1420



Yung Pak Date
Mechanical Engineer, General Surgery Devices Branch



Carlos Pena, Ph.D. Date
Acting Chief, General Surgery Devices Branch

Concur
 Do Not Concur
Comments:

Indications for Use

510(k) Number (if known): K041263

Device Name: NeuroGuide Analysis System

Indications For Use: For clinical use the NeuroGuide Analysis system is to be used by qualified medical or clinical professionals for the statistical evaluation of the human electroencephalogram (EEG).

Prescription Use _____
(Part 21 CFR 801 Subpart D)

AND/OR

Over-The-Counter Use X
(21 CFR 801 Subpart C)

(PLEASE DO NOT WRITE BELOW THIS LINE-CONTINUE ON ANOTHER PAGE IF NEEDED)

Concurrence of CDRH, Office of Device Evaluation (ODE)

Page 1 of _____

From: Reviewer(s) - Name(s) Yung Pak
Subject: 510(k) Number K041263
To: The Record - It is my recommendation that the subject 510(k) Notification:

- Refused to accept.
- Requires additional information (other than refuse to accept).
- Is substantially equivalent to marketed devices.
- NOT substantially equivalent to marketed devices.
- Other (e.g., exempt by regulation, not a device, duplicate, etc.)

See 1/13/04 fax for additional info

- Is this device subject to Section 522 Postmarket Surveillance? YES NO
- Is this device subject to the Tracking Regulation? YES NO
- Was clinical data necessary to support the review of this 510(k)? YES NO
- Is this a prescription device? YES NO
- Was this 510(k) reviewed by a Third Party? YES NO
- Special 510(k)? YES NO
- Abbreviated 510(k)? Please fill out form on H Drive 510k/boilers YES NO

- Truthful and Accurate Statement Requested Enclosed
- A 510(k) summary OR A 510(k) statement
- The required certification and summary for class III devices
- The indication for use form

Combination Product Category (Please see algorithm on H drive 510k/Boilers) _____

Animal Tissue Source YES NO Material of Biological Origin YES NO

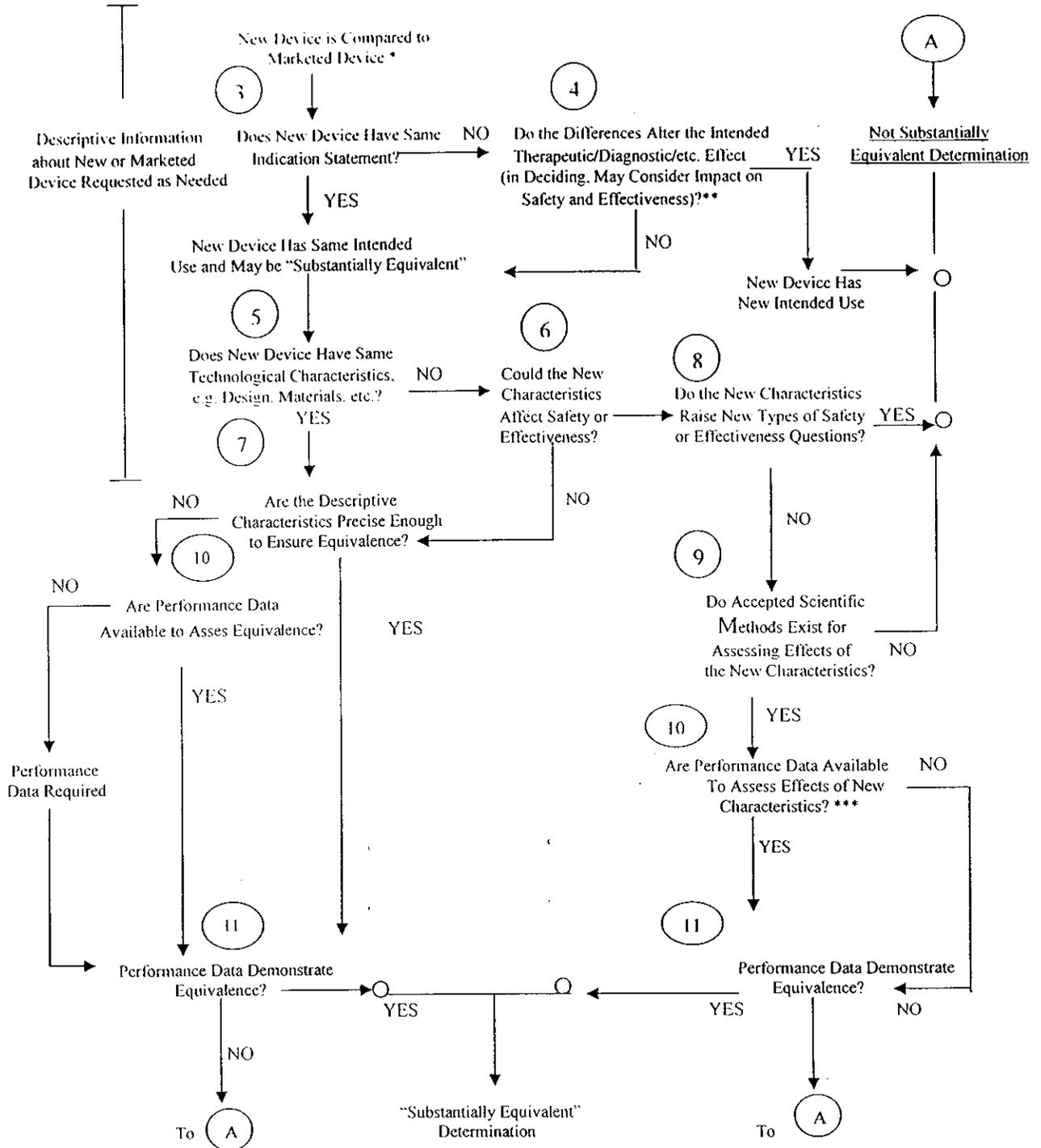
The submitter requests under 21 CFR 807.95 (doesn't apply for SEs):
 No Confidentiality Confidentiality for 90 days Continued Confidentiality exceeding 90 days

Predicate Product Code with class: _____ Additional Product Code(s) with panel (optional): _____

Review: Carla DeLa HF2410 07.14.04
~~Acting~~ (Branch Chief) (Branch Code) (Date)

Final Review: _____ (Date)
(Division Director)

510(k) "SUBSTANTIAL EQUIVALENCE" DECISION-MAKING PROCESS



* 510(k) Submissions compare new devices to marketed devices. FDA requests additional information if the relationship between marketed and "predicate" (pre-Amendments or reclassified post-Amendments) devices is unclear.

** This decision is normally based on descriptive information alone, but limited testing information is sometimes required.

*** Data maybe in the 510(k), other 510(k)s, the Center's classification files, or the literature.

**SCREENING CHECKLIST
FOR ALL PREMARKET NOTIFICATION [510(k)] SUBMISSIONS**

510(k) Number: _____

The cover letter clearly identifies the type of 510(k) submission as (Check the appropriate box):

- Special 510(k) - Do Sections 1 and 2
- Abbreviated 510(k) - Do Sections 1, 3 and 4
- Traditional 510(k) or no identification provided - Do Sections 1 and 4

Section 1: Required Elements for All Types of 510(k) submissions:

	Present or Adequate	Missing or Inadequate
Cover letter, containing the elements listed on page 3-2 of the Premarket Notification [510(k)] Manual.		
Table of Contents.		
Truthful and Accurate Statement.		
Device's Trade Name, Device's Classification Name and Establishment Registration Number.		
Device Classification Regulation Number and Regulatory Status (Class I, Class II, Class III or Unclassified).		
Proposed Labeling including the material listed on page 3-4 of the Premarket Notification [510(k)] Manual.		
Statement of Indications for Use that is on a separate page in the premarket submission.		
Substantial Equivalence Comparison, including comparisons of the new device with the predicate in areas that are listed on page 3-4 of the Premarket Notification [510(k)] Manual.		
510(k) Summary or 510(k) Statement.		
Description of the device (or modification of the device) including diagrams, engineering drawings, photographs or service manuals.		
Identification of legally marketed predicate device. *		
Compliance with performance standards. * [See Section 514 of the Act and 21 CFR 807.87 (d).]		
Class III Certification and Summary. **		
Financial Certification or Disclosure Statement for 510(k) notifications with a clinical study. * [See 21 CFR 807.87 (i)]		
510(k) Kit Certification ***		

- * - May not be applicable for Special 510(k)s.
- ** - Required for Class III devices, only.
- *** - See pages 3-12 and 3-13 in the Premarket Notification [510(k)] Manual and the Convenience Kits Interim Regulatory Guidance.

Section 2: Required Elements for a SPECIAL 510(k) submission:

	Present	Inadequate or Missing
Name and 510(k) number of the submitter's own, unmodified predicate device.		
A description of the modified device and a comparison to the sponsor's predicate device.		
A statement that the intended use(s) and indications of the modified device, as described in its labeling are the same as the intended uses and indications for the submitter's unmodified predicate device.		
Reviewer's confirmation that the modification has not altered the fundamental scientific technology of the submitter's predicate device.		
A Design Control Activities Summary that includes the following elements (a-c):		
a. Identification of Risk Analysis method(s) used to assess the impact of the modification on the device and its components, and the results of the analysis.		
b. Based on the Risk Analysis, an identification of the required verification and validation activities, including the methods or tests used and the acceptance criteria to be applied.		
c. A Declaration of Conformity with design controls that includes the following statements:		
A statement that, as required by the risk analysis, all verification and validation activities were performed by the designated individual(s) and the results of the activities demonstrated that the predetermined acceptance criteria were met. This statement is signed by the individual responsible for those particular activities.		
A statement that the manufacturing facility is in conformance with the design control procedure requirements as specified in 21 CFR §20.30 and the records are available for review. This statement is signed by the individual responsible for those particular activities.		

Section 3: Required Elements for an ABBREVIATED 510(k)* submission:

	Present	Inadequate or Missing
For a submission, which relies on a guidance document and/or special control(s), a summary report that describes how the guidance and/or special control(s) was used to address the risks associated with the particular device type. (If a manufacturer elects to use an alternate approach to address a particular risk, sufficient detail should be provided to justify that approach.)		
For a submission, which relies on a recognized standard, a declaration of conformity [For a listing of the required elements of a declaration of conformity, SEE Required Elements for a Declaration of Conformity to a Recognized Standard, which		

is posted with the 510(k) boilers on the H drive.]		
For a submission, which relies on a recognized standard without a declaration of conformity, a statement that the manufacturer intends to conform to a recognized standard and that supporting data will be available before marketing the device.		
For a submission, which relies on a non-recognized standard that has been historically accepted by FDA, a statement that the manufacturer intends to conform to a recognized standard and that supporting data will be available before marketing the device.		
For a submission, which relies on a non-recognized standard that has <u>not</u> been historically accepted by FDA, a statement that the manufacturer intends to conform to a recognized standard and that supporting data will be available before marketing the device <u>and</u> any additional information requested by the reviewer in order to determine substantial equivalence.		
Any additional information, which is not covered by the guidance document, special control, recognized standard and/or non-recognized standard, in order to determine substantial equivalence.		

- * - When completing the review of an abbreviated 510(k), please fill out an Abbreviated Standards Data Form (located on the H drive) and list all the guidance documents, special controls, recognized standards and/or non-recognized standards, which were noted by the sponsor.

Section 4: Additional Requirements for ABBREVIATED and TRADITIONAL 510(k) submissions (If Applicable):

	Present	Inadequate or Missing
a) Biocompatibility data for all patient-contacting materials, OR certification of identical material/formulation:		
b) Sterilization and expiration dating information:		
i) sterilization process		
ii) validation method of sterilization process		
iii) SAL		
iv) packaging		
v) specify pyrogen free		
vi) ETO residues		
vii) radiation dose		
viii) Traditional Method or Non-Traditional Method		
c) Software Documentation:		

Items with checks in the "Present or Adequate" column do not require e additional information from the sponsor. Items with checks in the "Missing or Inadequate" column must be submitted before substantive review of the document.

Passed Screening Yes No

Reviewer: _____

Concurrence by Review Branch: _____

Date: _____

The deficiencies identified above represent the issues that we believe need to be resolved before our review of your 510(k) submission can be successfully completed. In developing the deficiencies, we carefully considered the statutory criteria as defined in Section 513(i) of the Federal Food, Drug, and Cosmetic Act for determining substantial equivalence of your device. We also considered the burden that may be incurred in your attempt to respond to the deficiencies. We believe that we have considered the least burdensome approach to resolving these issues. If, however, you believe that information is being requested that is not relevant to the regulatory decision or that there is a less burdensome way to resolve the issues, you should follow the procedures outlined in the "A Suggested Approach to Resolving Least Burdensome Issues" document. It is available on our Center web page at: <http://www.fda.gov/cdrh/modact/leastburdensome.html>

THE 510(K) DOCUMENTATION FORMS ARE AVAILABLE ON THE LAN UNDER 510(K) BOILERPLATES TITLED "DOCUMENTATION" AND MUST BE FILLED OUT WITH EVERY FINAL DECISION (SE, NSE, NOT A DEVICE, ETC.).

"SUBSTANTIAL EQUIVALENCE" (SE) DECISION MAKING DOCUMENTATION

K _____

Reviewer: _____

Division/Branch: _____

Device Name: _____

Product To Which Compared (510(K) Number If Known): _____

	YES	NO	
1. Is Product A Device			If NO = Stop
2. Is Device Subject To 510(k)?			If NO = Stop
3. Same Indication Statement?			If YES = Go To 5
4. Do Differences Alter The Effect Or Raise New Issues of Safety Or Effectiveness?			If YES = Stop NE
5. Same Technological Characteristics?			If YES = Go To 7
6. Could The New Characteristics Affect Safety Or Effectiveness?			If YES = Go To 8
7. Descriptive Characteristics Precise Enough?			If NO = Go To 10 If YES = Stop SE
8. New Types Of Safety Or Effectiveness Questions?			If YES = Stop NE
9. Accepted Scientific Methods Exist?			If NO = Stop NE
10.. Performance Data Available?			If NO = Request Data
11. Data Demonstrate Equivalence?			Final Decision:

Note: In addition to completing the form on the LAN, "yes" responses to questions 4, 6, 8, and 11, and every "no" response requires an explanation.

1. Intended Use:

2. Device Description: Provide a statement of how the device is either similar to and/or different from other marketed devices, plus data (if necessary) to support the statement. Is the device life-supporting or life sustaining? Is the device implanted (short-term or long-term)? Does the device design use software? Is the device sterile? Is the device for single use? Is the device over-the-counter or prescription use? Does the device contain drug or biological product as a component? Is this device a kit? Provide a summary about the device's design, materials, physical properties and toxicology profile if important.

EXPLANATIONS TO "YES" AND "NO" ANSWERS TO QUESTIONS ON PAGE 1 AS NEEDED

1. Explain why not a device:

2. Explain why not subject to 510(k):

3. How does the new indication differ from the predicate device's indication:

4. Explain why there is or is not a new effect or safety or effectiveness issue:

5. Describe the new technological characteristics:

6. Explain how new characteristics could or could not affect safety or effectiveness:

7. Explain how descriptive characteristics are not precise enough:

8. Explain new types of safety or effectiveness questions raised or why questions are not new:

9. Explain why existing scientific methods can not be used:

10. Explain what performance data is needed:

11. Explain how the performance data demonstrates that the device is or not substantially equivalent:

ATTACH ADDITIONAL SUPPORTING INFORMATION

Internal Administrative Form

	YES	NO
1. Did the firm request expedited review?		
2. Did we grant expedited review?		
3. Have you verified that the Document is labeled Class III for GMP purposes?		
4. If, not, has POS been notified?		
5. Is the product a device?		
6. Is the device exempt from 510(k) by regulation or policy?		
7. Is the device subject to review by CDRH?		
8. Are you aware that this device has been the subject of a previous NSE decision?		
9. If yes, does this new 510(k) address the NSE issue(s), (e.g., performance data)?		
10. Are you aware of the submitter being the subject of an integrity investigation?		
11. If, yes, consult the ODE Integrity Officer.		
12. Has the ODE Integrity Officer given permission to proceed with the review? (Blue Book Memo #I91-2 and Federal Register 90N0332, September 10, 1991.		

