*******NOTICE OF GRANT AWARD***************
RESEARCH
Department of Health and Human Services
National Institutes of Health

NATIONAL INSTITUTE OF NEUROLOGICAL DISORDERS AND STROKE

Grant Number: 2 R01 NS034086-10
Principal Investigator: HSIAO, STEVEN S PHD
Project Title: Attention and Tactile Processing in Somatosensory Cortex

SPOND PROJECTS OFFICER
JOHNS HOPKINS UNIVERSITY
3400 N CHARLES STREET
Baltimore, MD 21218
UNITED STATES
Award e-mailed to: NIH@RESOURCE.CA.JHU.EDU

Project Period: 09/30/1995 - 02/28/2010

Dear Business Official:

The National Institutes of Health hereby awards a grant in the amount of $493,781 (see 'Award Calculation' in Section I) to JOHNS HOPKINS UNIVERSITY in support of the above referenced project. This award is pursuant to the authority of 42 USC 241 42 CFR 52 and is subject to terms and conditions referenced below.

Acceptance of this award including the Terms and Conditions is acknowledged by the grantee when funds are drawn down or otherwise obtained from the grant payment system.

Award recipients are responsible for reporting inventions derived or reduced to practice in the performance of work under this grant. Rights to inventions vest with the grantee organization provided certain requirements are met and there is acknowledgement of NIH support. In addition, recipients must ensure that patent and license activities are consistent with their responsibility to make unique research resources developed under this award available to the scientific community, in accordance with NIH policy. For additional information, please visit http://www.iedison.gov.

If you have any questions about this award, please contact the individual(s) referenced in the information below.

Sincerely yours,
Rita Sisco
Grants Management Officer
NATIONAL INSTITUTE OF NEUROLOGICAL DISORDERS AND STROKE

See additional information below

SECTION I - AWARD DATA - 2 R01 NS034086-10

AWARD CALCULATION (U.S. Dollars):

Salaries and Wages $200,543
Fringe Benefits $54,265
Personnel Costs $254,808
Supplies $30,625
Travel Costs $4,375
Other Costs $13,125
Federal Direct Costs $302,933
Federal F&A Costs $190,848
APPROVED BUDGET $493,781
TOTAL FEDERAL AWARD AMOUNT $493,781

Recommended future year total cost support, subject to the availability of funds and satisfactory progress of the project, is as follows:
11 $511,774
12 $570,440
13 $590,300
14 $610,159

FISCAL INFORMATION:
CFDA 93.853
Number: [Redacted]
EIN: [Redacted]
Document Number: RNS034086C

NS/8426310/ 493,781/ 511,774/ 570,440/ 590,300/ 610,159

NIH ADMINISTRATIVE DATA:
PCC: EDWARECN / OC: 41.4B / Processed: SISCOR 050513 0300

SECTION II - PAYMENT/HOTLINE INFORMATION - 2 R01 NS034086-10

For Payment and HHS Office of Inspector General Hotline Information, see the NIH Home Page at http://grants.nih.gov/grants/policy/awardconditions.htm

SECTION III - TERMS AND CONDITIONS - 2 R01 NS034086-10

This award is based on the application submitted to, and as approved by, the NIH on the above-titled project and is subject to the terms and conditions incorporated either directly or by reference in the following:
a. The grant program legislation and program regulation cited in this Notice of Grant Award.

b. The restrictions on the expenditure of federal funds in appropriations acts, to the extent those restrictions are pertinent to the award.

c. 45 CFR Part 74 or 45 CFR Part 92 as applicable.

d. The NIH Grants Policy Statement, including addenda in effect as of the beginning date of the budget period.

e. This award notice, INCLUDING THE TERMS AND CONDITIONS CITED BELOW.

(see NIH Home Page at http://grants.nih.gov/grants/policy/awardconditions.htm for certain references cited above.)

This grant is awarded under the terms and conditions of the Federal Demonstration Partnership Phase IV.

An unobligated balance may be carried over into the next budget period without Grants Management Officer prior approval.

This grant is subject to Streamlined Noncompeting Award Procedures (SNAP)

Treatment of Program Income:
Additional Costs

SECTION IV - NINDS SPECIAL TERMS AND CONDITIONS

This grant has been selected under the NINDS plan to redistribute grant workload more evenly throughout the year. Consequently, the budget period reflects a 02/28/2006 end date. Subsequent budget periods will begin on March 1, and will be for a 12-month duration. Although this grant will have a slightly shorter budget period this year, it is awarded the full 12-month level of funds for the budget period. Additional time may be requested at the end of the project period, if needed.

In order to meet Institute program objectives within Fiscal Year 2005 budget constraints, this grant is reduced to a level below that recommended. Future year levels of support are determined by applying an administrative reduction.

Total direct funds (salary, fringe benefits and tuition remission) for the graduate student are provided at the NIH maximum allowable level of $35,568 per year as outlined in the NIH Guide for Grants and Contracts, February 4, 2005. http://grants.nih.gov/grants/guide/notice-files/NOT-OD-04-023.html

Documents (other than future year non-competing continuation applications) applicable to this grant should be faxed to (301)451-5635 or mailed to:

Grants Management Branch
National Institutes of Neurological Disorders and Stroke
6001 Executive Boulevard, Suite 3290, MSC 9537
Rockville, MD 20852 (Express Mail)
Bethesda, MD 20892-9537 (Regular Mail)

Future year non-competing continuation applications should be submitted to the new centralized mailing address for all NIH Institutes/Centers:
The program official is responsible for the scientific, programmatic and technical aspects of this project. The grants management specialist is responsible for the negotiation, award and administration of this project and for interpretation of grants administration policies and provisions. These individuals work together in overall project management. Prior approval requests (countersigned by the PI & authorized business official) should be submitted in writing to the Grants Management Specialist. Requests may be made via e-mail provided they are routed through these same officials (listed below.) For additional information, you may access the NIH home page at http://www.nih.gov/ and the NINDS Home Page at http://www.ninds.nih.gov.

EMMELINE EDWARDS, Program Official
Phone: 301-496-9964 Email: ee48r@nih.gov Fax: 301-402-2060

Pamela L Mayer, Grants Specialist
Phone: 301-496-4207 Email: mayerp@mail.nih.gov Fax: 301-451-5635

SPREADSHEET
GRANT NUMBER: 2 R01 NS034086-10
P.I.: HSIAO, STEVEN S
INSTITUTION: JOHNS HOPKINS UNIVERSITY

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<th>YEAR 12</th>
<th>YEAR 13</th>
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F&A Costs 2

132,643  148,558

..........................END OF NGA..........................

http://query7.cit.nih.gov/projectnag.cfm?ApplId=6085200&requesttimeout=180

04/13/2008
1. TITLE OF PROJECT (Do not exceed 56 characters, including spaces and punctuation.)
   Attention and Tactile Processing in Somatosensory Cortex

2. RESPONSE TO SPECIFIC REQUEST FOR APPLICATIONS OR PROGRAM ANNOUNCEMENT OR SOLICITATION ☒ NO ☐ YES
   (If "Yes," state number and title)

3. PRINCIPAL INVESTIGATOR/PROGRAM DIRECTOR

   3a. NAME (Last, first, middle)
       Hsiao, Steven S

   3b. DEGREE(S)
       Ph.D, MS

   3c. POSITION TITLE
       Associate Professor

   3d. MAILING ADDRESS (Street, city, state, zip code)
       3400 N. Charles St.
       Baltimore, Maryland 21218

   3e. DEPARTMENT, SERVICE, LABORATORY, OR EQUIVALENT
       Krieger Mind/Brain Institute

   3f. MAJOR SUBDIVISION
       School of Arts and Science

   3g. TELEPHONE AND FAX (Area code, number and extension)

4. HUMAN SUBJECTS RESEARCH

   4a. Research Exempt ☐ No ☐ Yes
   - If "Yes," Exemption No.

   4b. Human Subjects Assurance No.
       0FA00005834

5. VERTEBRATE ANIMALS ☐ No ☐ Yes

   5a. If "Yes," IACUC approval Date
       04/27/04

6. DATES OF PROPOSED PERIOD OF SUPPORT (month, day, year—MM/DD/YYYY)

   From 07/01/2005 Through 06/30/2010

7. COSTS REQUESTED FOR INITIAL BUDGET PERIOD

   7a. Direct Costs ($) 369,209
   7b. Indirect Costs (%) 36%
   7c. Total Costs ($) 545,821

8. COSTS REQUESTED FOR PROPOSED PERIOD OF SUPPORT

   8a. Direct Costs ($) 2,188,784
   8b. Indirect Costs (%) 36%
   8c. Total Costs ($) 3,583,604

9. APPLICANT ORGANIZATION

   Name Johns Hopkins University

   Address Krieger Mind/Brain Institute
       3400 N. Charles St.
       Baltimore, Md 21218

10. TYPE OF ORGANIZATION

    Public: ☐ Federal ☐ State ☐ Local
    Private: ☐ Private Nonprofit ☑
    For-profit: ☐ General ☐ Small Business
    Woman-owned ☐ Socially and Economically Disadvantaged ☐

11. ENTITY IDENTIFICATION NUMBER

    EIN

    DUNS NO. 00-191-0777

12. ADMINISTRATIVE OFFICIAL TO BE NOTIFIED IF AWARD IS MADE

    Name

    Title Sponsored Projects Officer

    Address 3400 N. Charles Street

    Tel: ☐ Personal info ☑ FAX: ☐ Personal info

    E-Mail: ☐ Personal info

13. OFFICIAL SIGNING FOR APPLICANT ORGANIZATION

    Name

    Title Sponsored Projects Officer

    Address 3400 N. Charles Street

    Tel: ☐ Personal info ☑ FAX: ☐ Personal info

    E-Mail: ☐ Personal info

14. PRINCIPAL INVESTIGATOR/PROGRAM DIRECTOR ASSURANCE:
I certify that the statements herein are true, complete and accurate to the best of my knowledge. I am
aware that any false, fictitious, or fraudulent statements or claims may subject me to
criminal, civil, or administrative penalties. I agree to accept responsibility for the scientific
conduct of the project and to provide the required progress reports if a grant is awarded as a result of this application.

15. APPLICANT ORGANIZATION CERTIFICATION AND ACCEPTANCE:
I certify that the statements herein are true, complete and accurate to the best of my knowledge, and
accept the obligation to comply with Public Health Services terms and conditions if a grant is
awarded as a result of this application. I am aware that any false, fictitious, or fraudulent
statements or claims may subject me to criminal, civil, or administrative penalties.

Signature of Principal Investigator (or Program Director): [Signature]

Date: 10/21/04

Signature of Official Named in 13.