To: Robert Thatcher, Ph.D.

From: Yung Pak

Re: K041263 – Neuroguide Analysis System

Date: July 13, 2004

The following additional information is needed to complete the 510(k) review. Please provide software documentation which includes functional requirements and system specification, hazard analysis, software design, software development, software verification, validation and testing. Please refer to FDA guidance titled "Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices" in the website www.fda.gov/cdrh/ode/html

Your 510(k) will be on phone hold and we will resume the review when the requested information is received. If you have any questions, please contact me at (301)594-2036 ext. 144.

A handwritten signature in black ink, appearing to read "Yung Pak", is located in the lower right quadrant of the page.

Pak, Yung

From: Schlosser, Michael J*
Sent: Wednesday, June 30, 2004 8:58 AM
To: Pak, Yung
Subject: K041263 NeuroGuide system

Yung,

I have read through the literature references provided in the 510(k) application for the NeuroGuide Analysis System.

In brief, this system is stand-alone software that accepts data digital EEG data recorded from a patient and performs spectral analysis using analyses such as fast fourier transforms. The software provides output to the clinician in the form of statistical summary tables, relative power, and topographical maps.

The system is indicated to be used by a qualified medical or clinical professional for the post-hoc statistical evaluation of human EEG. The instructions for use specify that the NeuroGuide does not diagnose any condition and only provides displays of the digital EEG and statistical analyses of selected segments. The instructions go on to state that quantitative EEG (qEEG) is not a substitute for clinical training, evaluation of the raw EEG by a competent and trained clinician and is only to be used as an adjunct to a complete patient evaluation.

The system utilizes a look up table function to generate Z scores that are based on a reference population. A publication of this reference EEG data was provided by the sponsor (Thatcher et al 2003) and included normative EEG data collected on 625 subjects with ages from 2 months to 85 years old. This reference describes the rigorous statistical approach used to generate the normative data, segmented by age, from which comparisons can be made. Additionally, the sponsor has provided published articles demonstrating the ability of these analyses techniques to differentiate various grades of traumatic brain injury patients from each other based on the qEEG measurements with high specificity and sensitivity.

These references support the use of qEEG analysis as a valid clinical technique. Further, the use of qEEG to analyze large volumes of continuous EEG data from patients is a common clinical practice. Given the adequate IFU that warn the user that qEEG is not a diagnostic tool, nor does it substitute for clinical judgement and visual inspection of the raw EEG signals, there does not appear to be any new safety or effectiveness issues raised by this device. I would therefore find it is clinically SE to the predicate device.

Michael J Schlosser, MD
Medical Officer
DGRND/GSDB

THIS MESSAGE IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please immediately notify the sender immediately by e-mail or phone.

Pak, Yung

From: Vishnuvajjala, R. Lakshmi
Sent: Thursday, July 01, 2004 3:32 PM
To: Pak, Yung
Subject: FW: K041263, Neuroguide analysis system

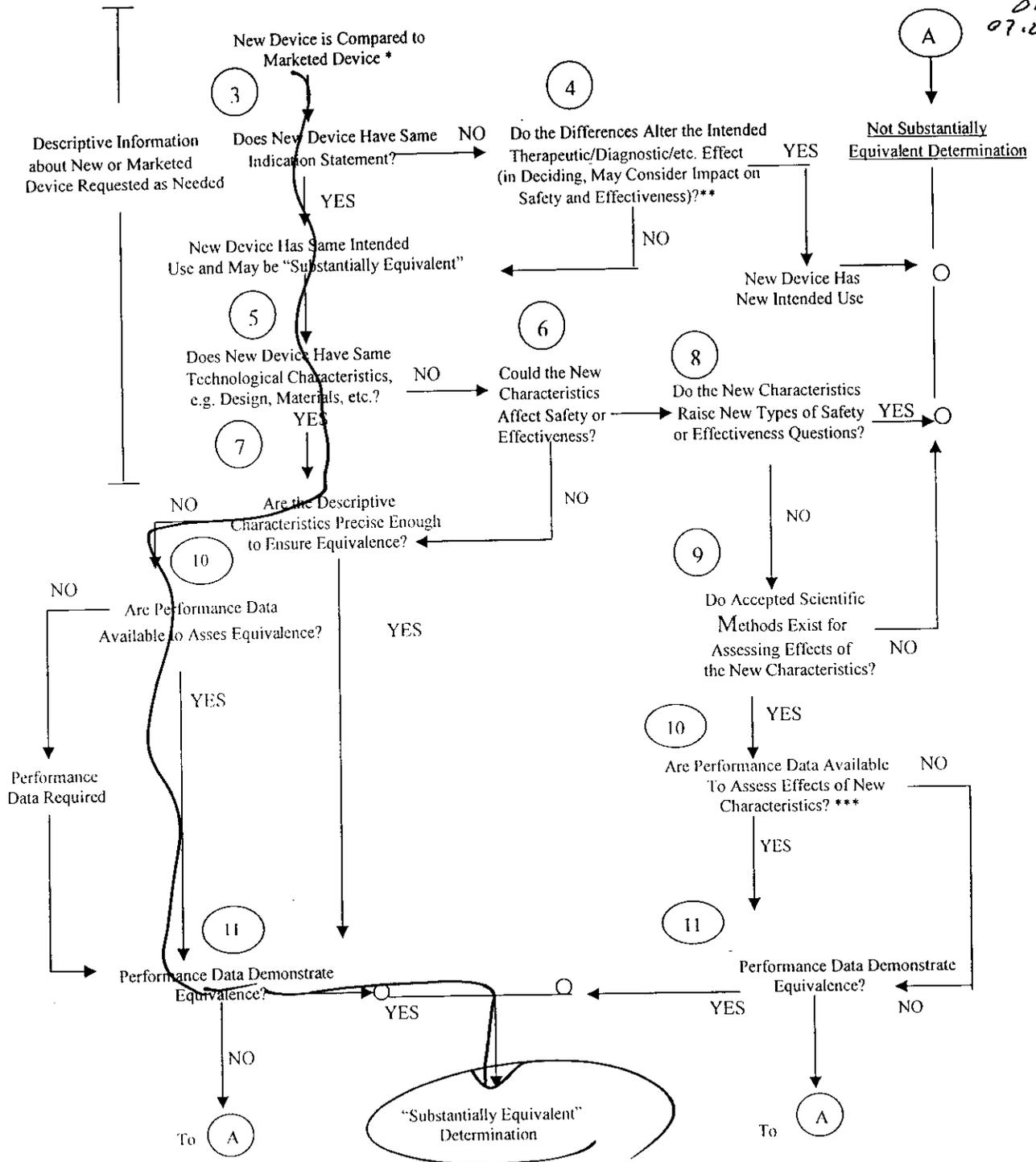
-----Original Message-----

From: Vishnuvajjala, R. Lakshmi
Sent: Thursday, July 01, 2004 1:27 PM
To: Krause, David
Cc: Lao, Chang S.
Subject: K041263, Neuroguide analysis system

I am the team leader for the diagnostic devices in DBS and Chang Lao just gave me this 510(k) as it appears to be a diagnostic device. Neither he nor I can find any statistical hypotheses or statistical analyses. The literature submitted may have statistical analysis in them, but the papers are in neuroscience journals and not statistics journals. They require clinical review rather than statistical review. If the reviewing clinician has any specific questions, we can help.

Lakshmi Vishnuvajjala

510(k) "SUBSTANTIAL EQUIVALENCE" DECISION-MAKING PROCESS



- * 510(k) Submissions compare new devices to marketed devices. FDA requests additional information if the relationship between marketed and "predicate" (pre-Amendments or reclassified post-Amendments) devices is unclear.
- ** This decision is normally based on descriptive information alone, but limited testing information is sometimes required.
- *** Data maybe in the 510(k), other 510(k)s, the Center's classification files, or the literature.

July 22, 2004

Food and Drug Administration
Center for Devices and
Radiological Health
Office of Device Evaluation
Document Mail Center (HFZ-401)
9200 Corporate Blvd.
Rockville, Maryland 20850

APPLIED NEUROSCIENCE INC.
228 176TH TERRACE DRIVE
ST. PETERSBURG, FL 33708
ATTN: ROBERT W. THATCHER

510(k) Number: K041263
Product: NEUROGUIDE
ANALYSIS SYSTEM

The additional information you have submitted has been received.

We will notify you when the processing of this submission has been completed or if any additional information is required. Please remember that all correspondence concerning your submission MUST be sent to the Document Mail Center (HFZ-401) at the above letterhead address. Correspondence sent to any address other than the one above will not be considered as part of your official premarket notification submission. Also, please note the new Blue Book Memorandum regarding Fax and E-mail Policy entitled, "Fax and E-Mail Communication with Industry about Premarket Files Under Review. Please refer to this guidance for information on current fax and e-mail practices at www.fda.gov/cdrh/ode/a02-01.html.

The Safe Medical Devices Act of 1990, signed on November 28, states that you may not place this device into commercial distribution until you receive a letter from FDA allowing you to do so. As in the past, we intend to complete our review as quickly as possible. Generally we do so 90 days. However, the complexity of a submission or a requirement for additional information may occasionally cause the review to extend beyond 90 days. Thus, if you have not received a written decision or been contacted within 90 days of our receipt date you may want to check with FDA to determine the status of your submission.

If you have procedural or policy questions, please contact the Division of Small Manufacturers International and Consumer Assistance (DSMICA) at (301) 443-6597 or at their toll-free number (800) 638-2041, or contact me at (301) 594-1190.

Sincerely yours,

Marjorie Shulman
Supervisory Consumer Safety Officer
Premarket Notification Section
Office of Device Evaluation
Center for Devices and
Radiological Health

K041263/S001

Applied Neuroscience, Inc.



228 176th Terrace Drive
Redington Shores, Fl 33708
727-392-7851, rwthatcher@yahoo.com

July 20, 2004

Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Boulevard
Rockville, Maryland 20850 USA

Re: 510(k) Number: K041263

Dear Sirs;

Enclosed is an original and two copies of the requested software documentation including functional requirements and system specification, hazard analysis, software design, verification, validation and testing as per the FDA guidance titled "Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices". Applied Neuroscience, Inc. has already submitted a 510(k) application and this is in response to an identified deficiency of insufficient software documentation.

Sincerely,

Robert W. Thatcher, Ph.D.
President

sk8

FDA/CDRH/ONE/PMO
2004 JUL 22 A 9:21

To: Robert Thatcher, Ph.D.

From: Yung Pak

Re: K041263 – Neuroguide Analysis System

Date: July 13, 2004

The following additional information is needed to complete the 510(k) review. Please provide software documentation which includes functional requirements and system specification, hazard analysis, software design, software development, software verification, validation and testing. Please refer to FDA guidance titled "Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices" in the website www.fda.gov/cdrh/ode/html

Your 510(k) will be on phone hold and we will resume the review when the requested information is received. If you have any questions, please contact me at (301)594-2036 ext. 144.



SOFTWARE DOCUMENTATION

Section Number 2.1 and 3.1 – Level of Concern is Minor

The level of concern is minor because failures or latent design flaws would not be expected to result in any injury to the patient and/or operator. The answer to all five questions in section 2.2.2 – Decision Process (www.fda.gov/FDA/57_FINAL_SOFTWARE_GUIDANCE_COPY_2.htm) is No, Therefore, the level of concern is minor. The Neuroguide analysis software does not diagnose and is used only as an adjunct to other measures and in conjunction with conventional visual examination of the EEG tracings. The trained expert who uses the neuroguide analysis software (NAS) has the option to ignore the results or to validate the results using independent tests to confirm or reject the Neuroguide spectral analyses and statistics. The NeuroGuide software uses defensive programming in that design and programming efforts are made to minimize intentional and accidental error to the extent possible (see section No. 3.3 below).

Section Number 3.2 – Software Description

The NeuroGuide Analysis System (NAS) is a software program for the post-hoc statistical analysis of the human electroencephalogram (EEG). EEG recorded on a separate device (i.e., the host system) is transferred to the NAS for display and user-review. The system requires that the user select reliable samples of artifact-free, eyes-closed or eyes open resting EEG from the recording for analysis. Analysis consists of the Fast-Fourier Transformation (FFT) and direct Fourier Transform (Complex Demodulation) of the data to extract the spectral power at 0.5 Hz resolution and each of the five primary frequency bands (delta, theta, alpha, beta and gamma) and standard ratios of frequency bands of the EEG. The results of this analysis are then subjected to univariate, bivariate, and multivariate statistical analyses and displayed in statistical tables and topographical color maps of absolute and relative power, power ratios, power asymmetry, coherence and phase delays for 19 monopolar and all of the possible 171 combinations of 19 electrode bipolar derivations of the EEG. In all over 1,200 measures are derived for comparison against a carefully constructed and statistically controlled age grouped, normative reference database in which the variables have been transformed and confirmed for their Gaussian distribution. Each variable extracted by the analysis is compared to the database using parametric statistical procedures that express the differences between the patient and an appropriate age-matched reference group in the form of Z-scores. Univariate and Multivariate features are compared to the normative database using Gaussian Univariate and Multivariate distance statistics. The Gaussian multivariate distance statistic controls for the interrelationship of the measures of brain cortical function in the feature set, and provides an accurate estimate of their difference from normal. The univariate statistics allow for single electrode and ≤ 1 Hz resolution while the multivariate measures permit an evaluation of regional indices of brain function. Extracted feature sets are further analyzed to determine if a pattern in the EEG (statistically significant feature score values identified for the patient) are consistent with patterns in the EEG identified in prior neuroguide evaluations of clinical patients with

known disorders. A step-wise discriminate analysis program identifies patterns in the EEG that are commonly present in traumatic brain injured patients and learning disabled children. The multivariate discriminant functions provide a probability estimate of the presence or absence of a pattern in the EEG that has been found to be prevalent in individuals constituting the normative and clinical database. The discriminant function is not intended as a diagnostic program, instead it serves as a pattern recognition program and probability estimate of the presence of certain EEG patterns. The discriminant program is restricted by confining potential outcomes to specific patient symptoms, eyes closed resting conditions, greater than 30 seconds of EEG and limited ages derived from the patient history profile. Established discriminant functions were evaluated through the use of Receiver Operating Characteristic (ROC) curves for their sensitivity and specificity. The outcome of the statistical analysis is presented in report form that includes (a) patient demographic and history information, (b) selected EEG epochs, (c) statistical tables of monopolar, bipolar, and multivariate extracted feature values, and topographical brain maps. This information is to be read and interpreted within the context of the current clinical assessment of the patient by the attending physician/clinician. Multivariate linear regression as well as discriminant analysis are also used to identify the maximal correlation between EEG features and performance on neuropsychological tests performed on normal subjects ranging in I.Q. from approximately 80 to 150. A prediction with 95% confidence band is computed for each subtest of the neuropsychological tests. The decision to accept or reject the results of the neuroguide analysis, and incorporate these results into their clinical appraisal of the patient, is dependent upon the judgment of the attending physician or clinician. Windows operating system (Windows 97, 98, ME, 2000, XP and NT) is used to interface the microcomputer hardware platform, the stored or archived digital EEG data, statistical processing programs, data storage, and output devices. NeuroGuide also provides for statistical validation using repeated measures analysis of variance, paired t-tests and independent t-tests for both test re-test designs and group analyses.

Section Number 3.3 & 4.3 – Device Hazard Analysis - Minor

The Neuroguide analysis system is standalone software that is not in contact with a patient and is designed to facilitate visual and mathematical evaluation of the EEG. Training and expertise in EEG analysis is required in order for an individual to evaluate the EEG patterns. The risk is minor because the device itself does not provide a diagnosis. The expert who reads, interprets and evaluates the quantitative values and visual EEG patterns has the option to ignore the numbers and EEG patterns or to use this information along with other information as a supplement to the conventional EEG. When the results are used in this manner, the likelihood of introducing error into diagnosis and treatment is substantially reduced. That is, the test is viewed as an adjunct to the evaluation of the patient, and does not serve as a primary basis for a diagnosis.

Potential minor adverse effects (identification and causes):

- 1- If the NeuroGuide Analysis System is used as the only or the sole diagnostic system (a use that is specifically contraindicated by Applied Neuroscience, Inc. and the system's developers) in the absence of other clinical data from more traditional means of patient evaluation.

- 2- Relying only upon the use of a single index (such as relative power, or the topographical maps alone) without reviewing the traditional EEG, the epochs selected for analysis, or the complete set of statistical summary tables is also contraindicated and a source of potential error.
- 3- Additional sources of error could arise from the inappropriate selection of EEG samples, e.g., selecting artifact and not EEG, or selecting EEG representative of other states, such as drowsiness or eyes-open EEG when comparing to an eyes closed database, or by purposely selecting conditions for testing other than those specified.
- 4- Additionally, it is possible that errors will occur through the purposeful falsification of symptoms in the patient history and patient age.

Risk management and methods of control to minimize or eliminate potential minor concern

- 1- Neuroguide labeling and software documentation specifically states that the Neuroguide analysis system is an adjunct to the evaluation of a patient and does not serve as a primary basis for diagnosis. The discriminant functions are used as pattern recognition software that gives a probability value to the match of a particular EEG pattern that is commonly present in certain defined clinical populations. Warning statements are contained in the software documentation emphasizing that only qualified and trained individuals should use the Neuroguide software for clinical or research purposes.
- 2- The Neuroguide software displays the conventional EEG and the quantitative analysis of the EEG simultaneously on the same screen display. Thus, visual examination of the EEG tracings is a built in defensive programming requirement because quantitative analyses can not be performed without visual examination of the EEG tracings.
- 3- Over 1,200 quantitative numerical values are produced by the Neuroguide analysis system on any ≥ 2 sec. selection of EEG thus minimizing the likelihood that an unqualified individual will only examine a single index. Training in both conventional EEG and spectral analysis EEG always involves the analysis of multiple factors or indices and the Neuroguide software does not limit the analysis to a single value or a single index.
- 4- The Neuroguide software minimizes artifact using defensive programming that allows users to visually select artifact free segments of EEG while simultaneously computing the split-half and test re-test reliability of the selections. The simultaneous reliability measures minimize the likelihood of selecting artifact because the standard criteria of reliability $> 90\%$ will not be met when sample length is too short and when artifact is present. The test re-test reliability compares the first $\frac{1}{2}$ of the EEG selection to the last $\frac{1}{2}$ of the EEG selections and thus helps guard against selecting drowsiness or other state changes that may have occurred during the end of the recording as compared to the beginning of the recording. For example, the recommended value of test re-test reliability $> 90\%$ will not be met if drowsiness in the second half of the recording is present.
- 5- While it is impossible to prevent purposeful misrepresentation of a patient's age or other clinical information, the Neuroguide software minimizes such conduct by

providing the users with a subject information window that must be filled in before the quantitative analysis can be conducted. If an erroneous age is accidentally entered, then the user can easily correct this error by clicking Window > Subject Information and then typing in the correct age. If there is a mismatch between the date of birth and date of test or age information in the EEG data header and the age entered by the user, then the discriminant functions and multivariate statistics are not computed. Another safeguard build into NAS is the eyes closed condition, greater than 30 seconds of data and exact age criteria must be met before the EEG data selections can be submitted for discriminant analyses. The age requirements are ± 13 years of age for the traumatic brain injury discriminant and ± 6 years of age for the learning disabilities discriminant and prediction of neuropsychological test scores.

Section Number 3.4 & 4.2 – Software Requirement Specification (SRS)

1- Hardware and Operating System Requirements

- a- IBM compatible hardware platform (PC), any processor speed, 128 mbyte RAM is recommended, minimum of 100 mbytes of hard disk space, standard display.
- b- Operating system is Windows 97, 98, ME, 2000, XP or NT
- c- There are no special interface requirements other than a disk drive and a printer.

2- Programming language and program size:

- a- Programming language is C and the program size when resident in memory is 13.5 mbytes.
- b- The version number is displayed upon launch and can be viewed by clicking Help > About Neuroguide.

3- Software Performance and Functional Requirements

Software performance testing of the NAS included the evaluation of the algorithms and statistical methods used for data analysis. Specifically, control signals, in the form of signal generated waveforms, were analyzed for frequency and auto and cross spectral power, coherence, phase, amplitude asymmetry and amplitude ratios. EEG signals were analyzed for conformity between the host digital EEG system and the NAS. The NAS includes a feature that reproduces sampling frequency in the host digital EEG system, and permits the visualization and evaluation of the EEG waveform for accuracy between the host system and the NAS translation. In addition, data obtained in previous implementations of the NeuroGuide analysis method were evaluated for consistency and accuracy -- the results of the NAS's analysis of stored subject data had to conform to that of the prior analysis (which was conducted using the same method and procedures, algorithms and method of analysis as that implemented on the NAS). The user of the

NAS can verify the accuracy of the EEG spectral analyses by using built in calibration signals.

The ability of the NAS to accurately translate and present EEGs from clinical patients was confirmed by the non-clinical testing. In order for the NAS to be effective for clinical use the results of the analysis (both statistical tables and topographical brain maps) had to be in agreement with the results of the analysis conducted on the host system used in the processing of patient and normative information at the Applied Neuroscience Laboratory. In addition, the outcome of the discriminant analysis had to be consistent, not resulting in errors of misclassification (that is, the classification on the NAS had to be consistent with that of the host system used to acquire the EEG samples). These tests confirmed that when eyes-closed or eyes-open resting, and artifact-free EEG was selected for analysis, the results were reproducible within an acceptable degree of variation consistent with reliability estimates identified in normative and clinical studies (see Figures 3, 4 & 5 and Table II below).

Subjects upon which this device has been tested included individuals who were either volunteers or clinical patients referred for QEEG evaluation to the Applied Neuroscience Laboratory Department of Psychiatry University of Maryland School of Medicine, and/or Shock Trauma and the Applied Neuroscience Institute at the University of Maryland Eastern Shore, or as part of the DVHIP program. The results of the analysis are usually conveyed to the referring physician and/or Ph.D. clinician who was asked to use the information as an adjunct to their clinical interpretation of the patient's traditional EEG. The information was provided in report form (including EEG epochs selected for analysis, statistical tables and topographic brain maps, and the result of the discriminant analysis) to permit the physician or Ph.D. clinician to determine its relevance to their clinical evaluation and diagnosis or treatment of the patient.

The normative reference database was compiled under well supervised and careful construction procedures as specified in grant applications to the NIH and USDA and as approved by the University of Maryland Institutional Review Board (IRB) in 1979-1987. Under University of Maryland faculty copyright rules and as principal investigator the raw digital values and selections, arrangements, coordinations and derivatives were analyzed and published in numerous peer reviewed journals over the last 25 years.

Software Requirement for the Computation of the Fourier Power Spectrum using the Auto and Cross Spectral Matrix of all combinations of 1 to 19 International 10/20 System EEG electrode locations.

The Neuroguide software consists of power spectral procedures described below that are used for linked ears, average reference and Laplacian digital values for both the eyes-closed and eyes-open conditions, thus producing for a given subject a total of six different 81 point FFT power spectral density values. These values are then used to compute means and standard deviations for different age groups. The FFT normative database uses, five sequential age groupings that were selected to cover the age range from two months to 82 years. The age groupings were: (a) two months to 5.99 years (N =

122), (b) 6.0 years to 9.99 years (N = 147), (c) 10 to 13 years (N = 72), (d) 13 to 16 years (N = 117) and (e) 16 to 82 years (N = 167). The direct Fourier Transforms and Joint Time Frequency transforms (e.g., complex demodulation) use means and standard deviations of normal reference subject's temporal variability and time series features at different age groupings and different degrees of freedom than for the FFT.

Summary of Program EEG Spectral Requirements

- 1- The EEG selections and/or edits are tagged and are spliced together as a continuous stream of digital EEG data from 1 to 19 channels at a sample rate of 128 samples/sec (down sampling or up sampling to produce 128 samples/sec.). In order to remove possible splice artifact the time series is low pass filtered at 40 Hz (5th order Butterworth IIR filter).
- 2- The FFT parameters are: epoch = 2 seconds made up of 256 time points and a frequency range from 0.5 to 40 Hz at a resolution of 0.5 Hz using a cosine taper window to minimize leakage. Each 2 second FFT is 81 rows (frequencies 0 to 40 Hz) X 19 columns (electrode locations) = 1,539 element cross-spectral matrix for each subject.
- 3- In order to minimize the effects of windowing in the FFT (Kaiser and Sterman, J. Neurotherapy, 4(3): 85-92, 2001) a EEG sliding average of the 256 point FFT cross-spectral matrix was computed for each normal subject's edited EEG by advancing in 64 point steps (75% overlap) and recomputing the FFT and continuing with the 64 point sliding window of 256 point FFT cross-spectrum for the entire edited EEG record. Each of the 81 frequencies for each 19 channels is log₁₀ transformed to better approximate a normal distribution. The total number of 2 second windows is the N that is entered into the analysis of variance and t-tests and it is used to compute the degrees of freedom for a given statistical test.
- 4- A mean, variance, standard deviation, sum of squares, and squared sum of the real (cosine) and imaginary (sine) coefficients of the cross-spectral matrix is computed across the sliding average of edited EEG for all 19 leads for the total number of 81 and 1,539 log transformed elements for each subject. This creates the following six basic spectral measurement sets and their derivatives 1- Cross-Spectral Power (square root of the sums of squares of the real and imaginary coefficients); 2- Auto-Spectral Power which is the diagonal of the cross-spectral matrix where the imaginary coefficient = 0 and power = sine square; 3- Coherence = square of the cross-spectrum divided by the product of the two auto-spectra; 4- Phase = arctangent of the ratio of the real/imaginary components for frequencies from 0.5 to 40 Hz; 5- Real coefficients; 6 – Imaginary coefficients.
- 5- The results of the computations in steps 2 to 4 are stored in the NeuroGuide Analysis File, designated as *.NGA. These results are used in the comparative statistical analyses. Z scores are defined as $Z = \frac{\hat{X} - x_i}{St.Dev.}$ where \hat{X} = mean of the normative reference database value at a given age and x_i = the subject's EEG value and St. Dev. =

standard deviation of the normative reference database value at a given age. Multivariate statistics are similarly defined in standard statistical text books.

The number of normative reference subjects at different ages is shown in Figure 1.

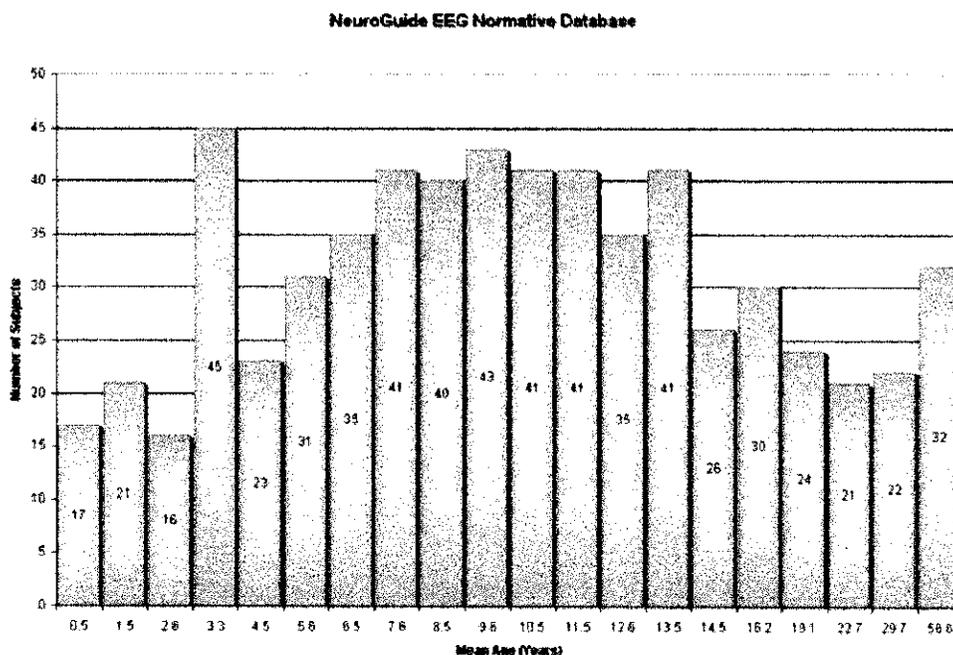


Figure 1 above is the number of subjects per year in the Lifespan EEG reference normative database (y-axis). The database ranges in age from two months of age being the youngest subject and 82.3 years of age being the oldest subject (x-axis). This figure shows the number of subjects constituting mean values which range from a mean of .5 years to 62.6 years of age and constituting a total of 625 subjects. Exclusion/inclusion criteria: (a) a neurological history questionnaire given to the child's parents and/or filled out by each subject, (b) psychometric evaluation of IQ, and/or school achievement, (c) for children the teacher and class room performance as determined by school grades and teacher reports and presence of environmental toxins such as lead or cadmium. A neurological questionnaire was obtained from all of the adult subjects more than 18 years of age and those in which information was available about a history of problems as an adult were excluded. Selection criteria were: 1- no history of neurological disorders, 2- normal development milestones, 3- normal intelligence, 4- performing at grade level in all academic subjects, 5- no history of learning disabilities or attention deficit disorders or hyperactivity, etc. It is important that the demographic mixture of males and females, different ethnic groups and socioeconomic status be reasonably representative of expected North American clientele. The normative EEG database is made up of 58.9% males, 41.1% females, 71.4% whites, 24.2% blacks and 3.2% oriental. Socioeconomic status (SES) was measured by the Hollingshead four factor scale (details of all tests and criteria are published in Thatcher, R. W., McAlaster, R., Lester, M. L., Horst, R. L. & Cantor, D.S. (1983). Hemispheric EEG asymmetries related to cognitive functioning in

children. In A. Perecuman (Ed.), *Cognitive processing in the right hemisphere* (pp. 125-145). New York: Academic Press and Thatcher, R. W., Walker, R. A. & Guidice, S. (1987). Human cerebral hemispheres develop at different rates and ages. *Science*, 236, 1110-1113.