[Signature]

Date: 10/21/04
Funds are requested to continue our studies of the how shape is represented and processed in the somatosensory system and to determine how those representations are modulated by selective attention. In this proposal we concentrate on determining how information from multiple digits are integrated to form central representations of object shape. These studies build on our previous studies showing that many neurons in somatosensory cortex show feature selective responses to oriented bars, the selectivity is in skin centered coordinates, and the sensitivity is modulated by changes in hand conformation. From those findings we hypothesize that shape perception is based on populations of neurons integrating points of contact with the positions of the fingers. There are two specific aims. The first is to investigate how the points of contact are integrated during the processing of two-dimensional shapes. In these experiments, shapes that contact multiple digits are decomposed into features that will be presented to the hand either alone or in combination with other features while the animal performs a tactile-visual matching task. This study will determine how independent views of objects are integrated across digits to form neural representations of two-dimensional objects. The study will also determine the role that attention plays in the binding of tactile features. The second aim is to determine how feature selectivity is modulated by hand conformation. In these experiments, animals will be trained to grasp three-dimensional objects with one or more digits. The objects are chosen such that they span the conformational space that animals and humans use when grasping objects. These experiments will test the hypothesis that shape perception is encoded by populations of neurons with feature selective responses tuned to specific hand conformations. Experiments will be performed in primary (SI) and secondary (SII) somatosensory cortex.
<table>
<thead>
<tr>
<th>Section</th>
<th>Page Numbers</th>
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<tbody>
<tr>
<td>Face Page</td>
<td>1</td>
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<tr>
<td>Description, Performance Sites, and Personnel</td>
<td>2</td>
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<tr>
<td>Table of Contents</td>
<td>3</td>
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<tr>
<td>Detailed Budget for Initial Budget Period (or Modular Budget)</td>
<td>4-5</td>
</tr>
<tr>
<td>Budget for Entire Proposed Period of Support (not applicable with Modular Budget)</td>
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<tr>
<td>Budgets Pertaining to Consortium/Contractual Arrangements (not applicable with Modular Budget)</td>
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<td>Biographical Sketch – Principal Investigator/Program Director <em>(Not to exceed four pages)</em></td>
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<td>Other Biographical Sketches <em>(Not to exceed four pages for each – See instructions)</em></td>
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<td>Resources</td>
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<td>Research Plan</td>
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<td>Introduction to Revised Application <em>(Not to exceed 3 pages)</em></td>
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<tr>
<td>Introduction to Supplemental Application <em>(Not to exceed one page)</em></td>
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<td>A. Specific Aims</td>
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<td>B. Background and Significance</td>
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<tr>
<td>C. Preliminary Studies/Progress Report/</td>
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<tr>
<td>Phase I Progress Report (SBIR/STTR Phase II ONLY)</td>
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<tr>
<td><em>SBIR/STTR Phase I: Items A-D limited to 15 pages</em></td>
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<td>D. Research Design and Methods</td>
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<td>G. Literature Cited</td>
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<td>H. Consortium/Contractual Arrangements</td>
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<td>I. Letters of Support <em>(e.g., Consultants)</em></td>
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<td>J. Product Development Plan <em>(SBIR/STTR Phase II and Fast-Track ONLY)</em></td>
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<td>Checklist</td>
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<td>Appendix <em>(Five collated sets. No page numbering necessary for Appendix.)</em></td>
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<td>Appendices NOT PERMITTED for Phase I SBIR/STTR unless specifically solicited.</td>
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<td>Number of publications and manuscripts accepted for publication <em>(not to exceed 10)</em></td>
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<td>Other items <em>(list)</em></td>
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PHS 398 (Rev. 05/01) Page 3 Form Page 3
## Detailed Budget for Initial Budget Period

### Direct Costs Only

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<th>Name</th>
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<th>% Effort on Proj</th>
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**Subtotals**

- Consultant Costs: None
- Equipment (Itemize)
  - None
- Supplies (Itemize by category)
  - Lab supplies
  - Computers
- Travel
  - Present data at annual conferences - 4 people
    - 5,000
- Patient Care Costs
  - Inpatient: None
  - Outpatient: None
- Alterations and Renovations (Itemize by category)
  - None
- Other Expenses (Itemize by category)
  - Animal procurement
  - Animal care
  - Publications

**Subtotal Direct Costs for Initial Budget Period**

- Direct Costs: $396,209
- Facilities and Administrative Costs: 0

**Total Direct Costs for Initial Budget Period**

- $396,209

SBIR/STTR Only: Fee Requested

PHS 398 (Rev. 05/01)
# Detailed Budget for Initial Budget Period

**Direct Costs Only**

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<th>Name</th>
<th>Role on Project</th>
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**Subtotals**

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<th>Supplies (Itemize by category)</th>
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<th>Outpatient</th>
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**Subtotal Direct Costs for Initial Budget Period**

**Consortium/Contractual Costs**

**Direct Costs**

**Facilities and Administrative Costs**

**Total Direct Costs for Initial Budget Period** *(Item 7a, Face Page)*

**SBIR/STTR Only: Fee Requested**

*Form Page 4*
## BUDGET FOR ENTIRE PROPOSED PROJECT PERIOD
**DIRECT COSTS ONLY**

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**TOTAL DIRECT COSTS FOR ENTIRE PROPOSED PROJECT PERIOD (Item 8a, Face Page)** $2,188,784

**SBIR/STTR Only**
**Fee Requested**

**SBIR/STTR Only: Total Fee Requested for Entire Proposed Project Period**
(Add Total Fee amount to "Total direct costs for entire proposed project period" above and Total F&A/indirect costs from Checklist Form Page, and enter these as "Costs Requested for Proposed Period of Support on Face Page, Item 8b.

$  

**JUSTIFICATION.** Follow the budget justification instructions exactly. Use continuation pages as needed.

**Personnel:**
Steven Hsiao, Ph.D., principal Investigator [ ] [ ] [ ] % Effort, will direct and participate in all aspects of the project. He is the director of the Neuroscience graduate program.
Equipment: None

Supplies:
General laboratory supplies: These consist of purchasing torque and stepper motors and cross-slide stages, force gages and other equipment necessary to do the experiments. In addition these expenses include money to purchase drugs, surgical equipment and supplies, materials for the shops to manufacture equipment for the lab, blank electrodes, and office supplies. We estimate that we purchase about 4 computers a year. The computers necessary for the lab and are used to run the stimulators, collect the data, run a database etc. We also request funds to purchase software and to keep our Matlab, and statistical package licenses up to date.

Other expenses:
Animal purchase and care: The request is for 3 monkeys per year, which is about the rate that we now use animals. The cost of animals varies greatly but ranges from $2500 to $4000. Animal services charges a caging fee of $8.10 per day. Publication costs are based on an estimated 2-3 publications per year.

Justification of budget for future years.
Personnel have been increased at an annual rate or 3% to cover the expected increases in salaries. Supplies, travel and all other reoccurring expenses have been increased at 3% per year.
BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed for Form Page 2.
Follow the sample format for each person. DO NOT EXCEED FOUR PAGES.

NAME
Steven S. Hsiao

POSITION TITLE
Associate Professor

EDUCATION/TRAINING (Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)

<table>
<thead>
<tr>
<th>INSTITUTION AND LOCATION</th>
<th>DEGREE (if applicable)</th>
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<td>Duke University, Durham NC</td>
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<tr>
<td>Johns Hopkins University, Baltimore</td>
<td>Postdoc</td>
<td>1991-1992</td>
<td>Neuroscience</td>
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</table>

NOTE: The Biographical Sketch may not exceed four pages. Items A and B (together) may not exceed two of the four-page limit. Follow the formats and instructions on the attached sample.

A. Positions and Honors. List in chronological order previous positions, concluding with your present position. List any honors. Include present membership on any Federal Government public advisory committee.

Academic positions:
Assistant Professor, Neuroscience, Johns Hopkins University 1992-1999
Associate Professor, Neuroscience, Johns Hopkins University 1999-
Associate Professor, Biomedical Engineering, Johns Hopkins University 2000-
Lecturer Whiting school part-time programs in Eng., Johns Hopkins University 2000-
Associate Professor, Psychological and Brain sciences, Johns Hopkins University 2001-

Other positions and experience
President -Baltimore chapter of the Society for Neuroscience 2001-2002
Director Neuroscience Graduate program 2000-

B. Selected peer-reviewed publications (in chronological order). Do not include publications submitted or in preparation.


C. Research Support. List selected ongoing or completed (during the last three years) research projects (federal and non-federal support). Begin with the projects that are most relevant to the research proposed in this application. Briefly indicate the overall goals of the projects and your role (e.g. PI, Co-Investigator, Consultant) in the research project. Do not list award amounts or percent effort in projects.

ONGOING RESEARCH SUPPORT
R01 NS 34086-07 Hsiao (PI) 09/30/1995-06/30/2005
NIH/NINDS
Attention and tactile processing in Somatosensory cortex
The goal of the study is to understand how tactile form and texture are represented in the somatosensory cortex and to determine how these representations are affected by the attentional state of the animal.
Role PI

R01 NS43188-01A1 Niebur (PI) 12/01/2003- 11/31/2008
NIH/NINDS
Neural Temporal Coding Mechanisms of Tactile Attention
The goal of this study is to investigate the degree that attention can be focused in the somatosensory system and to investigate the role that temporal codes play in the selection mechanism.
Role – Co-investigator

Previous grants
P01 NS 38034-03 Johnson (PI) 07/01/1999-06/30/2004
NIH/NINDS
Three-dimensional tactile and visual form perception
The goal of this program project is to investigate the neural mechanisms of three-dimensional form perception and the integration of sensory information within and between the visual and somatosensory systems.
Role: Director of project 3 – Neural mechanisms of size and shape perception.
RESOURCES

FACILITIES: Specify the facilities to be used for the conduct of the proposed research. Indicate the performance sites and describe capacities, pertinent capabilities, relative proximity, and extent of availability to the project. Under "Other," identify support services such as machine shop, electronics shop, and specify the extent to which they will be available to the project. Use continuation pages if necessary.

Laboratory:
There is a fully equipped laboratory in the Mind/Brain Institute that will be devoted to the studies proposed in this project. The laboratory contains 2 shielded rooms and a central work area where animal preparation takes place. There is also another room available where human psychophysics can be performed. These facilities are adequate to perform all of the proposed experiments.

Clinical:
NA

Animal:
The department of Animal Medicine at the Johns Hopkins University administers and maintains animal facilities capable of housing up to 25 animals. These facilities are located on the

Computer:
We have various networked PC’s that are used for laboratory control, data collection and analysis. In addition each member of the lab has their own computer. There are also several printers available. The institute has a network administrator that services the mail and insures that the computers are virus free.

Office:
Office space is provided by the Mind/Brain Institute for all the members of the laboratory.

Other:
The Mind/Brain institute provides a library, machine shop, electronics shop, histology laboratory, and electrode manufacturing room (shared resources). The machine and electronic shops are staffed by two people each. The histology laboratory and electrode making facility is staffed by a single person.