The steps involved in the cross-validation of the normative reference database and the clinical validation of the database by correlation with neuropsychological test scores is shown in figure 2 below:

Normative Database Validation Steps

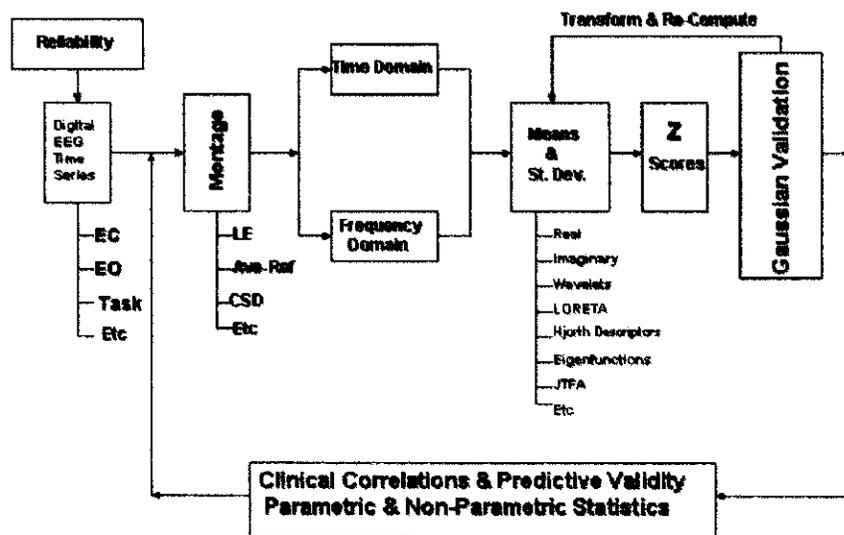
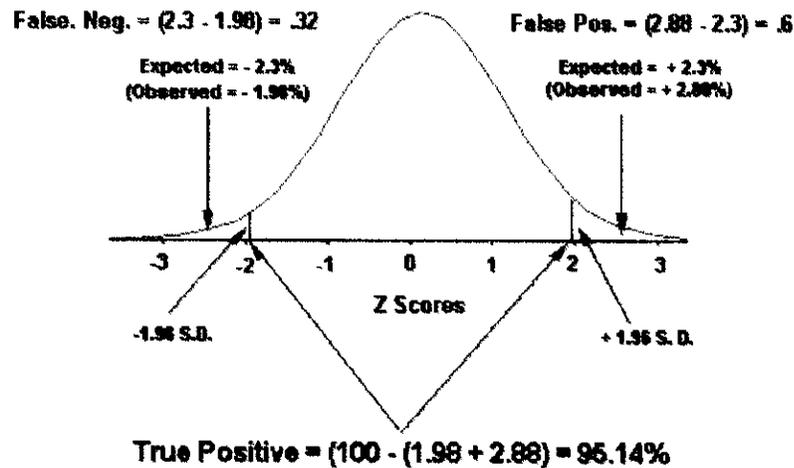


Figure 2 (above) is an illustration of the step by step procedures that were used to Gaussian cross-validate using a leave-one-out validation procedure and then by correlations with clinical measures in order to estimate the predictive and content validity of any EEG normative database. The feedback connections between Gaussian cross validation and the means and standard deviations refers to transforms to approximate Gaussian if the non-transformed data is less Gaussian. The clinical correlation and validation arrow to the montage stage represents repetition of clinical validation to a different montage or reference or condition such as eyes-open and eyes-closed conditions. (published in Thatcher et al, *J. Neurotherapy*, 7(3/4): 87-121, 2003).

The normative reference EEG database values are well behaved and approximate a Gaussian or normal distribution. The results of the cross-validation tests are shown in Table I.

Sensitivity Based on Deviation from Gaussian
Cross-Validation Accuracy N = 625 Subjects



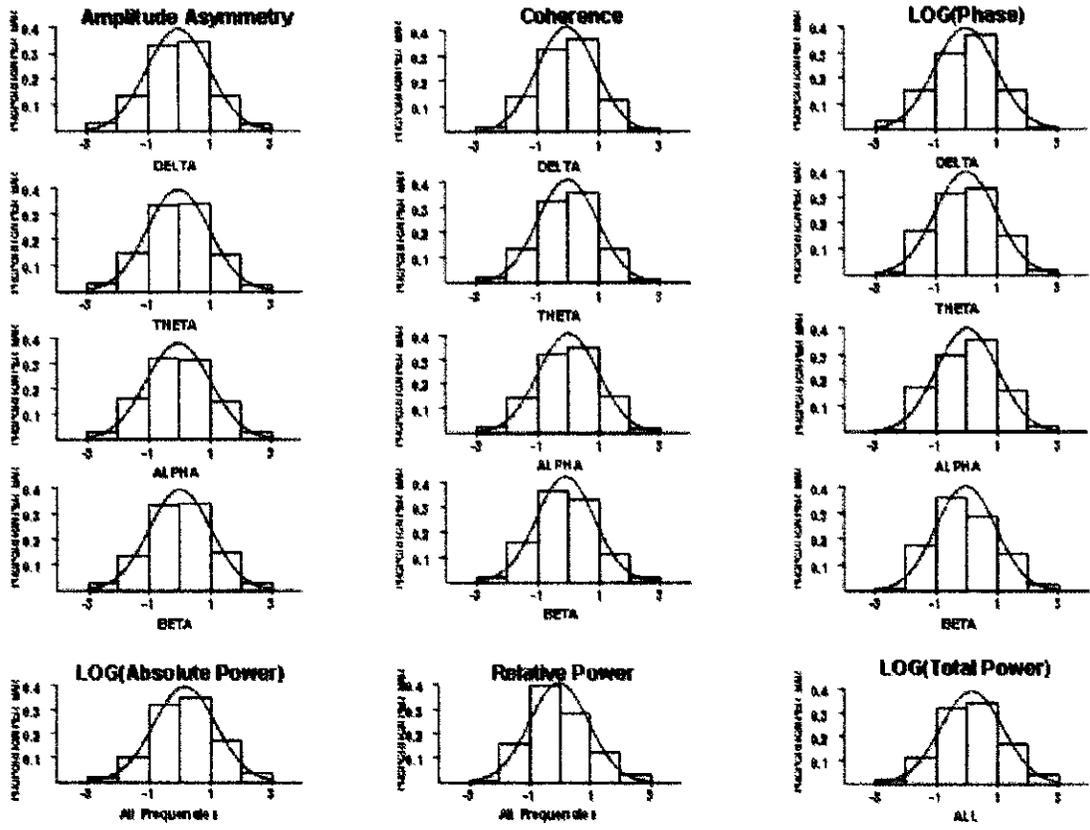
$$\text{Sensitivity} = \frac{TP}{TP + (FP + FN)} = \frac{95.14}{95.14 + 1.0} = 98.96\%$$

$$\text{Specificity} = \frac{TN}{TN + (FP + FN)} = \text{Undefined}$$

Figure 3 above is an illustration of the leave-one-out validation procedure with respect to a normal curve showing values of Z (± 1.96), which includes the proportion which is .95 of the total area. The left and right tails of the distribution show probability values of .025 (one-tailed). The results of the cross-validation of 625 subjects showed a classification accuracy that was normally distributed with 2.28% of the Z-scores $> \pm 2$ standard deviations (SD) and 0.16% of the Z-scores $> \pm 3$ SD. The clinical evaluation of EEG measures rely upon such a normal distribution by estimating the probability of finding an observed EEG value in a given range of a normal population and then empirically testing the sensitivity of the database by cross-validation.

Figure 4 below are histograms of the Z-Score cross-validation for all ages. Measures of skewness and kurtosis and tests of Gaussian demonstrated that the Neuroguide normative reference database approximates a Gaussian distribution and thus meets the statistical criteria for a normal distribution as shown in Figure 3.

Cross-Validation Birth to 82 Year EEG Normative Database



FFT Normative Database Sensitivities

2 STDEVs	CALC SENSITIVITY: $FP=TP/(TP+FP)$ or $FN=TP/(TP+FN)$			
AGES	(+/- 2 SD)	(>= 2 SD)	(<= -2 SD)	
0-5.99	0.95448265	0.9771774	0.97730526	+/- 2 Std. Dev.
6-9.99	0.95440363	0.9772031	0.97720054	
10-12.99	0.9543997	0.97724346	0.97715624	
13-15.99	0.95440512	0.97723601	0.97716911	
16-ADULT	0.9543945	0.97718143	0.97721307	
ALL	0.95442375	0.97720714	0.97721661	

3 STDEVs	CALC SENSITIVITY: $FP=TP/(TP+FP)$ or $FN=TP/(TP+FN)$			
AGES	(+/- 3 SD)	(>= 3 SD)	(<= -3 SD)	
0-5.99	0.99743698	0.99871123	0.99872774	+/- 3 Std. Dev.
6-9.99	0.99744112	0.99871611	0.99872601	
10-12.99	0.99744688	0.99873171	0.99871516	
13-15.99	0.99743186	0.99871951	0.99871234	
16-ADULT	0.99743635	0.99870216	0.99873619	
ALL	0.99744002	0.99871716	0.99872266	

Table I above shows the results of the cross-validation tests of the normative reference database (published in Thatcher, R.W., Walker, R.A., Biver, C., North, D., Curtin, R., Quantitative EEG Normative databases: Validation and Clinical Correlation, J. Neurotherapy, 7 (No. 3/4): 87 – 122, 2003).

Figure 5 below is an example of 1 Hz resolution color topographic maps of Z scores computed using the same equations and methods as in Figure 3 and Table I.

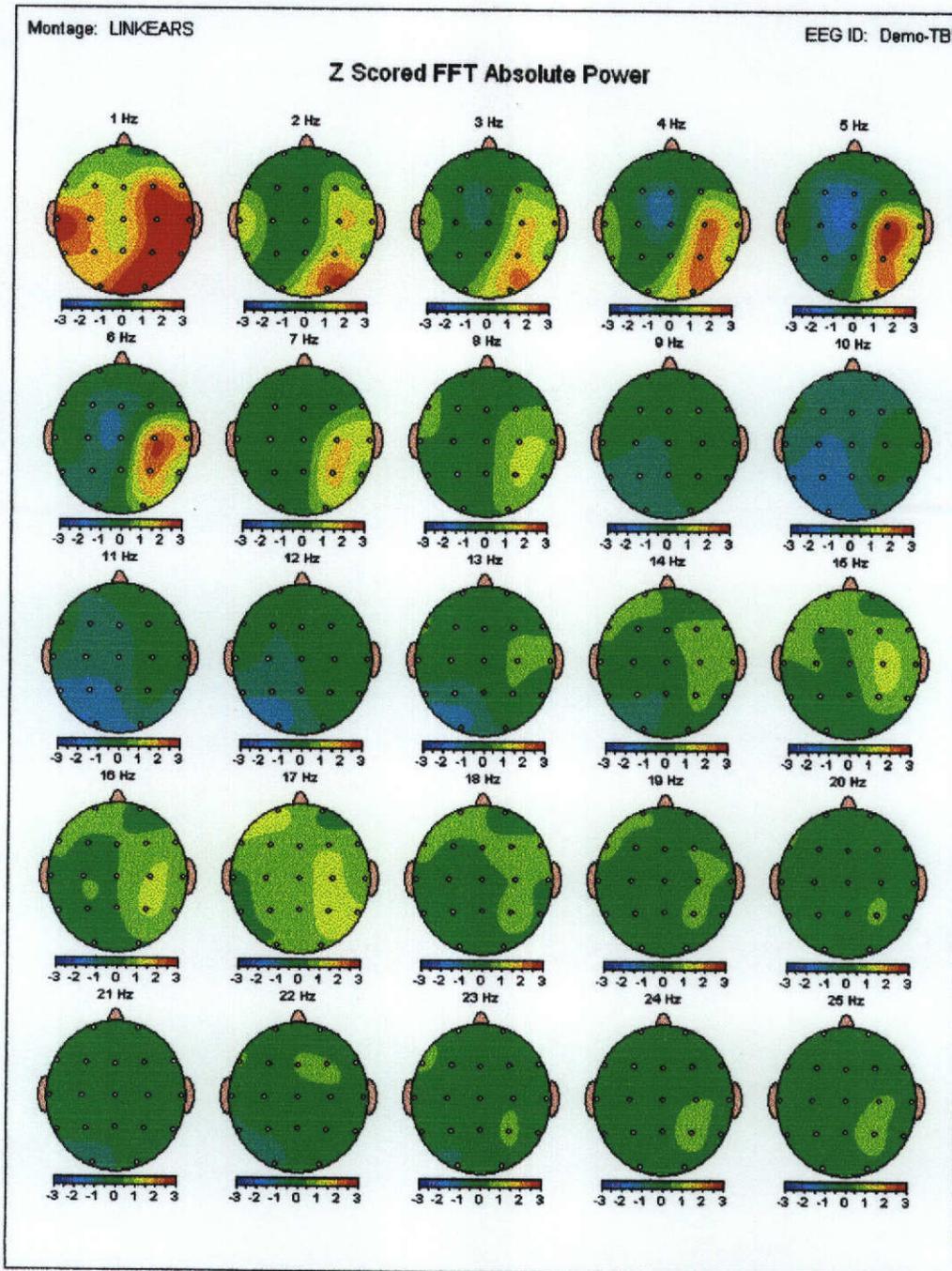


Figure 6 below are the Receiver Operating Characteristic curves (ROC) for the traumatic brain injury discriminant function and severity index which also used the normative reference database. The ROC provides an estimate of false positive and false negative classification rates for the detection of patterns in the EEG that are commonly present in individuals who have suffered a traumatic brain injury. The discriminant functions have been independently cross-validated and published in the peer review literature in Thatcher, R.W., Walker, R.A., Gerson, I. and Geisler, F. EEG discriminant analyses of mild head trauma. EEG and Clin. Neurophysiol., 73: 93-106, 1989 and Thatcher, R.W., North, D., Curtin, R., Walker, R.A., Biver, C., J.F. Gomez M., and Salazar, A. An EEG Severity Index of Traumatic Brain Injury, J. Neuropsychiatry and Clinical Neuroscience, 13(1): 77-87, 2001.

Sensitivity-Specificity (ROC) of Traumatic Brain Injury Discriminant Functions

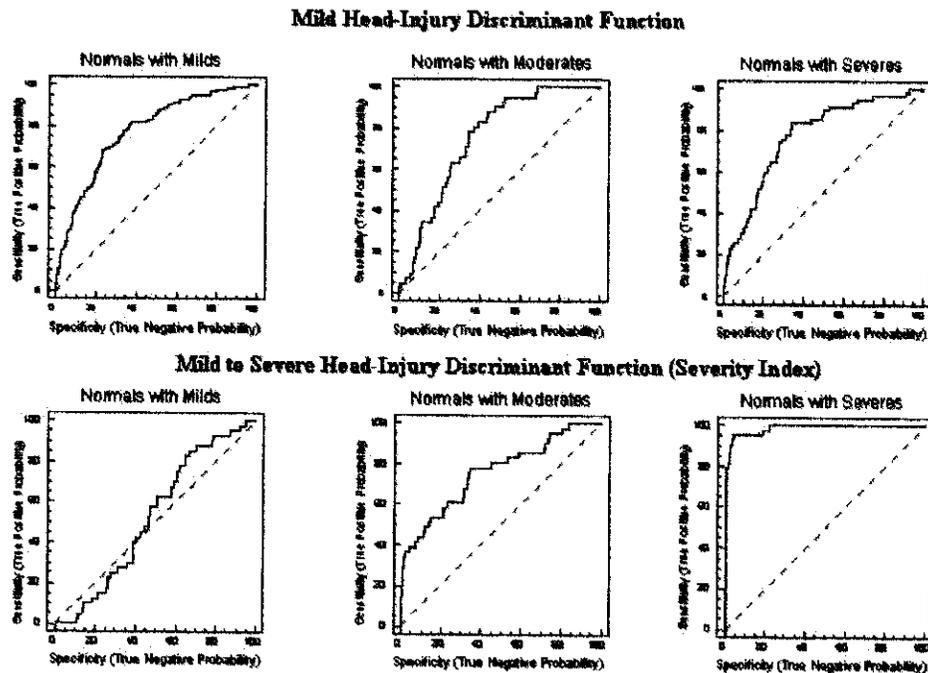


Table II shows the Pearson Product-moment correlation results, mild vs. severe EEG discriminant scores, compared with hospital admission information. This table shows an example of clinical validation by correlation with TBI severity measures

Variable	Correlation	P Values
Loss of consciousness	0.561	0.001
Posttraumatic amnesia	0.169	NS
Glasgow Coma Score	-0.853	0.001

From Thatcher, R.W., North, D., Curtin, R., Walker, R.A., Biver, C., J.F. Gomez M., and Salazar, A. An EEG Severity Index of Traumatic Brain Injury, J. Neuropsychiatry and Clinical Neuroscience, 13(1): 77-87, 2001.

Figure 7 below is an example of the neuroguide software display of the discriminant functions in which all of the variables that are used in the analysis are displayed for the user so that one can verify and validate which variables are most deviant and most contributory to a given predicted classification. The discriminant function is used as a pattern recognition program to provide a probability of the detection of a pattern in the EEG that is commonly present in clinically confirmed TBI patients. The discriminant functions are not intended to render a diagnosis, instead they are intended to provide information to a competent professional as to whether or not there is a pattern in the EEG that is associated with TBI. A warning is given to users of the discriminant analysis that this analysis is not intended to diagnose a patient, but rather is an adjunct to other measures and is to be used to confirm and disconfirm hypotheses and to evaluate which aspects of the EEG patterns are contributing to the classification prediction. The wording of the warning is contained in the output page for the discriminant function and it is as follows: "The Discriminant Analysis and Severity estimate are to be used by experienced and qualified professionals for the post-hoc statistical evaluation of the human electroencephalogram (EEG). The Discriminant Analysis and Severity estimate are to be viewed as an adjunct to the evaluation of the patient and they do not serve as a primary basis for a diagnosis. Warning: Inclusion criteria include a history of traumatic brain injury and greater than 13 years of age must be adhered to."

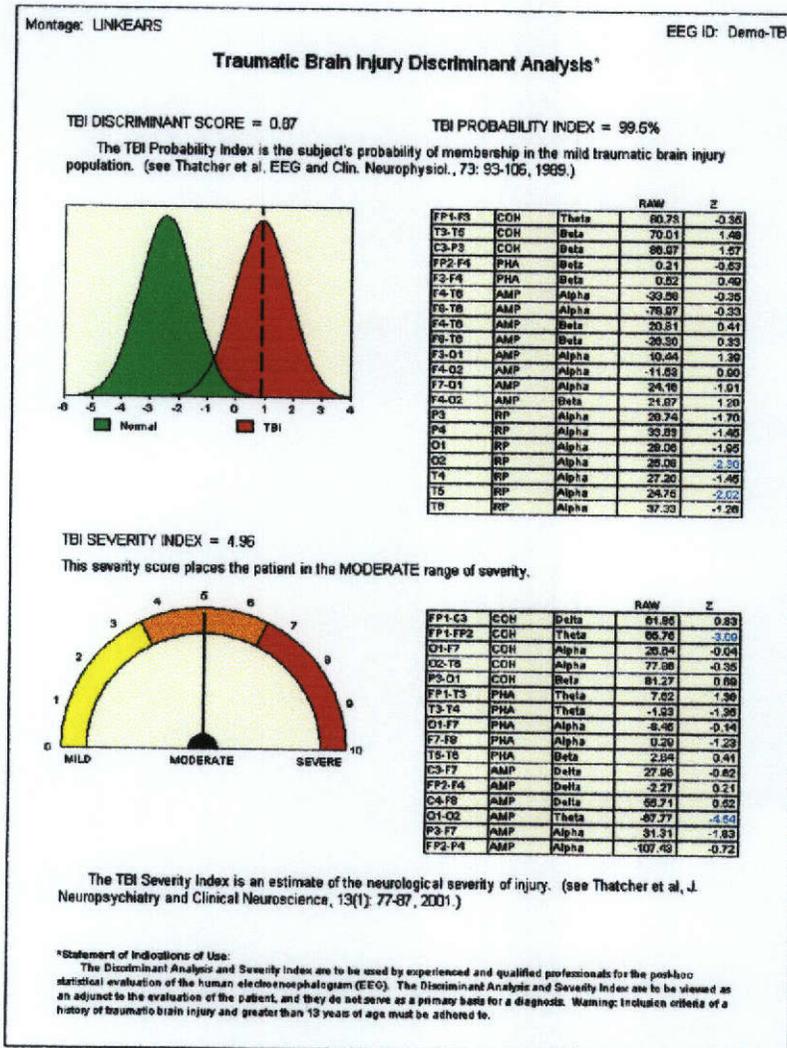


Table III below is an example of the clinical validation of the traumatic brain injury severity index or severity estimate.

TABLE V

Correlation Results: MILD .vs. SEVERE of EEG_Discriminant Scores .vs. NeuroPsych Tests		
Pearson Product-Moment Correlation	Correlation	Probability
WAIS TEST-Scaled Scores		
Vocabulary	-0.416	0.06
Similarities	-0.640	0.001
Picture Arrangement	-0.576	0.01
Performance	-0.504	0.01
Digit Symbol	-0.524	0.01
BOSTON NAMING TEST		
# of Spontaneous Correct Responses	-0.482	0.05
WORD FLUENCY TEST-Total Correct Words		
COWA	-0.568	0.01
Animals	-0.630	0.001
Supermarket	-0.709	0.001
ATTENTION TEST-Raw Scores		
Trail Making A-Response Time	0.627	0.001
Trail Making B-Response Time	0.627	0.001
Stroop-Word	-0.427	0.05
Stroop-Color	-0.618	0.001
Stroop-Color+Word	-0.385	ns
WISC TEST-Executive Functioning-Raw Scores		
Perseverative Responses	0.408	0.05
% Concept Level Responses	-0.200	ns
Categories Completed	-0.187	ns
Design Fluency - # Originals	-0.454	0.05
Design Fluency - # Rule Violations	0.304	ns
WECHSLER MEMORY TEST-Raw Scores		
Logical Memory II	-0.382	ns
Visual Production II	-0.509	0.01
Digit Span (Forward+Backward)	-0.336	ns
Digit Span (Forward)	-0.225	ns
%-tile Rank Forward	-0.300	ns

QEEG Correlations with Cognitive Function in > 200 Long-Term Outcome TBI Patients (N's vary from 225 to 287 TBI subjects, 2 months to 1,444 days)

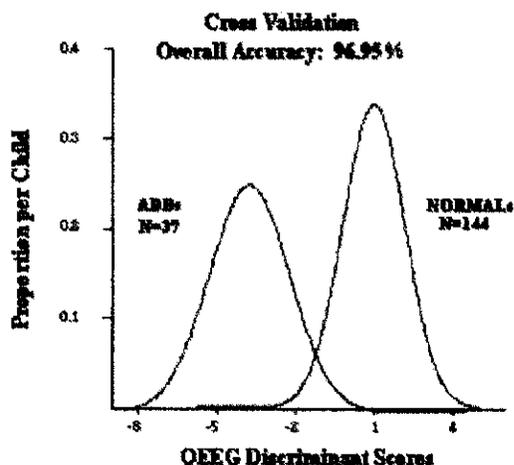
From J. Neuropsychiatry & Clin. Neurophysiol., Vol. 13:1, 77-87, 2001.

Table III above – The results of clinical validation analyses involving correlations between neuropsychological test performance and the TBI EEG discriminant function and severity index. From Thatcher, R.W., North, D., Curtin, R., Walker, R.A., Biver, C., J.F. Gomez M., and Salazar, A. An EEG Severity Index of Traumatic Brain Injury, *J. Neuropsychiatry and Clinical Neuroscience*, 13(1): 77-87, 2001. These analyses along with the correlations with the severity of injury upon admission to a hospital (Table II) were used for content validation of the NAS and users of the NAS can refer to the scientific published literature to verify that their procedures and results are in accordance with the standards published in the literature.

The learning disabilities discriminant function software is used to identify patterns in the EEG that are commonly present in individuals with a history of problems in school involving achievement test scores in reading, spelling and arithmetic. The discriminant function software is used as a pattern recognition program to provide a probability of the detection of a pattern in the EEG that is commonly present in clinically confirmed learning disabled children. The discriminant functions are not intended to render a diagnosis, instead they are intended to provide information to a competent professional as to whether or not there is a pattern in the EEG that is also present in a group of LD subjects. The presence or absence of a given pattern is not definitive and the discriminant analysis is only an adjunct to other clinical information and is not to be used as a sole diagnostic measure. The user of NAS is referred to the scientific literature and warned that the discriminant values are only an adjunct to visual analysis of the EEG

tracings to be used to confirm or reject hypotheses that may arise based on the patient's clinical history and other information.

A. Discriminant Function for Learning-Disabled Children with ADD



B. Sensitivity/Specificity of Learning-Disabled Discriminant Function with ADD

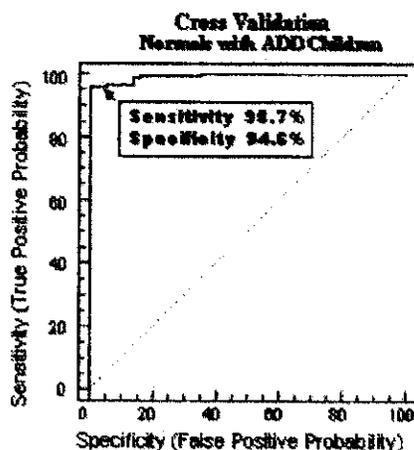


Figure 8 above – Receiver Operating Characteristic curves (ROC) for the learning disability discriminant function and severity index. The ROC provides an estimate of false positive and false negative classification rates for the detection of patterns in the EEG that are commonly present in individuals who are performing two grade levels or more below normal on reading, spelling and math school achievement tests. From Thatcher, R.W., North, D., Biver, C. EEG discriminant analyses of children with learning disabilities. International Society of Neuronal Regulation Annual Meeting.

Houston, Texas, September, 2003 and Thatcher, R.W., North, D., Biver, C. EEG analyses of children with learning disabilities. Eleventh Annual Future Health Congress, Palm Springs, California, February, 2004.

Figure 9 below is an example of the neuroguide display of the discriminant functions in which all of the variables that are used in the analysis are displayed for the user so that one can verify and validate which variables are most deviant and most contributory to a given predicted classification. The discriminant function is used as a pattern recognition program to provide a probability of the detection of a pattern in the EEG that is commonly present in clinically confirmed learning disabled children. The discriminant functions are not intended to render a diagnosis, instead they are intended to provide information to a competent professional as to whether or not there is a pattern in the EEG that is associated with LD. A warning is given to users of the discriminant analysis that this analysis is not intended to diagnose a patient, but rather is an adjunct to other measures and is to be used to confirm and disconfirm hypotheses and to evaluate which aspects of the EEG patterns are contributing to the classification prediction. The wording of the warning is contained in the output page for the discriminant function and it is as follows: “The Discriminant Analysis and Severity estimate are to be used by experienced and qualified professionals for the post-hoc statistical evaluation of the human electroencephalogram (EEG). The Discriminant Analysis and Severity estimate are to be viewed as an adjunct to the evaluation of the patient and they do not serve as a primary basis for a diagnosis. Warning: Inclusion criteria include no history of traumatic brain injury and greater than 6 years of age to adulthood must be adhered to.”

Montage: LINEARS

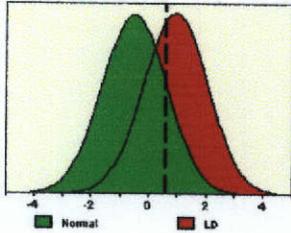
EEG ID: Demo-TBI

Learning Disability Discriminant Analysis*

LD DISCRIMINANT SCORE = 0.57

LD PROBABILITY INDEX = 66.0%

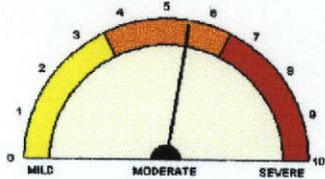
The Learning Disability Probability Index is the subject's probability of membership in the Learning Disability (LD) population.



			RAW	Z
F8	RATIO	T/B	1.03	-0.38
F3	JAP	Theta	8.31	-0.48
C8-C4	AMP	Theta	-100.98	-10.35
F7-T8	AMP	Alpha	-88.67	-9.02
T8-O2	CDM	Theta	20.36	-0.12
T8-Fz	CDM	Alpha	34.04	0.70
FP1-T5	PHA	Beta	-21.00	-0.88
T4-T8	PHA	Delta	0.25	-0.13
F8-T8	PHA	Delta	-8.08	-0.12
T4-Pz	PHA	Theta	-2.85	-1.24
FP1-Pz	PHA	Delta	-27.67	-0.93
F8-Pz	PHA	Beta	0.00	-0.29
C3-O2	PHA	Alpha	-18.38	-0.25
FP1-F4	PHA	Alpha	-0.22	0.00

LD SEVERITY INDEX = 5.50

This severity score places the patient in the MODERATE range of severity.



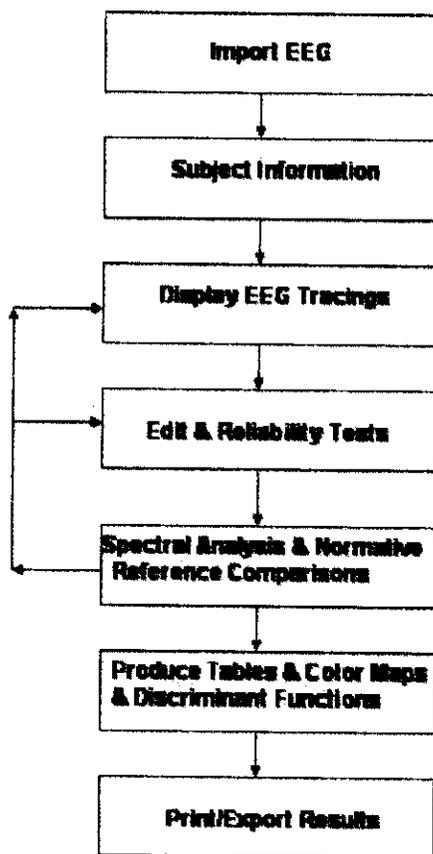
The LD Severity Index is an estimate of the neurological severity of Learning Disability.

***Statement of Indications of Use:**

The Discriminant Analysis and Severity Index are to be used by experienced and qualified professionals for the post-hoc statistical evaluation of the human electroencephalogram (EEG). The Discriminant Analysis and Severity Index are to be viewed as an adjunct to the evaluation of the patient, and they do not serve as a primary basis for a diagnosis. Warning: Inclusion criteria of no history of traumatic brain injury and age between 6 years and adulthood must be adhered to.

Section Number 3.5 - Architecture Design Chart

Neuroguide Architectural Design Chart



Section Number 3.9 - Validation, Verification and Testing

1- The software version number

Version 2.0 will be the version number for the first release. The version number and release date are shown upon launching the software and also by clicking Help > About NeuroGuide

2-Software Verification test plan with pass/fail criteria, data, and an analysis of the results.

2.2 – Pass/fail criteria for host amplifier calibration: Figure 10 below is an example of the calibration frequency responses of host EEG amplifier systems. A NeuroScan pocket trace EEG calibrator as well as a Grateful Head EEG calibrator were

used to inject 20 uV, 40 uV and 80 uV calibration sine wave signals into the amplifiers of Host EEG amplifier systems from 0 to 40 Hz and thus producing frequency response curves. Figure 10 below is an example of the frequency response curves using calibration microvolt sine waves to exactly match the frequency response of the normative database amplifier frequency characteristics.