MAJOR EQUIPMENT: List the most important equipment items already available for this project, noting the location and pertinent capabilities of each. We have a 7 channel Reitbock microdrive, MCP+ amplifier and MSD spike sorter from Alpha Omega Corp. and two vibration isolation tables. In addition we have two Forcers/Platen systems that will be used to present the stimulus patterns to the hand and two eyes scan devices to monitor the animal’s behavior.
Research Plan

A. Specific aims: Tactile shape perception from the hand is based on integrating information from cutaneous mechanoreceptors with information about the positions and orientations of the fingers. How this is accomplished is not known, though studies in our lab have suggested the following neural mechanism for haptic shape perception. When the hand is in contact with an object, mechanoreceptors in the skin are activated at multiple points of contact. The receptors at these locations provide views about local surface features of the shape such as spatial form and texture. This input is then combined with input from proprioceptors, which designate where the points of contact lie in relationship to each other in three-dimensional space. Shape perception is then based on a matching process whereby these three-dimensional "views" of the object are matched against stored representations of objects. Recently, we have found that a large fraction of the neurons in primary (SI) and secondary (SII) somatosensory cortex are: (1) sensitive to local spatial features such as the orientation of a bar indented into the finger pad, (2) show orientation selectivity that is similar across finger pads, (3) respond more effectively when bars that are presented to adjacent fingers are aligned than when they are not aligned, and (4) the cutaneous responses of many neurons, especially those in SII cortex, are affected by hand conformation. Specifically, while orientation selectivity of neurons remained in skin-centered coordinates, their sensitivity changed with hand conformation. Based on these results we hypothesize that neurons signaling a particular shape become selectively activated when the hand is in a conformation that is compatible with the object's shape and that touching the shape causes those neurons to fire. Likewise, changing hand conformation deselects those neurons. In this proposal we test this view based hypothesis of tactile shape processing in combined psychophysical experiments in humans and neurophysiological experiments in awake non-human primates (Macaca mulatta) performing two- (2D) and three-dimensional (3D) shape discrimination tasks. The neurophysiology experiments will be performed in SI and SII cortex in which animals will be trained to compare "views" of shapes presented to the hand with shapes presented visually on a screen in front of the animal. There are two specific aims.

Aim 1: Determine how two-dimensional shapes that span multiple digits are represented in somatosensory cortex. There are two objectives of this aim. The first is to determine how individual features of two-dimensional shapes presented to multiple finger pads are combined in somatosensory cortex, since integration between views presented to different finger pads must play an important role in shape perception. In the neurophysiology experiments, 2D shapes will be decomposed into features that will be presented individually or in combination to the finger pads. One possibility is that neurons are selective for a specific feature and adding views that contain different features will not alter the response. Another possibility is that the neurons represent complex shapes and adding views will enhance (if the neuron is representing all or part of the shape) or suppress the neural responses (if it is not). The second objective is to determine the role of selective attention in two-dimensional shape processing. One possibility is that individual features of objects are not combined to form complex representations in the absence of attention to the object. Another is that neurons are simply not active when the subject is not attending to the shape. In these experiments the animals will be presented with different combinations of views of shapes and will be required to indicate whether the view is compatible with the shape presented on a video monitor in front of the subject.

Aim 2: Determine how the sensitivity to cutaneous input is modulated by hand conformation during grasping of three-dimensional shapes. In previous studies we have found that the cutaneous responsiveness of neurons is affected by hand conformation. The aim is to investigate this more closely by determining the sensitivity of neurons in 3D conformational space. The animals will touch 3D objects of varying size and shape with one or more digits and indicate whether the object matches the object on the screen. This study will determine the role that hand conformation plays in the representation of 3D objects.
B. Background and Significance

**Significance:** The experiments proposed here are aimed at understanding how shape and in particular three-dimensional (3D) objects are represented in the nervous system. Our ability to recognize and interact with objects with our hands is fundamental to behavior. Although shape perception has been extensively studied in both vision and touch, the neural mechanisms underlying this ability have remained elusive. In vision, object recognition is based on inferring the 3D structure of objects from two-dimensional (2D) images. The 2D images, which originate in the retinas, flow centrally where they are combined and processed by neurons along the ventral stream to ultimately activate neurons in the inferotemporal cortex (IT) where neurons are tuned to complex shapes like faces. The problem of 3D shape processing in vision is difficult. First the visual system must segment images into figure and ground. Then the 3D shape of objects must be inferred from cues in the two 2D images. The problems that the tactile system faces to recognize objects are different. In touch, the hand contacts objects directly and as such the tactile system has direct access to the 3D shape of objects from the proprioceptive feedback it receives from the joints, muscles, and skin of the hand. This suggests that tactile shape perception must be the result of a central mechanism that integrates cutaneous information about local spatial features with proprioceptive information about the relative positions of those features in 3D space. In both systems, object perception is the product of neural inputs being matched against stored representations of objects.

**Working Hypothesis:** Recent studies in our lab (see preliminary studies/progress report section) show that many neurons in the somatosensory cortex have selectivity for cutaneous features such as the orientation of bars indented into the skin and that the sensitivity of the neurons is modulated by hand conformation. Based on these findings, we hypothesize that populations of neurons represent object shape in the somatosensory system, with cutaneous responses tuned to different hand conformations. When the hand contacts an object, each point of contact produces a view of the local surface features in 3D space. The views of the object from each contact point are combined with each other to specify a sparse representation of an object that is then matched against stored objects that contain similar features at the same relative locations. In this hypothesis, we define a view as the cutaneous image in 3D space that the brain sees from patches of skin that move as a unit. Using this definition, we propose that the hand has about 18 potential views of an object—three from each of the distal, middle, and proximal finger pads of digits 2-5; two from the distal and proximal pads of the thumb; and one each from the whorls, thenar eminence, hypothenar eminence, and palm. This mechanism is like methods that are used in computer based visual object recognition algorithms whereby multiple views of an object are combined into a single model representation (Lowe DG, 2004; Lowe DG, 2001).

**Outline:** Below, we review human psychophysical and neurophysiological studies of tactile shape processing. First we review the results of studies from human and non-human primates in which 2D shapes were used as stimuli and discuss studies of the effects of selective attention on the processing of 2D shapes. Then we review studies of 3D tactile shape processing and end with a discussion of which areas of the brain we plan to study and why.

**Aim 1: Representation of two-dimensional shapes.** Numerous studies have investigated the processing of spatial patterns presented to a single finger pad (Hsiao et al., 2003b). These studies have shown that, like in the visual system, there are two separate streams for processing spatial information. The slowly adapting type 1 (SA1) system is responsible for processing information related to texture and form, and the rapidly adapting (RA1) system is responsible for processing information related to motion (Johnson et al., 2000). Evidence that the SA1 system is responsible for spatial form comes from studies showing that the SA1 afferents innervate the skin of the fingertips.
densely in both monkey (about 117 afferents/cm²) (Darian-Smith and Kenins, 1980) and man (70 afferents/cm²) (Johansson and Vallbo, 1979a), and respond with high spatial resolution to embossed gratings (resolve gaps 1.0 mm apart or greater) (Phillips and Johnson, 1981), letters (resolve embossed letters 5.0 mm high and greater) and dot patterns (resolve dots spaced 1.0 mm apart or greater) (Hsiao et al., 1996), and are highly sensitive to local curvature on the skin (Blake et al., 1997b; Goodwin et al., 1997; LaMotte and Srinivasan, 1996). These afferents provide the central nervous system with a crisp isomorphic representation of the spatial structure of stimuli indenting into the skin (Phillips et al., 1988; Goodwin, 1998; Khalsa et al., 1998) and underlie the ability of humans to recognize 2D spatial patterns presented to a single finger pad (Johnson and Phillips, 1981; Vega-Bermudez et al., 1991). These afferents are also responsible for texture perception. The evidence for this claim comes from combined psychophysical and neurophysiological studies showing that the SA1 afferents alone account for psychophysical roughness judgments in humans (Blake et al., 1997a; Connor et al., 1990; Connor and Johnson, 1992; Yoshioka et al., 2001). These results suggest that the SA1 afferent system is the spatial system and plays a similar role in touch as the parvocellular system plays in vision (Hsiao, 1998).

The RA1 system, which receives its inputs from RA afferents that also innervate the skin densely (141 afferents/cm² in man and 155 afferents/cm² in monkeys) (Darian-Smith and Kenins, 1980; Johansson and Vallbo, 1979b), is responsible for the perception of low frequency vibrations and the perception of tactile motion. The evidence for this claim comes from psychophysical and neurophysiological studies showing that: 1) the minimum amplitude necessary to cause these afferents to fire matches the vibratory perceptual thresholds in man and monkey (Mountcastle et al., 1972; Talbot et al., 1968), 2) these afferents respond well to movement across the skin (Gardner and Palmer, 1990), and 3) these afferents are responsible for signaling micro slips that occur when lifting objects (Johansson and Westling, 1987; Srinivasan et al., 1987; Srinivasan et al., 1990; Westling and Johansson, 1987). These results suggest that the RA1 system is the motion system and plays a similar role in touch as the magnocellular system plays in vision (Hsiao, 1998).

While much is known about the processing from a single finger pad, relatively little is known about how information is integrated across fingers and finger pads. Some psychophysical studies suggest that the interactions between fingers are minimal. Loomis and Klatzky (1991) tested the ability of human subjects to identify objects either visually or by touch and found that while performance improved considerably when the size of the visual field was doubled (simulating touching a surface with two fingers), subjects showed little improvement in performance when two rather than one finger was used to identify objects. Similarly, Craig (1985) showed that patterns presented to a single finger pad are identified more accurately and rapidly than when the same patterns are divided in half and presented to separate fingers on the same hand. Other psychophysical evidence suggests that there are considerable interactions when tactile information is presented to multiple digits on the same hand and to opposite hands. Evans et al. (1992) showed that performance in identifying a spatial pattern is high when identical stimuli are presented to two fingers and low if conflicting stimuli are presented to an adjacent finger even when subjects are told to ignore stimuli on the adjacent finger. The effect occurs regardless of whether the two fingers are adjacent or non-adjacent but does not occur if the patterns are presented to opposite hands. Recently we have investigated (see progress report) the interactions when bars are placed on two adjacent fingers (Hsiao et al., 2003a). In these studies subjects were presented with bars on the distal pads of two fingers that were aligned, misaligned, or placed at different angles. Subjects were asked to report which pair of stimuli was aligned. We found that while the threshold for detecting whether two tactile bars are aligned distally across two adjacent fingers is poor (greater than 5 mm), the threshold for detecting whether bars are angularly aligned is good (less than 10 degrees). For a comparison, the alignment threshold for bars presented to a single finger pad is about 1.0 mm. These results demonstrate that the angular orientation of edges and not their absolute alignment is processed across fingers. Other studies have
shown that information about the curvature of surfaces is integrated across fingers. In those studies, Pont et al. (1999) tested the ability of subjects to detect curvature using static and dynamic touch and found that discrimination using multiple fingers is better than discrimination using a single finger.

There have been few neurophysiological studies of integration of stimuli across digits. Recently we recorded (see progress/report for details) from neurons in SI and SII cortex while stimulating the distal finger pads of one to six fingers using oriented bar stimuli. We found that in general: 1) the rate evoked by multiple bars was lower than what would be predicted from the linear sum of the responses when the finger pads were stimulated alone, 2) neurons were not sensitive to where the bars were placed distally/proximally on the finger pads, and 3) neurons were sensitive to the relative orientation of the bars on adjacent fingers. The mean rates were significantly higher when the bars were aligned across the fingers independent of their absolute orientation. These results support our psychophysical findings showing that subjects are sensitive to the relative orientation but not the distal/proximal alignment of bars (Hsiao et al., 2003a). In another study, we stimulated six finger pads (three on each hand), and found that in SII cortex neurons have wide varieties of receptive field types with over 70% of the neurons having purely excitatory or purely inhibitory responses from both hands. Of the 14 neurons that had orientation-tuned responses on both hands, 13 had similar tuning across both hands. These results show that shape information is integrated across fingers of the same hand and across fingers of opposite hands (Nakama, 2003).

**Effects of attention:** Numerous studies have shown that selective attention plays a critical role in how tactile stimuli are perceived and processed in the somatosensory system (for a review see Hsiao and Vega-Bermudez (2002)). Psychophysical studies of tactile attention have shown that when presented with competing stimuli, some tactile stimuli are processed pre-attentively and consequently are perceived more rapidly and “pop-out”. These include material properties such as the texture and temperature of surfaces (Lederman and Klatzky, 1997). In contrast, features related to the relative location of stimuli on separate finger pads, to the orientation of features, or to the 3D shape of objects do not. These results suggest that tactile shapes are not processed pre-attentively. Recent studies have suggested that the degree that attention can be focused in the somatosensory system is modality dependent. In earlier studies, Craig (1985) provided evidence that the hand is under a single focus of attention when attending to stimuli that only activate the RA1 system. In those studies subjects attended to spatial patterns generated using an Optacon, which selectively activates RA1 afferents. Subjects were presented with stimuli to pairs of fingers on the same hand or to fingers on opposite hands and asked to identify the stimuli on a single finger. He found that while subjects could ignore distractor stimuli presented to fingers of the opposite hand, they could not ignore distractors presented to digits of the same hand. These results suggest that the minimum focus of attention when performing tasks based on inputs from the RA1 system is the entire hand. Recently we tested whether the same result occurs in subjects performing a roughness perception task that depends on inputs from the SA1 system (Dorsch et al., 2001). In these studies, subjects estimated the roughness of surfaces presented to pairs of fingers, single fingers, or to one side of a finger while distractor stimuli were presented to fingers of the opposite hand, adjacent fingers, or to the other half of the finger. We found that distractor patterns had significant effects on roughness perception when applied to one side of a finger and minimal to no effects when applied to fingers of the opposite hand or to adjacent fingers. These results suggest that the focus of attention when processing information related to inputs from the SA1 system is the finger pad. Furthermore, we conclude that within the tactile system the size of the focus of attention is modality dependent.

Neurophysiological studies of animals performing selective attention tasks have shown that neurons at practically all levels of processing in the somatosensory system are affected by the animal's focus of attention. In the thalamus the effects of attention are small (Bushnell et al., 1993; Tremblay et al., 1993; Bushnell and Duncan, 1987; Bushnell et al., 1985; Dubner et al.,
1989; Hayes et al., 1981; Morrow and Casey, 1992). In SI cortex, some studies report significant
effects (Tremblay and Chapman, 1997; Hsiao et al., 1993; Hyvärinen et al., 1980), and other studies
find no effects (Mountcastle et al., 1990). Hyvärinen et al. (1980) reported that about 16% of the
neurons in SI cortex are affected in animals trained to detect when a probe stopped vibrating.
Chapman et al. (1991) estimated that about 25% of the neurons in areas 1 and 3b are affected in
animals performing a texture discrimination task, whereas Hsiao et al. (1993) reported that about 50%
of the neurons are affected in animals performing a letter discrimination task. Recanzone et al.
(1992) showed that in SI cortex, changes in plasticity only occur in animals attending to the stimulus
and Lebedev et al. (1994) demonstrated that the responses may be affected by the animal's motor
set. In SII cortex, Poranen and Hyvärinen (1982) inferred from multiunit recordings that attentional
effects are common in animals performing a vibration task. Similarly, Hsiao et al. (1993) reported that
about 80% of the neurons in SII are affected in animals performing a letter discrimination task, with
neurons showing both enhanced and suppressed responses. Burton et al. (1997) reported that
neurons in SII had task related enhanced and suppressed responses to vibratory stimuli. A study by
Jiang et al., (1996) showed that while neurons in SI respond in a graded manner to textured stimuli,
neurons in SII do not. Rather, they report that neurons in SII respond well to changes in texture,
which they suggest is because neurons in SII cortex have task related rather than stimulus related
responses. Meftah et al. (2002) proposed a two-state model of attention in which there is an initial
stage (SI) in which salient features are enhanced and a second stage (SII) in which feature selection
occurs.

Recently we have found that attention affects the representation of stimuli in SII cortex. We
performed an information theoretic analysis of animals performing a bar orientation task and found
that attention increases the neuronal discriminability of oriented bars (Nakama, 2003). In addition we
have found that attention to a tactile stimulus both increases and decreases the degree of
synchronous firing between neurons (Steinmetz et al., 2000), which we hypothesize is the neural
correlate of attentional selection and binding (Niebur et al., 2002).

Aim 2: Representation of 3D objects and shapes. Psychophysical studies: We regularly interact
with hundreds of objects that we effortlessly grasp and manipulate. Psychophysical studies show that
in the absence of visual input, tactile object recognition from a single hand is highly accurate and
increases as the number of digits used to contact objects increases (Kappers and Koenderink,
1996; Davidson, 1972). Interestingly, accuracy seems to decrease if two hands are used (Kappers
and Koenderink, 1996). Klatzky and Lederman (1985) showed that blindfolded subjects perform at
an accuracy rate of 96%, with a mean response time of less than five seconds, when asked to identify
100 common objects. Subjects use different hand conformations and movement strategies to identify
objects. Lederman et al. (1993) showed that when subjects explore objects, they often use
stereotypical movement patterns or exploratory procedures (EP's) to explore for specific target
features. Among the eight kinds of EP's they report, two are critical for extracting information
concerning object shape. The first, called enclosure, involves dynamic molding of the palm and/or
fingers to the contours of the object. The second, called contour following, involves tracing the edges
of objects with the fingers. Both of these procedures require that information about hand position be
combined with tactile information from one or more digits. In a similar study, Loo et al., (1983)
showed that purely cutaneous information was sufficient for discrimination of small objects but
propiroceptive information is needed for the discrimination of large objects. Large objects are
recognized more effectively when touched from the back (which is the normal way we grasp objects)
than when touched from the front (Newell et al., 2001). In a recent series of experiments Voisin et al.,
(Voisin et al., 2002b; Voisin et al., 2002a) showed that the discrimination of a 2D angle requires both
cutaneous and proprioceptive input. In their studies they showed that performance is degraded
significantly when subjects are deprived of either cutaneous input (skin anesthetized) or proprioceptive input (hand stationary and the angle moved).

The results from one study suggest that increasing the number of views may not increase object recognition performance. Loomis et al. (1991) showed that in vision, accuracy improved considerably when the visual field size doubled (simulating touching a surface with two fingers) but in touch, performance with two fingers showed little improvement over a single finger. In addition they showed that a pattern presented to a single finger pad is identified more accurately and rapidly than the same pattern divided in half and presented to two digits. One difference between that study and the ones proposed here is that in those studies subjects used unnatural EP’s when identifying the objects, and therefore increasing the size of the field of view did not provide subjects with proprioceptive information that we hypothesize is important in haptic object recognition.

Proprioception is important for recognizing large curved surfaces. Subjects are less successful at identifying 3D curved surfaces when tracing them with a single finger than when they contact surfaces simultaneously with multiple fingers (Davidson, 1972). Further, studies of the ability of subjects to perceive curved surfaces show that performance increases with larger curved surfaces, hyperbolic surfaces are more difficult to identify than elliptical surfaces, surfaces with high curvature are identified more easily than those with low curvature (Kappers and Koenderink, 1996; Kappers et al., 1994)), and perception may be related to the overall gradient of a curved surface (Gordon and Morison, 1982).

Hand conformation affects perception. The Aristotle illusion is a prime example of proprioceptive input affecting cutaneous perception. Normally, a single edge feels continuous when touched by two fingers that are parallel to each other. However, Aristotle found that the same edge feels like two separate edges when touched by two fingers that are crossed: More recent studies have also demonstrated that hand conformation affects tactile perception. Rinker and Craig (1994) demonstrated that the perception of stimuli from a single finger pad is dramatically affected by the conformation of the hand. In this study, subjects reported the direction of stimuli moving across the thumb while a nontarget moving stimulus was presented to the index finger. They showed that when the hand is placed flat, stimuli moving in the opposite direction on the index finger interfered with perception on the thumb. However if the hand conformation is changed such that the index finger and thumb are opposed (precision grip configuration used when grasping objects) then the identical motion on the index finger now improves performance. In another study, Oldfield and Phillips (1983) showed that the perception of letters changed when subjects pronated or supinated their hand, showing that perception is based on objects and not on the local pattern of skin deformation. The most reasonable explanations for these findings is that perception from the finger pads is not based simply on the perception of local features on the skin but rather is based on cutaneous features in the context of hand conformation.

**Neurophysiological studies of 3D shape processing:** While much is known about the serial and parallel flow of information through the central somatosensory pathways, little is known about how information is represented within those pathways. The first cortical processing stage for somatosensory information is the four areas that make up SI cortex (Kaas et al., 1979). Area 3a receives inputs from the shell region of the ventrobasal complex of the thalamus (VB) and neurons in this area respond to joint position (Burchfiel and Duffy, 1972; Friedman and Jones, 1981; Jones and Porter, 1980). Area 3b lies adjacent to 3a and receives cutaneous inputs from the core region of VB. Area 3b is somatotopically organized and neurons in this area tend to have slowly adapting responses with small receptive fields composed of excitatory and inhibitory sub-regions (Bankman et al., 1990; DiCarlo et al., 1998; Hsiao et al., 1996). Animals with lesions of area 3b show severe deficits in practically all aspects of tactile perception including form, texture, and shape perception (Randolph and Semmes, 1974; Semmes and Turner, 1977). Area 1 also receives cutaneous inputs from VB;
however the projection to area 1 is less dense than to 3b, and area 1 also receives projections from area 3b (Jones and Powell, 1969). Neurons in area 1 have larger receptive fields than those in area 3b (Iwamura et al., 1993), tend to have both slowly and rapidly adapting responses (Sur, 1980), and respond well to motion (Gardner, 1984). Lesions of area 1 are less devastating for animals than lesions of area 3b, with animals showing specific deficits in making rough-smooth and hard-soft discriminations (i.e., texture discriminations) (Randolph and Semmes, 1974).