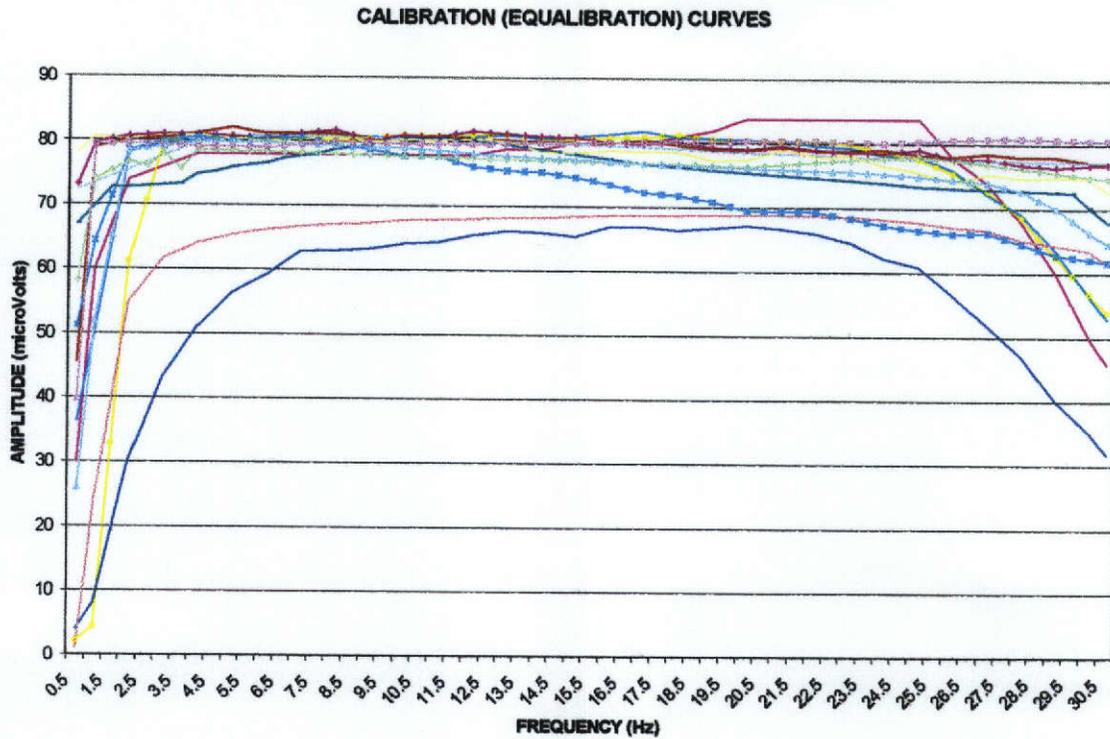
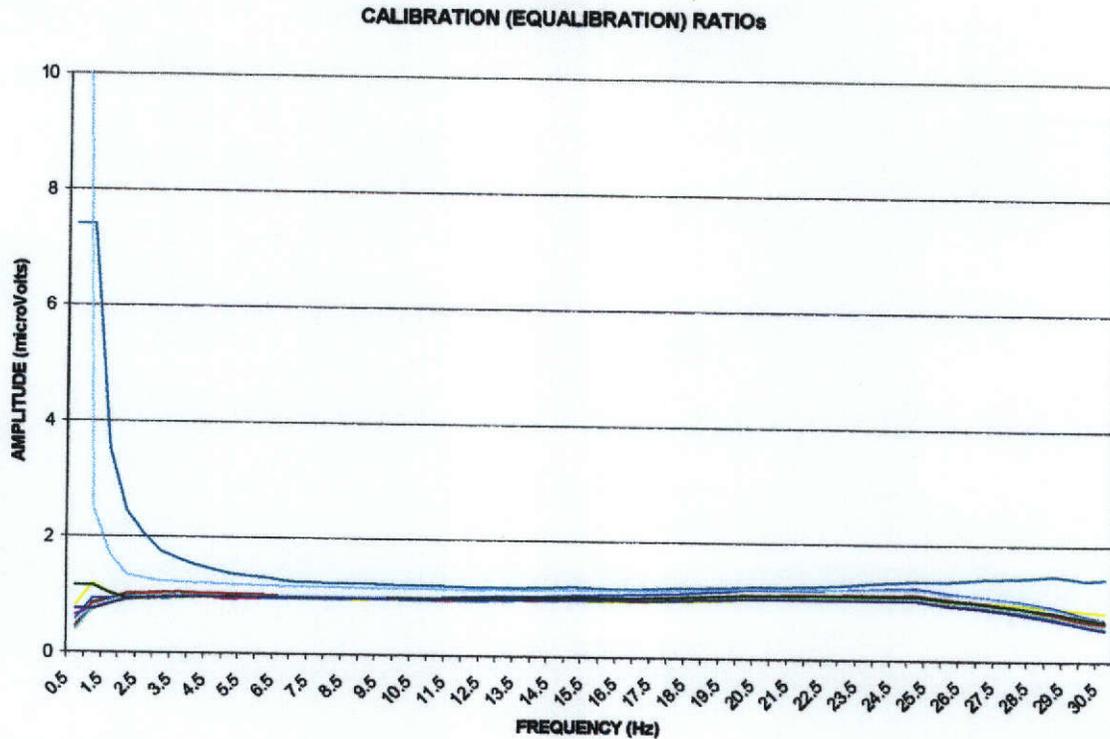


Figure 11 below is an example of the mathematical equilibration factors that are used to match the frequency characteristics of Host EEG amplifier systems to the normative database amplifier frequency characteristics.



Mathematical equilibration using the equilibration factors in figure 11 are an example of the verification and validation procedures used in Neuroguide to approximate as best as possible the Host EEG system to the NeuroGuide software. The pass criteria is met after the frequency characteristics of the host amplifier match the frequency characteristics of the normative database amplifiers.

2.3 – Pass/fail criteria for software calibration: Software verification is accomplished by the use of calibration sine waves of specific amplitudes, frequency, phase delays and with or without the mixture of Gaussian white noise. The pass/fail criteria are that an exact frequency match between the time domain and frequency domain must be achieved. If an exact match is not achieved then the test has failed.

Figure 12 below shows the user interface by which users select the verification calibration program inside of the NAS.

Verification Using Calibration Sine Waves

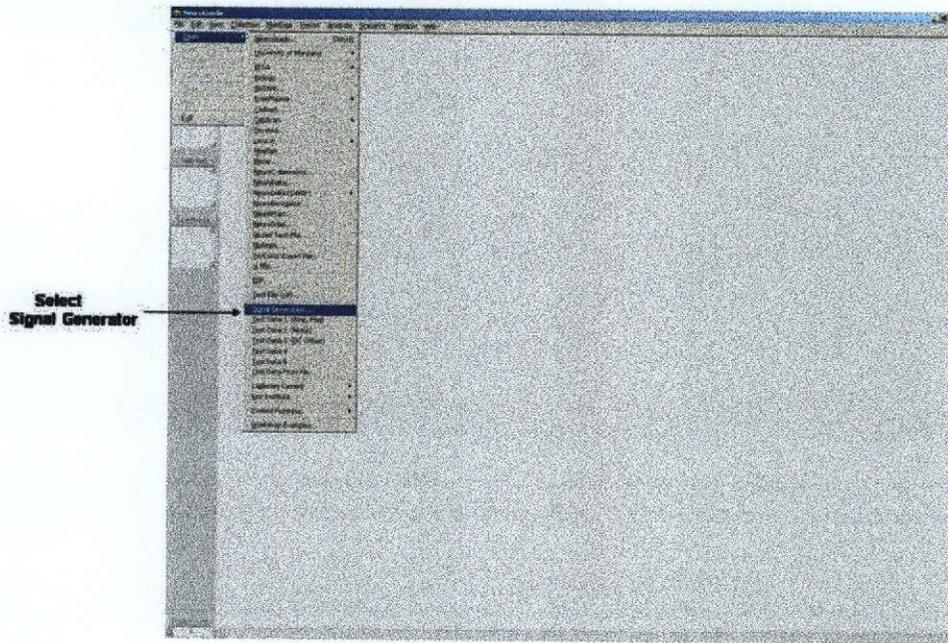
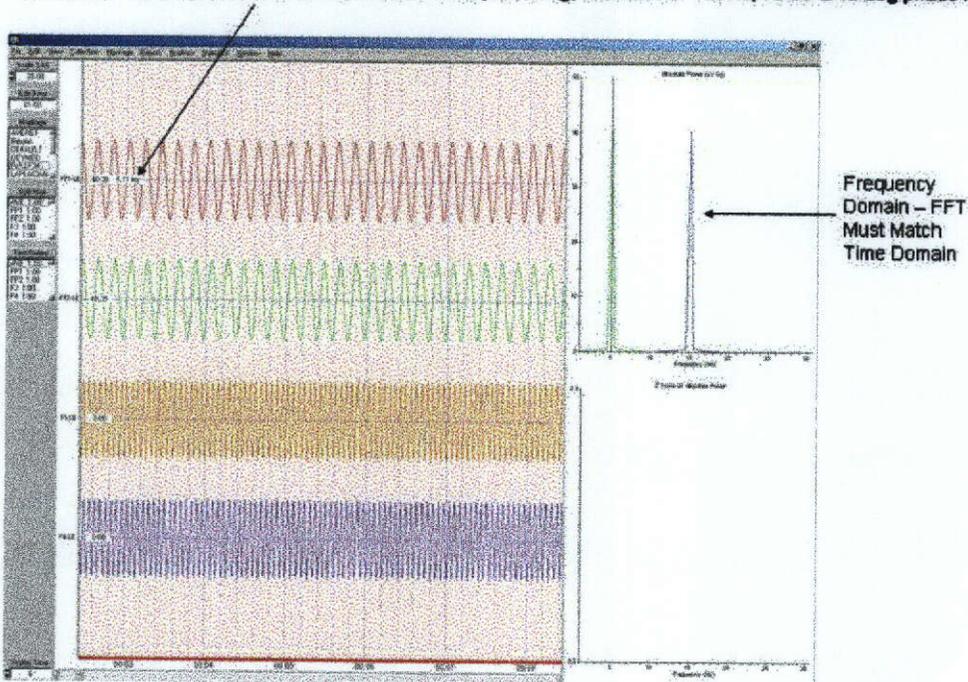


Figure 13 below shows an example of a sine wave verification test in which the fail/pass test is where the Time Domain = Frequency Domain.

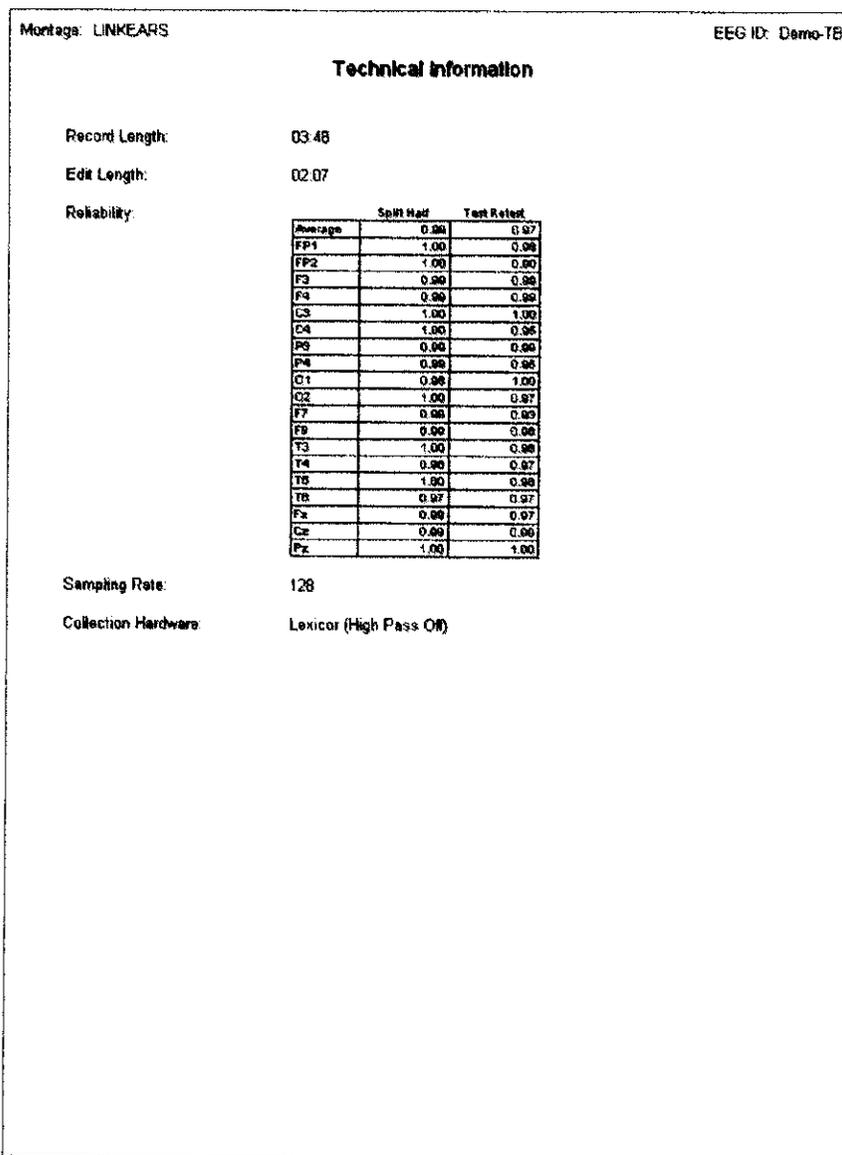
Verification Using Calibration Sine Waves – Channel Fp1 = 5 Hz 10 μ V & 0 phase lag, Channel Fp2 = 5 μ V & 45 deg. Phase lag, channel F3 = 15 Hz, 10 μ V & 0 phase lag, channel F4 = 15 Hz, 10 μ V & 45 deg phase lag



2.4 – Pass/fail criteria for multivariate discriminant analyses: The following pass/fail criteria must be met before the discriminant analyses will be computed: 1- EEG sample length must be ≥ 30 seconds; 2- eyes closed condition only; 3- test re-test and split-half reliability $\geq 90\%$; 4- age ≥ 13 for the TBI discriminant and ≥ 6 for the LD discriminant.

3- Software Validation and tests of reliability and validity

Figure 14 below is an example of the split-half and test re-test reliability statistics in which the criteria of $\geq 90\%$ reliability of the selected EEG segments is recommended. These statistics help validate the EEG selections and verify that artifact has been removed from the EEG selections. Short sample lengths of EEG and artifact result in reliabilities $< 90\%$. The reliability data are dynamically available in the EEG display screen to facilitate accurate editing and quality control in the selection of artifact free EEG.