Area 2 receives both deep and cutaneous inputs from VB; neurons in this area have more complex responses than neurons in the other three areas of SI (Iwamura et al., 1985). Besides receiving inputs from VB, area 2 also receives inputs from areas 3a, 3b, and 1, suggesting that it is a prime candidate for being the initial processing stage for 3D shape processing (Pons and Kaas, 1985; Porter and Izraeili, 1993). This hypothesis is supported by lesion and neurophysiological studies. Animals with lesions of area 2 are unable to discriminate gross object features such as whether cylinders are concave or convex, or whether objects are square or diamond shaped (Randolph and Semmes, 1974). Neurophysiological studies of area 2 also provide strong evidence for this region being involved in 3D form perception (Debowy et al., 2001; Gardner and Costanzo, 1981; Iwamura and Tanaka, 1978; Koch and Fuster, 1989). Iwamura (1978) studied over 1000 area 2 neurons and reported that about 26% of the neurons had simple cutaneous responses, 26% had complex cutaneous responses, 11% responded to movement of the joints, 40% had multidigit receptive fields, 20% responded to motion, 24% responded to simultaneous manipulation of the joints and punctate stimuli, many had inhibitory receptive fields, and others had responses that were tuned to specific textures or shapes. For example, some neurons were selective to balls or cylinders but not to edges, whereas others were responsive to oriented edges and not to cylinders. Some neurons responded when the hand was in a specific posture and others responded only during active manipulation of objects. Koch and Fuster (Koch and Fuster, 1989) recorded from areas 2 and 5 in animals trained to perform a match to sample task. They reported that neurons in both areas responded similarly to object shapes and concluded that these areas must lie at a similar level in the somatosensory hierarchy for processing object shape.

Two principal processing streams diverge from SI cortex. One processing stream is directed ventrally toward the second somatosensory cortex (SII) and the insula and is concerned with object form perception (Pons et al., 1992; Murray and Mishkin, 1984; Disbrow et al., 2001). Although SII also receives a direct projection from VB, three lines of evidence suggest that SII lies at a higher processing stage than SI cortex. First, lesions of SI cortex render neurons in SII silent (Pons et al., 1992). Second, while neurons in area 3b of SI cortex have small receptive fields restricted to single digits, neurons in SII tend to have larger receptive fields that often encompass multiple digits or the entire hand with many neurons having bilateral receptive fields (Hsiao et al., 1993; Robinson and Burton, 1980). Third, the receptive fields in SII are complex with about 80-90% of the neurons having responses that are affected by the attentive state of the animal. The results from recent studies in the lab (see progress report) suggest that SII cortex is composed of at least three separate functional fields opposed to two (Burton et al., 1995; Krubitzer et al., 1995) separate functional fields. We found that the area of cortex representing the hand in SII is about 10 mm long, with neurons in the anterior and posterior fields responding well to proprioceptive input, and neurons in the central field responding well to cutaneous input. Further, we have found that a large fraction of the neurons in SII have cutaneous responses that are affected by hand conformation. We hypothesize that tactile function is segregated in SII cortex, and that the three fields may be coding different aspects of object shape. This hypothesis is supported by lesion studies showing that animals with ablations of SII are unable to do tactile tasks involving form and texture discriminations (Murray and Mishkin, 1984; Ridley and Ettlinger, 1978). How and where tactile information is processed beyond SII cortex is largely unknown.
The other processing stream is directed caudally from SI to areas 5 and 7. Areas 5 and 7 are thought to be involved with perception of the immediate extrapersonal space, where the body is located in space, and with guidance of the body and hand to targets in that space (Mountcastle et al., 1975; Sakata and Iwamura, 1978). Area 5 is interconnected with all of the SI areas except area 3b (Burton and Fabri, 1995; Jones et al., 1978; Vogt and Pandya, 1978; Georgopoulos et al., 1984; Pearson and Powell, 1985; Pons and Kaas, 1986) and is tightly connected with area 7. Animals with lesions of areas 2 and 5 were unable to perform a wide range of form discrimination tasks. However, if area 2 is spared animals show only a mild deficit in roughness discrimination thresholds. Similarly animals with lesions of area 7 show only mild deficits in form discrimination (Semmes and Turner, 1977). These results suggest that areas 5 and 7 are not involved in representing object shape. However, there have been many neurophysiology studies that indicate that, besides having neurons that respond to both arm and hand movements (Ashe and Georgopoulos, 1994; Chapman et al., 1984; Kalaska et al., 1983), neurons in area 5 are also selective to the size, shape, and orientation of objects (Murata et al., 1996; Sakata and Iwamura, 1978). Sakata (1978) reported that neurons located in the anterior bank of the intraparietal sulcus, which is near the border between areas 2 and 5, had shape tuned responses with some neurons responding to rectangular blocks or straight edges and not to cylinders, whereas other neurons responded selectively to cylindrical bottles or apples. One hypothesis is that these neurons play a role in matching hand grips with the characteristics of objects, since accurate positioning of the finger pads on an object surface is a prerequisite for subsequent handling and manipulation (Jeanneord et al., 1995).

A working hypothesis for 3D object perception that is supported by neural imaging studies (Roland et al., 1988; Seitz et al., 1991) is that surface features are extracted by neurons in areas 3b and 1 and primitives for object shape and size are extracted by neurons in area 2 (Bodegard et al., 2001; Ostby and Romo, 2001). The areas involved in shape processing beyond SI are less clear. Although much of the evidence suggests that SII cortex plays an important role (see above), other areas of cortex have also been implicated, including the anterior parts of the intraparietal cortex (IPA), supramarginal gyrus (Bodegard et al., 2001), and possibly visual areas (Merabet et al., 2004; Zangaladze et al., 1999; Sadato et al., 1996).

C. Preliminary studies/Progress report.
Period covered: 07/01/2000 – 10/30/04 (4 Years 4 months)

The aims of the previous funding period were to: 1) determine how single and multiple edges presented within and across finger pads of the same and opposite hand are represented in the somatosensory system, and 2) determine how selective attention affects the representation of edge information when single and multiple edges are presented to the hands. The goals of the experiments were to understand the interactions between multiple edges presented to the digits. We have made significant progress in the previous granting period. Most of the data have been published in abstract form and longer publications will be submitted in the next few months.

Orientation is well represented in SI and SII cortex: (Hsiao et al., 2002) A significant fraction of our efforts have been made to understand how information about edges is perceived and represented in the somatosensory system (aim 1). We have found that about 75% (128/170) of area 3b neurons show tuned responses to oriented edges indented into the skin. All orientations are

Figure 1 Orientation tuning in SI and SII cortex. A. Dist. of peak tuning. B. Mean half max bandwidths. C. Aspect ratio = (max rate – min rate) / max rate.
approximately equally represented in the population responses (see Figure 1), with perhaps a small bias in tuning for vertical and horizontal edges. The mean bandwidth (width at half peak) of the tuning curves was about 67 degrees, which is similar to what is found in the visual system, and selectivity of these neurons to orientation was high with more than 60% of the neurons having aspect ratios greater than 0.5. Information about orientation is also well represented in SII cortex (Figure 1) with about 30% (273/952) of neurons showing orientation tuned responses. Neurons in SII that show tuned responses have similar bandwidths as area 3b neurons and tend to have more orientation selective responses, with 75% of the neurons having aspect ratios greater than 0.5.

**SII cortex is composed of three functional fields.** We have shown using both multunit mapping and single-unit recording techniques that SII cortex is composed of at least three cortical fields (Figure 2). The three fields differ mainly in their sensitivity to proprioceptive and cutaneous input, with neurons in the anterior and posterior fields responding particularly well to proprioceptive input (Figure 3) and neurons in the central field responding particularly well to cutaneous input and more frequently showing orientation tuning (Figure 3). A large fraction of 397 neurons in SII cortex had responses that were affected by proprioceptive input alone or by both cutaneous and proprioceptive inputs (Figure 3). These neurons were concentrated in the central field.

**Neurons in SII cortex have complex receptive field structures:** Neurons in SII cortex tend to have large receptive fields that span multiple digits on the same and opposite hands. We observed a wide range of receptive field types and sizes. Figure 4 shows that receptive field sizes in SII ranged from 1 to 12 finger pads (the maximum possible given that we only tested the distal, middle, and proximal pads of digits 2-5). We classified the neurons into six types based on whether they contained excitatory or inhibitory tuned pads, untuned pads, or combinations of both. About 30% of the neurons had mixed untuned and tuned pads. The rich mixtures and configurations of receptive fields (Figure 5) suggest that these neurons may be involved in encoding information about 2D and 3D shapes.

**Bilateral receptive field structures:** (Nakama, 2003; Nakama et al., 2001). We studied the responses of 209 neurons in SII cortex to

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**Figure 2** Locations of the three fields in SII cortex.

**Figure 3** Distributions of response types in SII along the AP axis. Top: cutaneous, Middle: proprio only, Bottom: proprio and cutaneous.

**Figure 4** Receptive field sizes of SII neurons.

**Figure 5** Sample receptive fields for 20 SII neurons. Each small square represents the response from a single finger pad. Within each small group: across are the digits D2-D5; down are the distal, middle and proximal pads. Cross-hatched: tuned pads, black: untuned excitatory pads, white: untuned inhibitory pads, grey: unresponsive pads.
bilateral stimulation with oriented bars (aim 1). Six fingers were stimulated with bars at four orientations of 1, 2, 4, or 6 bars simultaneously. The responses were analyzed using a linear regression model of the form $R = BX + e$, where $R$ is a vector of the evoked rates, $X$ is a 24-dimensional vector of the stimuli, $B$ represents the weights, and $e$ is the unexplained error. We found that 93% of the neurons in SII have bilateral inputs. In general, the responses were fit well by the linear model, although the recorded rates were lower than the rates predicted by stimulating each digit alone. Eighty percent of the neurons with bilateral receptive fields had receptive fields like those shown in Figure 6. The majority (66%, top row of Figure 6) had excitatory inputs from all 6 fingers. Neurons responded better to contralateral than to ipsilateral input (Figure 7).

**Figure 6** Bilateral RFs, each row is a receptive field type. White: excitatory, black: inhibitory.

**Figure 7** Normalized SII rates comparing ipsilateral vs contralateral responsiveness.

**Figure 8** Left: Raster plot showing the receptive field for a SII neuron. Colored bars indicate pads that showed significant orientation tuning. Right: Peak tuning for two other neurons.

**Neurons have similar orientation tuning preferences across finger pads of the same and opposite hand:** (Hsiao et al. 2002, Nakama 2003). The tuning curves for neurons that had orientation tuned responses tended to be similar across finger pads of the same and opposite hands (aim 1). Examples are shown in Figure 8. The neuron on the left had a RF that spanned the distal pads of digits 2–5, the middle pads of digits 2 and 3, and the proximal pad of digit 2. Figure 8 (right) shows examples of two typical neurons and illustrates that the preferred orientations are nearly identical across pads. Tuning was also similar across finger pads on opposite hands (Figure 9). These results suggest that in SII neurons integrate information about specific features across both digits and hands.

**Figure 9** Similar orientation-tuning across fingers on opposite hands.

**Figure 10** Stimulus protocol.
Invariant receptive field structures in SII cortex:

We investigated the receptive field structures on single finger pads of 61 neurons in SII cortex using the stimulus protocol shown in Figure 10. In this protocol we stimulated a single finger pad using bars of eight orientations and placed 1.0 mm apart for a total of 72 different stimuli. Neurons typically showed positionally invariant responses over the central 4 mm, with the rates decreasing toward the edges of the finger pad (Figure 11). We performed a spline fit to each of the eight orientations/positions and interpolated between those fits to produce a vector plot of the local (every 10 microns on the skin) orientation sensitivity of neurons. These gradient vector plots predict whether orientation sensitivity is due to excitatory regions, inhibitory regions, or positionally invariant tuning on the finger pad. For example, the vectors point toward the center of excitatory regions, point orthogonal to the centers of inhibitory regions, and point in the same direction for invariant fields. Of the 61 neurons studied, about 1/3 had orientation tuned responses that could be explained by zones of excitation (Figure 11, left) or inhibition (Figure 11, middle). The rest had either invariant (Figure 11, right) or complex receptive fields. These results show that most neurons in SII have positionally invariant responses over the central part of the finger pad.

Integration of information across finger pads of the same hand: (Hsiao et al., 2003a). We investigated the integration of edge information across finger pads of the same hand (aim 1). In psychophysical experiments, subjects performed a 2AFC task in which they were presented with two bars aligned across adjacent fingers or with two bars misaligned. Their task was to indicate which of the two pairs had the bars aligned. The results (Figure 13) show that thresholds (75%...
correct) are low when the stimuli are presented to a single finger and are high (5 mm) when the stimuli are presented to two fingers spread apart. Thresholds are low (<10 degrees) when the two bars are placed on two fingers but the angles are different. These results show that subjects are sensitive to the angular but not the linear alignment across the fingers. In the neurophysiological experiments we recorded from 98 neurons in SI cortex. Sixty-five of those neurons showed significant interactions when bars were presented to both digits. We made two general observations. First, the evoked rates were lower than the rates predicted from the sum of the rates when the fingers were stimulated alone. Second, neurons showed a variety of responses. An example is shown in Figure 14. This neuron responded best when the bars were linearly aligned across the finger pads and had much weaker responses when the angles were different on the two fingers. Other neurons (not shown) were particularly sensitive to unique shapes on the finger pads. The same stimuli were used in neurophysiology experiments. Neurons were driven better when the bars were aligned with the same angle across the two fingers than when they were displaced distally/proximally across the two fingers. The rates were nearly the same when bars are displaced up to 4 mm apart (Figure 15, left) but were significantly higher when the bars were aligned across the fingers (Figure 15, center, right). These results agree well with the psychophysical results and demonstrate that information about the angular alignment of bars is integrated across fingers.

Effects of attention: (Nakama, 2003). (Hsiao and Vega-Bermudez, 2001) We recorded the responses of 151 neurons in SII cortex in an animal trained to discriminate the orientation of bars presented to the distal pads of D2-4 of either the left or right hands, or to perform a visual discrimination task (aim 2). In the tactile task, the animal pushed a switch with its foot if the bar indenting the cued side was oriented at +45 degrees and pulled the switch if the bar was oriented at -45 degrees. On each trial either one or two digits were stimulated, with the second bar always stimulating a digit on the uncued side. For each neuron we computed the Kullback-Liebler

**Figure 16** Response of a single neuron in SII in an animal attending to ipsilateral stimulation (blue), contralateral stimulation (green), or visual stimulation (red). Stimuli were bars oriented at +45 deg (circles) or -45 deg (squares). Straight lines are spont. rate.

**Figure 17** KL distance between two orientations under contralateral (left) or ipsilateral (right) stimulation, under three behavioral conditions.

Continuation Format Page
distance (KL) as a measure of the difference in discriminability between the neural responses evoked while attending to the two orientations (Figure 17). We found that 97% (147/151) of the neurons in SII were affected by the animal's focus of attention and that the behavioral state affected both the ipsilateral and contralateral responsiveness of the neurons (Figure 16). Attention had greater effects on the responses to contralateral than to ipsilateral stimuli and had differential effects depending on the orientation of the bars (Figure 16). Attention increased the discriminability of the bars within 100 ms after stimulus onset and the effect persisted during the entire time the stimulus was applied to the finger (Figure 17).

The size and effects of the attentional focus are modality dependent: (Merabet et al., 2004; Hsiao and Vega-Bermudez, 2001). We have completed two studies investigating whether the effects of attention are modality dependent. In the first we performed a psychophysical study of the ability of subjects to focus their attention in a task that relied on the SA1 system. In this study subjects were asked to give subjective magnitude estimates of the roughness of various grades of sandpapers while simultaneously presented with distractor surfaces on a non-target finger (Figure 18A) or side of a finger (Figure 18B). We found that subjects can ignore distractors if they are presented to fingers on the other hand or on fingers of the same hand but cannot ignore them when presented to the same finger. The results show that when attending to a task that is mediated by the SA1 system, the minimum focus of attention is the finger pad. When combined with earlier studies (see B&S) we conclude that within the somatosensory system the size of the focus of attention is modality dependent.

In a collaborative study with a lab at Harvard (Merabet et al., 2004), we found that form and texture, both of which are mediated by the SA1 system, may be processed in different parts of the brain. In this study, subjects felt emboosed dots that linearly increased in spacing from 1.0 mm to 6.2 mm and were asked to judge either the spacing between the dots or the roughness of the surfaces. We found that subjects perceived a linear monotonic increase in dot spacing when asked to judge dot spacing and an inverted U-shape when asked to judge roughness. When TMS was applied to the somatosensory cortex the roughness curve was altered but the dot spacing curve remained the same. The opposite effect occurred when TMS was applied to the visual cortex. These results suggest that the visual cortex plays a role in tactile form processing and not in texture processing. One hypothesis is that objects are represented in the visual system and that tactile perception of shape is based on matching the tactile responses with those visually based representations.

Attention changes the degree of synchronous firing between neurons:

Figure 18. Subjective magnitude estimates of the roughness of sandpapers of varying grit. A: Distractors presented to an adjacent finger, B: Distractors presented to the medial side of a finger while subjects discriminated the lateral side.

Figure 19 Raster plots of two SII neurons (green and red) when the animal attended to the tactile stimulus (left) and to a visual stimulus while receiving the same tactile input (right). The blue dots are synchronous events (spikes within 2.5 ms).

Figure 20 Proportion of neurons affected by both cutaneous and proprioceptive input.
In a related study we found that the degree of synchronous firing between pairs of neurons changed with the attentive state of the animals (Figure 19). While most (65%) of the neurons showed synchronous firing when the animal performed a visual task unrelated to the tactile stimulus, the degree of synchrony changed when animals switched attention to the tactile stimulus, with about 80% of the neurons showing increased synchrony. These results suggest that in addition to modifying firing rate (Hsiao et al., 1993) attention also modifies the temporal firing patterns of neurons. Neurons receiving inputs from such neurons will be more likely to fire when the animal is attending to the stimulus. We hypothesize that this mechanism may play a role in the binding of features.

Firing rate is affected by hand conformation: (Pawluk et al., 2002). In a series of studies, we have investigated the role of proprioceptive input in the processing of cutaneous stimulation. We studied the responses of 510 neurons in SI cortex and 391 neurons in SII cortex using a protocol in which we systematically stimulated the distal pads of digits 2, 3, and 4 using an oriented bar while the hand was positioned in different conformations. The proportion of neurons that appear to be driven by both cutaneous and proprioceptive input ranged from 30-60% in SI and SII cortex (Figure 20). Changing hand conformation altered the sensitivity of the neurons to cutaneous input. Figure 21 shows an example of a neuron that showed orientation tuning and had its receptive field on D3a. This neuron became less sensitive to stimulation on D3 when digit 2 was abducted and digit 4 was adducted (compare green and orange curves). These results show that hand conformation plays a significant role in the sensitivity of neurons to cutaneous stimulation.

Responses remain in skin centered coordinates: (Pawluk et al., 2002) Figure 22 shows an example of a neuron that was not affected by changes in hand conformation. This neuron showed similar
orientation tuning on digits 2 and 3. While changing hand conformation did not affect the responses on digit 3, it did cause a shift in the orientation tuning of the neuron on digit 2. This shift in orientation tuning is explained by the relative angle change that occurs when digit 2 is abducted. That is, abducting the finger causes the bar to contact the skin at a different angle. These results suggest that the cutaneous feature selectivity of neurons, at least for orientation, remains in skin-centered coordinates with changes in hand conformation.

**Perception of object size depends on integrating finger spread with cutaneous input.** We studied the ability of subjects to estimate, using different contact forces, the size of objects that varied in shape and compliance. Size perception was unaffected by changing contact force, compliance, surface contact area, and shape. We also tested which cutaneous afferents signal contact by selectively adapting the skin using a 30 Hz adapting vibration. Adaptation of the RA1 afferents resulted in the objects feeling smaller. We hypothesize that size perception is based on estimating the spread between the fingers at contact, which is signaled by RA1 input.

**Hand conformations during grasping:** We investigated the conformational space that blindfolded subjects use when exploring 25 common tactile objects with their hands (e.g., cups, staplers, balls, cylinders). Hand conformation was measured for 14 joint angles, which included the mcp, pip, and abduction angles of digits 2-5 as well as two joints of the thumb using a Cyberglove (Immersion Corp.). A principal component analysis on the covariance matrix showed that a four-dimensional conformation space accounts for about 90% of the total variance. This result demonstrates that, although the hand has many degrees of freedom, most movements of the joints are highly correlated with each other in everyday use. Figure 23 shows the hand conformations used when grasping the objects in the 3D space spanned by the first three principal components. We then related this subspace to shape parameters by performing a linear regression of the conformations that are typically used while grasping shapes of varying diameter and convexity/concavity. We then plotted those weights in hand conformational space (vectors 1 and 2 in Figure 23). These parameters span a 2D plane in the conformational sub-space. Images of the hand conformations corresponding to vectors 1 and 2 are shown in the left and middle parts of Figure 24. The vector orthogonal to this plane (vector 3 in Figure 23) predicts that the hand conformations used when exploring these shapes correspond to conical shapes (Figure 24, right). Vectors orthogonal to these three vectors will be investigated to look for other relevant shape parameters.

**Figure 23** First three principal components of the hand conformational space. Each dot is a hand conformation. The 3 vectors are regressions of different shapes in this space.