The steps involved in the cross-validation of the normative reference database and the clinical validation of the database by correlation with neuropsychological test scores is shown in figure 15 (also Figure 2) below:

Normative Database Validation Steps

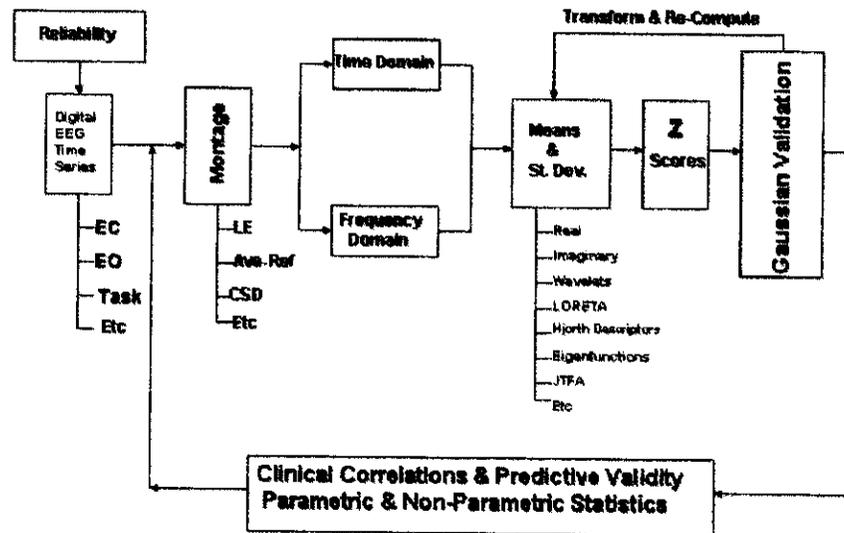
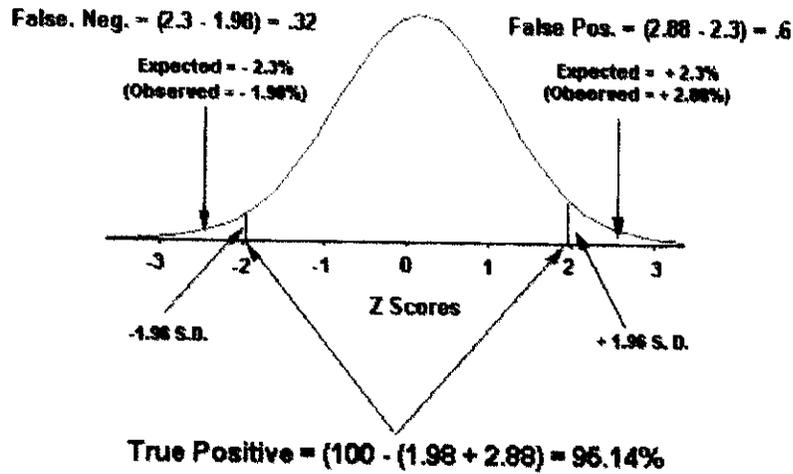


Figure 15 (above) is an illustration of the step by step procedures that were used to Gaussian cross-validate using a leave-one-out validation procedure and then by correlations with clinical measures in order to estimate the predictive and content validity of any EEG normative database. The feedback connections between Gaussian cross validation and the means and standard deviations refers to transforms to approximate Gaussian if the non-transformed data is less Gaussian. The clinical correlation and validation arrow to the montage stage represents repetition of clinical validation to a different montage or reference or condition such as eyes-open and eyes-closed conditions. (published in Thatcher et al, J. Neurotherapy, 7(3/4): 87-121, 2003). The normative reference EEG database values are well behaved and approximate a Gaussian or normal distribution. The results of the cross-validation tests are shown in Table I.

Sensitivity Based on Deviation from Gaussian
Cross-Validation Accuracy N = 625 Subjects



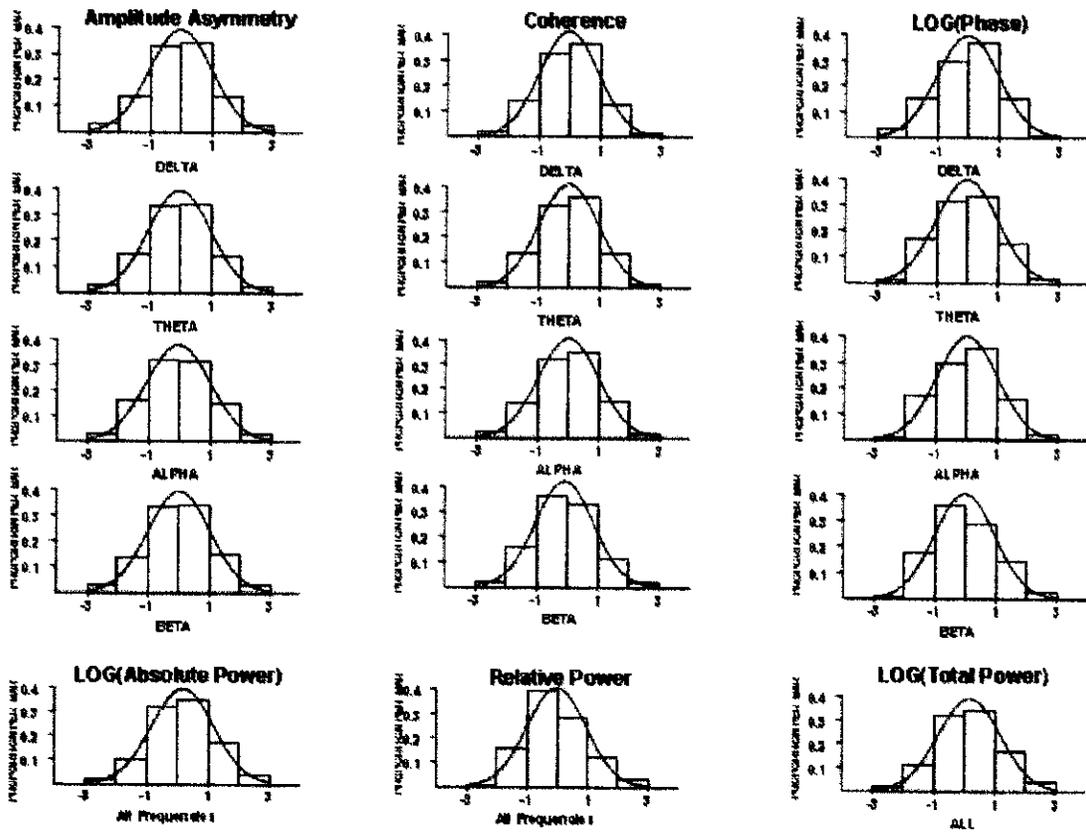
$$\text{Sensitivity} = \frac{TP}{TP + (FP + FN)} = \frac{95.14}{95.14 + 1.0} = 98.96\%$$

$$\text{Specificity} = \frac{TN}{TN + (FP + FN)} = \text{Undefined}$$

Figure 16 above (also figure 3) is an illustration of the leave-one-out validation procedure with respect to a normal curve showing values of Z (± 1.96), which includes the proportion which is .95 of the total area. The left and right tails of the distribution show probability values of .025 (one-tailed). The results of the cross-validation of 625 subjects showed a classification accuracy that was normally distributed with 2.28% of the Z-scores $> \pm 2$ standard deviations (SD) and 0.16% of the Z-scores $> \pm 3$ SD. The clinical evaluation of EEG measures rely upon such a normal distribution by estimating the probability of finding an observed EEG value in a given range of a normal population and then empirically testing the sensitivity of the database by cross-validation.

Figure 17 below (also figure 4) are histograms of the Z-Score cross-validation for all ages. Measures of skewness and kurtosis and tests of Gaussian demonstrated that the Neuroguide normative reference database approximates a Gaussian distribution and thus meets the statistical criteria for a normal distribution as shown in Figure 3.

Cross-Validation Birth to 82 Year EEG Normative Database



FFT Normative Database Sensitivities

2 STDEVs		CALC SENSITIVITY: $FP=TP/(TP+FP)$ or $FN=TP/(TP+FN)$		
AGES	(+/- 2 SD)	(>= 2 SD)	(<= -2 SD)	
0-5.99	0.95448265	0.9771774	0.97730526	+/- 2 Std. Dev.
6-9.99	0.95440363	0.9772031	0.97720054	
10-12.99	0.9543997	0.97724346	0.97715624	
13-15.99	0.95440512	0.97723601	0.97716911	
16-ADULT	0.9543945	0.97718143	0.97721307	
ALL	0.95442375	0.97720714	0.97721661	
3 STDEVs		CALC SENSITIVITY: $FP=TP/(TP+FP)$ or $FN=TP/(TP+FN)$		
AGES	(+/- 3 SD)	(>= 3 SD)	(<= -3 SD)	
0-5.99	0.99743698	0.99871123	0.99872774	+/- 3 Std. Dev.
6-9.99	0.99744112	0.99871611	0.99872501	
10-12.99	0.99744688	0.99873171	0.99871518	
13-15.99	0.99743186	0.99871951	0.99871234	
16-ADULT	0.99743635	0.99870216	0.99873619	
ALL	0.99744002	0.99871716	0.99872266	

Table I above shows the results of the cross-validation tests of the normative reference database (published in Thatcher, R.W., Walker, R.A., Biver, C., North, D., Curtin, R., Quantitative EEG Normative databases: Validation and Clinical Correlation, J. Neurotherapy, 7 (No. 3/4): 87 – 122, 2003).

Figure 18 below is an example of normative reference database validation that is an intrinsic part of the NAS software. The validity criteria are that different montages (linked ears, average reference and Laplacian) should yield comparable Z score distributions for different frequencies.

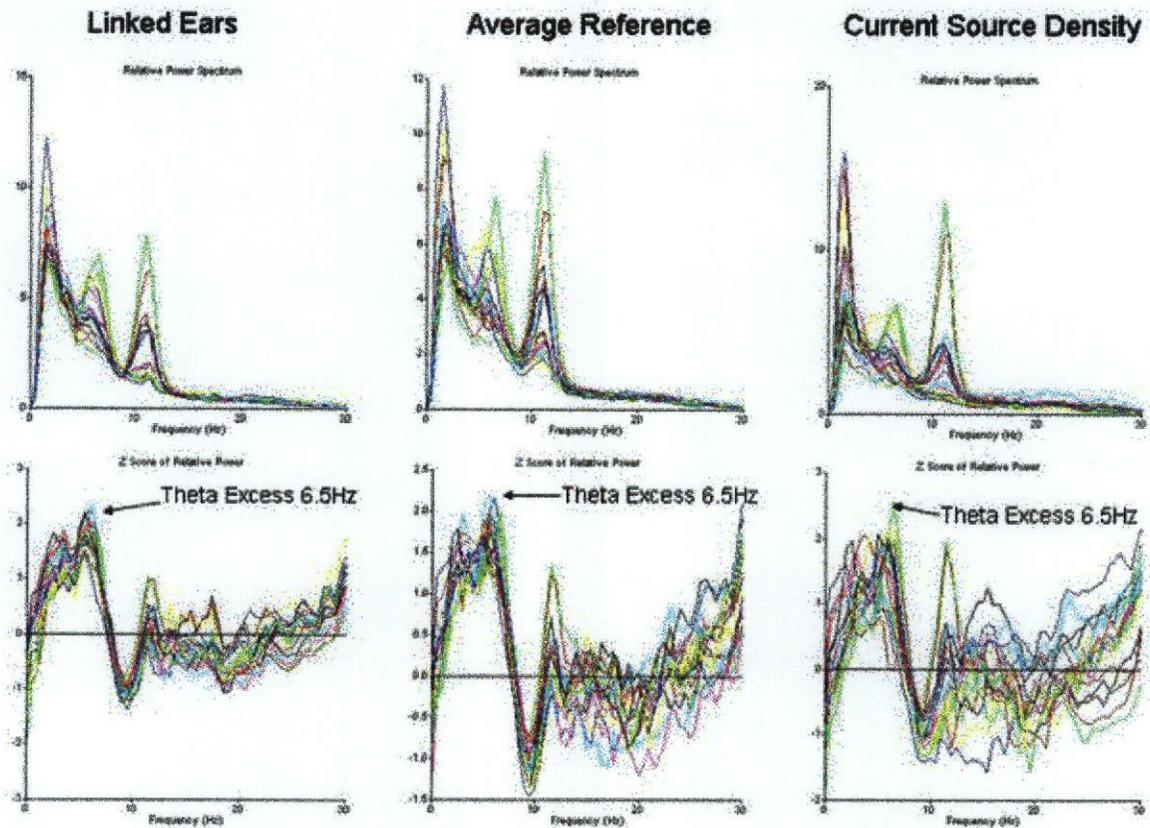


Figure 19 below are independent validation statistics using correlations between EEG and neuropsychological test scores. These statistics are also used to verify and validate the Neuroguide normative database. Figure 6 below is an example of the correlation between single EEG quantitative EEG measures and school achievement scores in normal children. (published in Thatcher, R.W., Walker, R.A., Biver, C., North, D., Curtin, R., Quantitative EEG Normative databases: Validation and Clinical Correlation, J. Neurotherapy, 7 (No. 3/4): 87 – 122, 2003).

Example of Content Validity of EEG Norms

Scatterplots of Amp. Asymmetry with IQ & School Achievement Tests Measures $P < .0001$

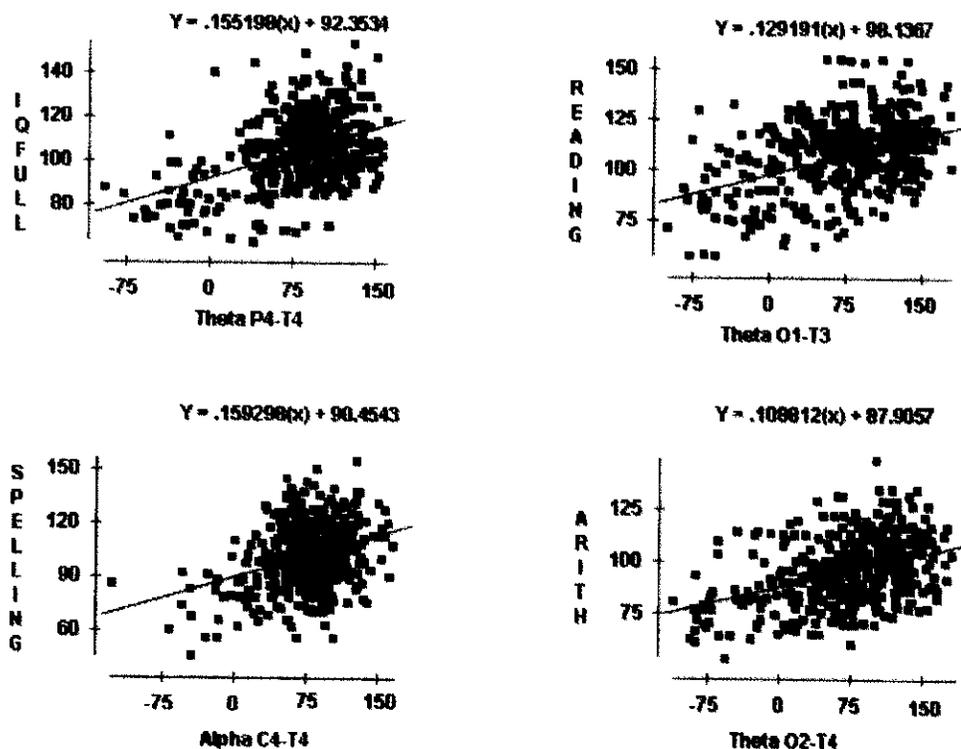


Figure 20 below are additional validation of the norms which are the correlations between multivariate EEG regressions and performance on neuropsychological tests in the normative reference database subjects. These measures are used in the neuroguide analysis system to produce predicted neuropsychological test scores as an adjunct to other measures and not to replace neuropsychological tests. Predictive validity by correlation to clinical measures and neuropsychological tests is useful for the user of any quantitative EEG system. (published in Thatcher, R.W., Walker, R.A., Biver, C., North, D., Curtin, R., Quantitative EEG Normative databases: Validation and Clinical Correlation, J. Neurotherapy, 7 (No. 3/4): 87 – 122, 2003).