**Figure 24** Hand conformations used when grasping common objects. Left: Cylinders of various diameters, Middle: convex and concave shapes, Right: conical shapes. These conformations capture much of the first three principal components of the hand conformational space.
Publications supported by this grant: (7 peer reviewed, 1 in revision, 5 chapters)


Abstracts (11)


D. Research Design and Methods

Introduction: The proposed experiments are aimed at understanding how two- and three-dimensional shapes are represented in the somatosensory system. These experiments build on our previous studies showing that: (1) a large fraction of the neurons in primary (SI) and secondary (SII) somatosensory cortex are sensitive to local spatial features such as the orientation of a bar indented into the finger pad, (2) they show orientation selectivity that is similar across finger pads of the same and opposite hands, (3) they respond more effectively when bars that are presented to adjacent fingers are aligned than when they are not aligned, (4) changing hand conformation alters the sensitivity but not the selectivity of SI and SII neurons, and (5) that neurons in SII cortex are clustered into at least three functional groups, with neurons in the anterior and posterior portions of SII responding preferentially to proprioceptive inputs and neurons in the central portion of SII responding preferentially to cutaneous inputs. These results suggest that the representation of object shape is based on neurons having cutaneous responses that are tuned both to cutaneous features and to the positions and orientations of the fingers in three-dimensional space. There are two aims in this study. The first aim has three objectives. The first objective is to investigate how two-dimensional shapes are represented in somatosensory cortex. The animal's hand will be held flat and stimuli will be systematically brought into contact with the distal and middle finger pads of digits 2-4. Using two-dimensional shapes that are decomposed into individual features, we will investigate neural tuning for cutaneous inputs to individual finger pads (single point of view) and tuning for combinations of inputs to multiple finger pads (multiple points of view). The second objective is to investigate the role of selective attention in combining views of two-dimensional contours. The third objective is to investigate the neural representation of two-dimensional shapes. The second aim is to investigate how cutaneous responses are modulated by hand conformation and ultimately to determine how three-dimensional shapes are represented in somatosensory cortex. Shapes are naturally three-dimensional and the effects of hand conformation should be reflected in the tuning properties of neurons encoding tactile shapes.

In the following sections we first describe the experimental designs. Then we describe general experimental design issues that are common to all of the neurophysiological experiments. This includes describing which areas of the brain will be studied, the anatomical and histological methods, animal training methods, methods to record and analyze the neurophysiological data, a brief description of the stimulator, and a description of hand holding methods. Finally, we discuss potential difficulties that we may encounter and an estimated time schedule.

Experimental Designs

Experiment 1(E1) addresses the first aim, which is to determine how two-dimensional shapes are represented in the somatosensory system.

Objective: Shape recognition requires that tactile information be integrated across digits. This experiment first investigates feature selectivity of individual finger pads to local contour features and 2D shapes. The local contour features will be combined systematically across finger pads to form the contour outlines of two-dimensional shapes. The experiment has multiple objectives. The first is to quantify the individual views that are encoded by a finger pad when contacting contour features alone. The second is to investigate the integration of views when combinations of contour features are presented to multiple finger pads. The third is to determine whether the responses to the contour of a shape are the same as the response to the shape itself.

Experimental design: Microelectrode penetrations will be made in either SI or SII cortex using a seven channel microelectrode drive (Mountcastle et al., 1991). Every neuron that has a receptive
field on the hand will be isolated and studied. The receptive field for each neuron will first be characterized using hand-held stimuli, which includes probing the cutaneous receptive field with small probes and oriented bars and determining whether the neuron has proprioceptive input by manually moving the positions of the digits. Next the hand will be secured to a mechanical holder that holds the hand flat with the palm facing upward. The hand holder is designed such that the degree that digits 2, 3, and 4 can be flexed or extended is under computer control. Digit 1 will not be studied in this experiment because it is difficult to hold it flat for long periods of time, and digit 5 will not be studied because of time limitations in the experiments. Once the fingers are secured, the centers of each of the pads of digits 2, 3, and 4 will be marked and entered into the computer by touching the centers with a microscribe (Immersion Corp). Three sets of recordings will be performed.

In the first set of recordings, six small oriented bars (8 mm in length with rounded ends) will be used to stimulate the distal and middle finger pads of digits 2-4. The bars will be mounted on the end of six independently controllable stimulus assemblies (see below for a description of the stimulator) that can rotate and move the bars to any x, y position over the hand. Each finger pad will then be studied with bars at four orientations (separated by 45 degrees) and indented at the center of the pad or displaced 2 mm away from the center (4 x 3 different kinds of stimuli for each finger pad). Every stimulus will be repeated eight times for a total of 576 trials (6 skin locations x 12 stimuli at each location x 8 repetitions).

In the second set of recordings, combinations of stimuli will be presented to two, three, four, five, and six pads. The stimuli will be selected from the initial set with the constraint that when combined, the bars form the contours of two-dimensional shapes. Examples of such stimuli are shown in Figure 25. All stimuli will be presented in a pseudorandom order. The rationale behind this experiment is that each contact point represents a view of the larger two-dimensional shape and that increasing the number of views increases the amount of information the animal has about the large shape. To test this hypothesis, the stimuli will be brought into contact with the skin in two ways. (1) The hand held flat regardless of which pads are being stimulated. In these trials, shape information should not be integrated across nonadjacent fingers when intermediate fingers are positioned at locations inconsistent with the 2D shape. (2) When possible, the fingers will be positioned such that only those fingers that are within the plane of the stimulus and are being stimulated are held flat. Other fingers will be extended below the plane to produce valid and consistent views of the shape. In previous studies we have found that the neural responses are enhanced when bars are aligned across adjacent fingers. This experiment will investigate the conditions that are necessary for the enhanced responses. For example, do enhanced responses occur when bars are aligned across nonadjacent fingers? For large shapes that are formed by all six bars, the number of combinations is approximately 44 trial types or 352 trials (8 repetitions). Studying each shape will take a maximum of 6 minutes (1 second per trial, 500 ms contact time). Thus we should be able to study the responses to about 10 different shapes and hand positions given an hour of recording time.

A question that emerges from the first part of this study is whether the responses to the contour of a 2D shape are the same as to the shape itself. To address this question, in the third set of recordings, neurons will be studied using 2D flat surfaces that have the same shape as the contour surfaces. In these trials the bars at the ends of the six stimulus assemblies will be replaced with 2D shapes that when pieced together form one or more of the contour shapes used in the first protocol. These stimuli will then be presented to the finger pads either alone or in combinations. It will take an additional 10 min to study each shape. If neurons respond selectively to a shape then the shape will
be moved to different locations on the hand to test whether the representation of the shape is positionally invariant.

**Data analysis:** The data analysis for this protocol is straightforward. The response R for any stimulus can be predicted by the linear combination of all of the stimulus patterns that are in contact with the hand. Using linear regression techniques (DiCarlo et al., 1998), we will analyze what linear combinations of features contribute to the neural response. For example if a neuron responds only to the orientation of a bar on a single finger, the input weights for that finger should be high and the weights for all other stimuli should be low. The analysis is similar to the one we used in our studies of the tuning properties of neurons across both hands (see progress report section). In this analysis the patterns of input weights provide an estimate of the feature space of the neurons. The data will be analyzed to determine whether contiguous shapes are represented more effectively in the neural responses.

The data from the initial mapping will also be used to estimate the detailed receptive field structures on individual finger pads. The analysis will be similar to the one that we used in previous studies in which we found that for a large fraction of the neurons in S1 cortex the orientation tuning could be explained by neurons having receptive fields that contained either mixed excitatory and inhibitory sub-regions or had spatially invariant responses (see preliminary results section).

**Anticipated results:** These experiments build on our previous studies in which we presented pairs of oriented bars to two, three, four, and six fingers on the same, and opposite hand (see progress report). In those studies we found that the sum of the rates evoked by multiple bars was less than the predicted sum. We found that integrating cutaneous information between fingers is a nonlinear process in which output rates are not predictable from the individual inputs. This study investigates this process in more detail by stimulating the fingers with features that underlie large shapes. We expect to find that neurons will show selectivity to two-dimensional shapes that are not predictable from the responses evoked when finger pads are stimulated alone. For example, if a neuron is active when horizontal bars are presented individually to the distal pads of digits 2, 3, and 4, a linear model would predict a response to stimulation of digits 2 and 4 without digit 3, whereas a neuron sensitive to continuous edges contacting all three digits might not respond at all under those conditions.

**Experiment 2 (E2) addresses the first aim and investigates the role of selective attention in processing two-dimensional shape information in the somatosensory system.**

**Objective:** While experiment 1 (E1) addresses the integration of shape information between fingers and finger pads, this experiment addresses the effect of selective attention on the neural responses. It is well accepted that selective attention plays a significant role in determining what gets processed in the somatosensory system (See Background & Significance). One concern that we have about experiment E1 is that in those experiments the animal will perform a visual fixation task that is designed to keep the animal in an alert state but does not require it to attend to the tactile stimulus. Because the animal's focus of attention is directed away from the tactile stimulus it is likely that the responses in that experiment will be different than if the animal were attending to the tactile patterns. In this experiment we address this concern by requiring the animal to make discriminations about shapes that are similar to the ones used in experiment E1. These experiments will investigate the role that attention plays in modulating the neural responses and will investigate the role of attention in binding information between different views of an object's shape.

**Experimental design:** First the receptive fields of neurons will be characterized as described in the initial part of experiment E1. The animal will then perform a behavioral task that requires it to switch
its focus of attention back and forth between a tactile task and a visual task. In the tactile task, animals will perform a cross-modal match-to-sample (MTOS) task. Animals will be trained to recognize a small, restricted set of object shapes. Trials begin with the animal fixating for 500 ms on a cross in the center of a video screen in front of the animal. A tactile pattern consisting of a single view (single contour feature) or multiple views (multiple contour features) of a two-dimensional shape will then be indented into the skin for 500 ms. Then, a shape will be presented on the video screen in front of the animal and the animal will be required to fixate for 500 ms on a dot to the left of the cross if the pattern of tactile input is consistent with the shape of the visual stimulus. The animal will fixate on a dot to the right if the two shapes are incompatible. The animal will receive a liquid reward when correct. The difficulty of the task will vary from trial to trial since in some trials the animal will receive multiple views of the shape presented on the screen while in others it will only receive a single view. In the visual task the animal will be required to fixate and track a dot placed at random locations on the screen. The animal will receive a liquid reward for fixating on the dot for 500 ms. The same tactile stimuli that were used in the tactile task will be presented to the animal's hand during the visual task. To control for eye movement effects in the visual task, some of the dots will be placed at the same locations that were used in the tactile task. As in experiment E1, non-stimulated fingers will be extended to mimic views that are consistent with hand conformation.

Characterizing the receptive fields of the neurons will take approximately 10 minutes. For the remaining 50 or so minutes the animal will switch its focus of attention between the two behavioral tasks. Approximately half of the time will be devoted to the tactile task and the other half to the visual task. In a typical recording session we estimate that we will be able to study the responses to about 3-4 different shapes.