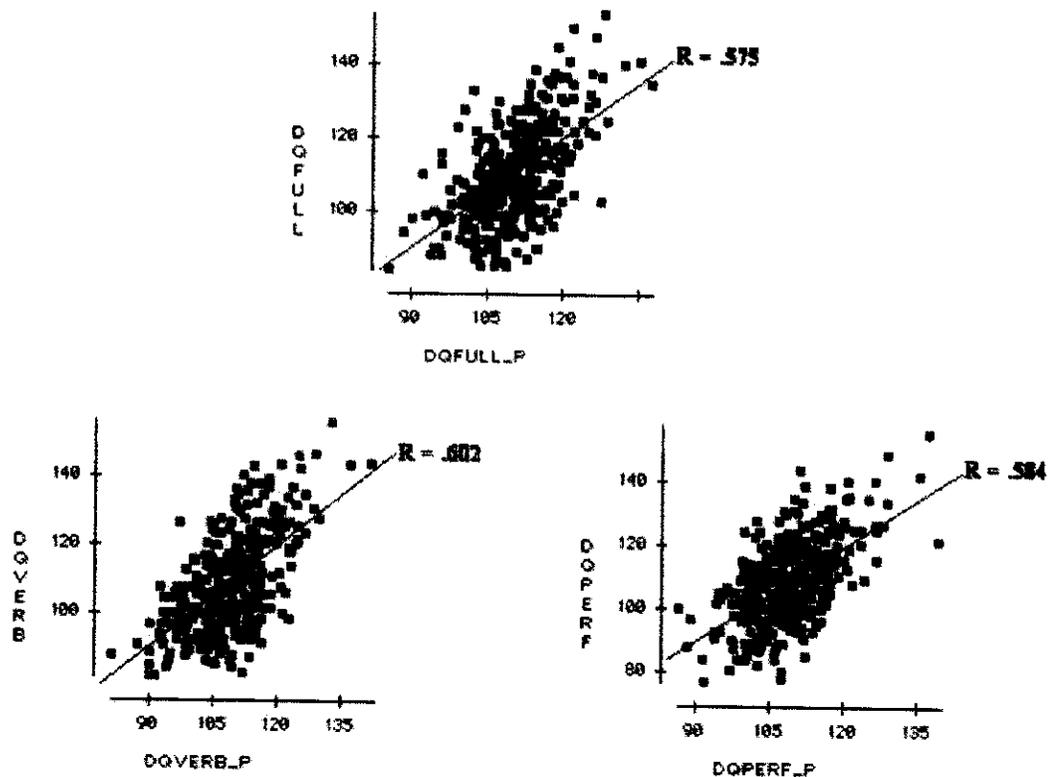
Correlation Between the Predicted vs. the Raw IQ Scores @ P < .0001 using NORMs Only

Figure 21 below are the Receiver Operating Characteristic curves (ROC) for the traumatic brain injury discriminant function and severity index which also used the normative reference database. The ROC provides an estimate of false positive and false negative classification rates for the detection of patterns in the EEG that are commonly present in individuals who have suffered a traumatic brain injury. The validity of the discriminant for the detection of a pattern commonly present in the EEG is seen in Figure 19 in which the top row is the “yes/no” detection of a pattern in the EEG independent of the severity of injury while the bottom row are the ROC curves of the severity index which steadily increase as a function of the severity of TBI. The discriminant functions have been independently cross-validated and published in the peer review literature in Thatcher, R.W., Walker, R.A., Gerson, I. and Geisler, F. EEG discriminant analyses of mild head trauma. *EEG and Clin. Neurophysiol.*, 73: 93-106, 1989 and Thatcher, R.W., North, D., Curtin, R., Walker, R.A., Biver, C., J.F. Gomez M., and Salazar, A. An EEG Severity Index of Traumatic Brain Injury, *J. Neuropsychiatry and Clinical Neuroscience*, 13(1): 77-87, 2001.

Sensitivity-Specificity (ROC) of Traumatic Brain Injury Discriminant Functions

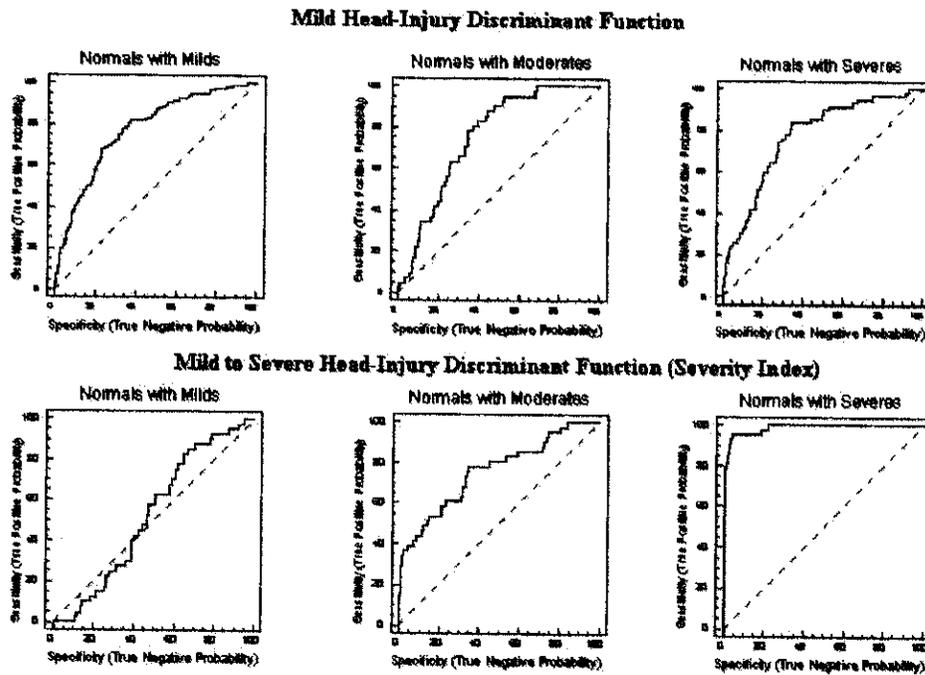


Figure 22 below is another example of verification and validation of the TBI pattern recognition discriminant for the evaluation of the severity of TBI in clinically confirmed TBI patients whose EEG was measured obtained from four different VA hospitals (Minneapolis, Tampa, Richmond VA & Palo Alto, CA) and three different military bases (Walter Reed Army, Balboa Naval Hospital & Wilford Hall Air Force). These measures were used as a part of the standard of care in the evaluation of TBI in these patients. The severity of TBI was greater in the VA hospital patients than in the military hospital patients as determined by standard clinical workups and neuropsychological tests. Verification and validation of the ability of the EEG discriminant to detect a pattern in the EEG that is correlated to the severity of injury is shown in Figure 21 for 505 TBI patients. From Thatcher, R.W., North, D., Curtin, R., Walker, R.A., Biver, C., J.F. Gomez M., and Salazar, A. An EEG Severity Index of Traumatic Brain Injury, *J. Neuropsychiatry and Clinical Neuroscience*, 13(1): 77-87, 2001.

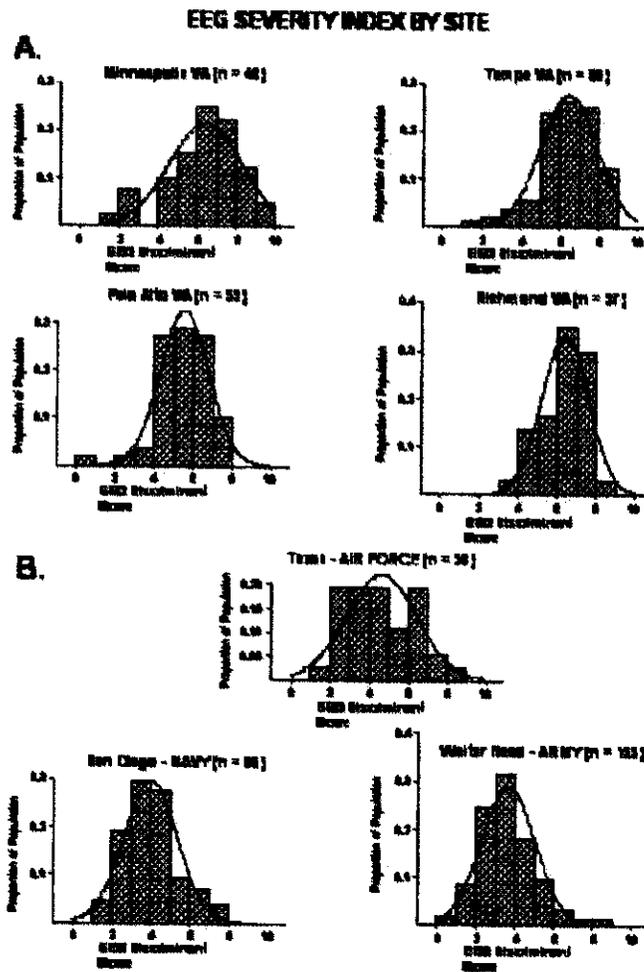


Table IV (same as Table II) shows the Pearson Product-moment correlation results, mild vs. severe EEG discriminant scores, compared with hospital admission information. This table shows an example of clinical validation by correlation with TBI severity measures

Variable	Correlation	P Values
Loss of consciousness	0.561	0.001
Posttraumatic amnesia	0.169	NS
Glasgow Coma Score	-0.853	0.001

From Thatcher, R.W., North, D., Curtin, R., Walker, R.A., Biver, C., J.F. Gomez M., and Salazar, A. An EEG Severity Index of Traumatic Brain Injury, *J. Neuropsychiatry and Clinical Neuroscience*, 13(1): 77-87, 2001.

Table III below is an example of the clinical validation of the traumatic brain injury severity index or severity estimate.

TABLE V

Correlation Results: MILD .vs. SEVERE of EEG_Discriminant Scores .vs. NeuroPsych Tests		
Pearson Product-Moment Correlation	Correlation	Probability
WAIS TEST-Scated Scores		
Vocabulary	-0.416	0.05
Similarities	-0.640	0.001
Picture Arrangement	-0.576	0.01
Performance	-0.504	0.01
Digit Symbol	-0.524	0.01
BOSTON NAMING TEST		
# of Spontaneous Correct Responses	-0.482	0.05
WORD FLUENCY TEST-Total Correct Words		
COWA	-0.568	0.01
Animals	-0.630	0.001
Supermarket	-0.709	0.001
ATTENTION TEST-Raw Scores		
Trail Making A-Response Time	0.627	0.001
Trail Making B-Response Time	0.627	0.001
Stroop-Word	-0.427	0.05
Stroop-Color	-0.618	0.001
Stroop-Color+Word	-0.385	ns
WISC TEST-Executive Functioning-Raw Scores		
Perseverative Responses	0.408	0.05
% Concept Level Responses	-0.200	ns
Categories Completed	-0.187	ns
Design Fluency - # Originals	-0.454	0.05
Design Fluency - # Rule Violations	0.304	ns
WECHSLER MEMORY TEST-Raw Scores		
Logical Memory II	-0.382	ns
Visual Production II	-0.509	0.01
Digit Span (Forward+Backward)	-0.336	ns
Digit Span (Forward)	-0.225	ns
%-tile Rank Forward	-0.300	ns

QEEG Correlations with Cognitive Function in > 200 Long-Term Outcome TBI Patients (N's vary from 225 to 287 TBI subjects, 2 months to 1,444 days)

From *J. Neuropsychiatry & Clin. Neurophysiol.*, Vol. 13:1, 77-87, 2001.

Table V above (same as Table III) – The results of clinical validation analyses involving correlations between neuropsychological test performance and the TBI EEG discriminant function and severity index. From Thatcher, R.W., North, D., Curtin, R., Walker, R.A., Biver, C., J.F. Gomez M., and Salazar, A. An EEG Severity Index of Traumatic Brain Injury, *J. Neuropsychiatry and Clinical Neuroscience*, 13(1): 77-87, 2001. These analyses along with the correlations with the severity of injury upon admission to a hospital (Table II) were used for content validation of the NAS and users of the NAS can refer to the scientific published literature to verify that their procedures and results are in accordance with the standards published in the literature.

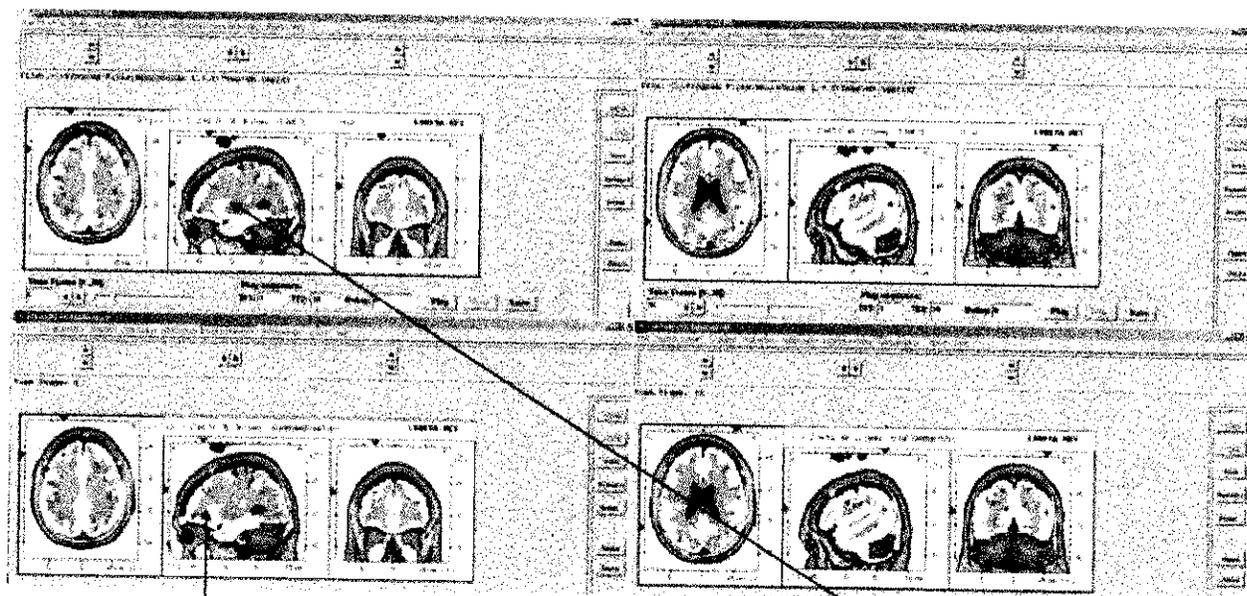
4- Example of Verification and validation of off-the-shelf Low Resolution Electromagnetic Tomography (LORETA) software

Figure 23 below is an example of how the Neuroguide software can be validated when used with off-the-shelf software. The example is the software algorithms used by the off-the-shelf Key Institute LORETA program in which validation and verification are accomplished by comparing ASCII time domain EEG data to the frequency domain in the off-the-shelf software.

Examples of Verification of Key Institute Cross-Spectral Equations

6 Hz Calibration – F3

16 Hz Calibration – P4



Bottom Row are Key Institute Cross Spectra of Exported ASCII data

Top Row are NeuroGuide Cross Spectra Of the Same ASCII Data

The Key Institute off-the-shelf software only an example of how users can verify and validate by exporting time series and frequency domain data to any off-the-shelf EEG spectral analysis software programs in order to confirm or validate. The universal and mathematical standard is the microvolt as defined by the laws of physics. Neuroguide software does not diagnose and only facilitates access to off-the-shelf software and the use of LORETA or any other off-the-shelf source localization program is at the discretion of the user and requires training and expertise. Validation by matching time domain values to frequency domain values in different host systems is an efficient and good validation procedure.

Section Number 3.12 - Version number and date for all levels of concern

The version number and revision date is displayed when the NAS is launched and by clicking Help > About NeuroGuide.