**Data analysis:** At least two kinds of analysis will be performed on the data. The first will determine how the different input stimuli affect neuronal firing rates and how those rates are affected by selective attention. There have been many studies showing that attention either increases or decreases the firing rates of neurons. However the message encoded by those rates is often not clear. This is especially true when different stimulus conditions, such as bars of varying orientation stimulating different fingers, can produce identical firing rates. Typically, the firing rate of a neuron is interpreted as signaling more or less of a specific stimulus attribute. For example, neurons that respond selectively to a specific stimulus attribute, such as orientation, are thought to be encoding information about that attribute. If so then what do changes in rate mean when a variety of different stimulus conditions, such as one or more oriented bars indenting different finger pads or the animal's behavioral state, produce identical rates? This analysis will determine the family of stimulus conditions that produce constant firing rates and determine how the rates evoked during those stimulus conditions are affected by the animal's focus of attention.

The second kind of analysis is to investigate the differences in the temporal firing patterns between neurons as more or fewer features are presented to the hand. In previous studies we have shown that the degree of synchronous firing increases when animals selectively attend to stimuli. One hypothesis is that this increase in synchronous firing is a mechanism for binding stimulus features. We will test this hypothesis by comparing the degree of synchronous firing between neurons when the same combinations of stimulus features are part of a target pattern and when they are not.

**Anticipated results:** We expect that the analysis of firing rates will show that neurons are selective for complex stimulus attributes that span multiple fingers. For example we expect to find that many neurons in area 3b have stimulus activation functions showing orientation tuning selectivity confined to single finger pads. We expect that the stimulus activation functions for neurons in SII cortex will be much more complex. If attention simply affects the gain in firing rate (McAdams and Maunsell, 1999) then the shape of this rate tuning function should become elevated when the animal attends to the
tactile stimulus. If synchrony is the mechanism of selective attention (Steinmetz et al., 2000) then we expect that only those neurons that are representing the attended stimulus will show increased synchronized firing and that neuron pairs that are not part of the representation will show decreased synchrony of firing. If this is the mechanism of attentional selection, then one prediction is that different pairs of neurons will become synchronized as the animal attends to different stimulus shapes. We hypothesize that increased synchrony will only be observed between those neurons that have receptive fields that are compatible with the features of the shape (see progress report for examples of the receptive fields of SII neurons).

**Experiment 3 (E3)** addresses the second aim and investigates the role of hand conformation in tactile shape processing in the somatosensory cortex. This experiment investigates how the sensitivity of neurons to cutaneous stimulation is modulated by hand conformation.

**Objective:** In previous studies we showed that the cutaneous responses of many neurons in SI and SII cortex are modulated by the positions of the fingers. In those studies the animal’s hand was secured to a motorized hand holder that controlled the degree of spread between digits 2 and 4 and the degree that digit 3 was flexed or extended. Briefly we found that while the orientation selectivity of neurons remained in skin-centered coordinates, the sensitivity of many neurons changed when either the position of the finger pad being stimulated or the positions of fingers adjacent to the stimulated finger changed. These results suggest that many neurons may respond optimally to cutaneous stimulation when the hand is in specific conformations. In these experiments we plan to explore the effect of hand conformation on the responses of neurons to cutaneous stimulation and test whether these neurons are encoding three-dimensional shape. To explore the conformational space, animals will grasp three-dimensional objects that vary in size and shape.

**Experimental design:** The conformational space in which the hand and fingers move is diverse and complex. One limitation of our previous studies is that we restricted the changes in hand conformation to just three degrees of freedom. This is a serious limitation if we are to fully explore the tuning properties of neurons in hand conformational space since the hand has 20 degrees of freedom. In these experiments animals actively explore three-dimensional objects with their hands. Active exploration has both advantages and disadvantages. The main advantage is that this is the natural way that objects are grasped. Thus, if neurons are tuned to hand conformation then this mode of exploration should produce the strongest neural responses. The responses should be further enhanced by the mechanisms of selective attention, since the animals will be actively engaged in the task. The main disadvantage is the loss of precise stimulus control over where and how the fingers contact the object. We plan to counter some of these disadvantages by limiting which fingers are allowed to contact the object. This is accomplished by placing the animal’s hand in a gantry that restrains the movement of the arm and palm. Small metal nail holders will be attached to the back of the five nails of digits 1-5 using cyanoacrylate glue (Pic/PIC Apart, MCM.

![Figure 26 Sample 3D contour shapes to be used in experiment E3.](image)
Electronics, Centerville, OH). Attached to each nail holder is a nylon fishing line that tethers the fingers to the frame of the gantry. The length of the tether lines will be under motor control, so that at one extreme the fingers can freely explore the object and at the other all five fingers are restrained so that the animal cannot touch the object.

For each trial, an object is placed in the center of the gantry and a visual cue is given to the animal to indicate that a trial has begun. The cue will then change to the image of an object and one or more of the tether lines will be allowed to move freely. The animals' task is to grasp the object with the fingers that it can move and indicate by making a saccade to the left if the object it is touching is the same as the object on the screen or make a saccade to the right if it is not. Animals will be given a liquid reward for correct responses. Allowing some tether lines to move freely while keeping the rest taut will control the number of views that the animal has of the object during each trial. Two kinds of shapes will be studied. One is cylinders of varying diameter and curvature (see Figure 26). The second is upright and inverted conical shapes in which the diameter of the base of the cone varies (Figure 26). Changing the diameters of the shapes and degree of curvature of the cylinders provides us with the ability to control the absolute and relative degree that the fingers are flexed. We choose these shapes since in preliminary studies we found that the hand conformations used to grasp these objects capture much of the variance that humans use when grasping a large number of everyday objects (see Preliminary Studies). Throughout the experiment, hand position and conformation will be monitored using a cyberglove (Measurand Co.), and contact with the object will be monitored using force sensors mounted to the objects and by knowing where the fingers are in space. As a control, for some trials the animal will be allowed to move its fingers and no object will be present. Fifteen objects (picked from the set shown in Figure 26) will be studied (3 inverted and upright conical surfaces, and 12 cylindrical surfaces) and all combinations of views will be tested (31). If each trial lasts 2 seconds and each stimulus combination is tested 5 times then a total of about 80 minutes is needed for each recording session.

**Data analysis:** The data will be analyzed using linear regression models to determine the relative contribution of the cutaneous and proprioceptive inputs to shape perception. The firing rate for each trial is assumed to be a linear combination of the inputs from each view, where the input for each view is defined as the local curvature on the skin and the three-dimensional position of that view. The analysis will produce estimates of the selectivity of the neurons to local and global curvature as well as a measure of the sensitivity of the neurons to a large number of hand conformations.

**Anticipated results:** We expect that this experiment will produce a number of new findings. For example, we expect to see that many neurons will show tuning to local (e.g., neurons in area 3b) and global (e.g., neurons in SII cortex) curvature. Further, we expect to see that many neurons (especially neurons in SII cortex) will have cutaneous responses that are modulated by hand conformation and that the modulation is tuned to specific hand conformations. If this is the case then we will test whether populations of these neurons could be encoding the 3D size and shape of objects.

**Experiment 4 (E4)** addresses both aims and investigates the role of hand conformation and view dependence on the ability of humans to perceive and discriminate 2D and 3D shapes.

**Objective:** Our working hypothesis is that hand conformations play an important role in tuning neurons to respond to specific object shapes. Although this hypothesis is reasonable, one could make an argument that, in a strict sense, it is either incorrect or too narrow. For example, in the preliminary results section we show that we tend to use a limited number of hand conformations when exploring objects. In addition, subjectively, tactile object recognition does not seem to require that we grasp objects in stereotypical ways. This suggests that specific hand conformations are not matched
to specific objects. There are two aims of these psychophysical experiments. The first is to determine whether discrimination performance increases as the number of views of an object increases. The second is to determine the role that hand conformation plays in tactile object recognition.

**Experimental design:** These experiments will be closely tied to the neurophysiology experiments (E2 and E3) described earlier and will use similar experimental setups. In the experiments, subjects will be required to identify 2D and 3D shapes using one or more tactile views of objects. Subjects will sit with their hands facing upwards and will be cued to explore an object (without visual feedback) using one to five fingers. A set of objects will then appear on a screen and the subject will be required to indicate which image best matches the object that the subjects felt with their hand. Two kinds of experiments will be performed. In one, subjects will discriminate 2D shapes (E2) and in the other subjects will discriminate 3D objects (E3). Hand conformation will be monitored and controlled such that in some cases subjects will be given views of objects in which hand conformation provides information about the shape of the object and in other cases the hand conformation will be incompatible with the shape (e.g., identifying a round shape with the hand held flat).

**Data analysis:** The subject's performance will be measured (percent correct and response latency) for each view, combinations of views, or hand conformation.

**Anticipated results:** We expect that we will find similar results to Loomis et al. (1991) when subjects are asked to identify objects without hand conformation information and that subjects will show a mild increase in accuracy and decrease in latency as the number of views increases. Further, we expect that performance will improve greatly when subjects are allowed to use hand conformation information. One possibility, if specific hand conformations play an important role in identifying specific objects, is that performance for specific objects will be "tuned" for specific hand conformations. Another possibility is that hand conformation is important but only a small set of conformations are used to identify objects. If this is the case then we expect to see that different classes of hand conformations are used to recognize different classes of objects (e.g., enclosures for round shapes and pencil grips for long shapes).

**General design issues**

**Cortical areas to be studied:** The neurophysiological studies will be performed in all areas of SI and SII cortex. Ablation studies in animals trained to recognize objects of varying size and shape suggest that critical areas involved in 3D shape processing are area 3b, area 2, and SII cortex. Neurophysiological studies suggest that area 2 and SII are particularly involved since many neurons in these areas respond to both cutaneous and proprioceptive inputs. In recent studies, we have found that the hand region of SII cortex is composed of three separate functional areas. Thus, the experiments will focus on the response properties of neurons in area 2 and the three fields of SII cortex.

**Animal behavior:** Animals will, as in our previous studies, be taught two tasks. In task 1 the animals will be performing a visual fixation task unrelated to the tactile stimulus. We use this task because it keeps the animals in a defined behavioral state in which they are awake and performing a task unrelated to the tactile stimulus. In this task, which we have been using for several years now, the animal is required to make saccades and fixate for 500 ms on a dot that appears at random locations on a video screen. Eye position is monitored using an infrared eye-tracking device (Arrington research). Animals are given a small liquid reward for correctly completing a trial. In task 2 the animals perform a match-to-sample task that requires them to match a tactile stimulus to a visual stimulus. This task is similar to tasks we have used previously in which animals were asked to match
a letter of the alphabet scanning across their finger pad with a letter presented on a screen. Training the animal to perform this task requires that it make associations between the visual and tactile stimuli. Animals will first be trained to fixate on the center of the screen and simultaneously the tactile shape and visual stimulus will be presented to the animal. If the patterns are the same then 500 ms later a dot will appear on the left of the fixation point and the animal will be rewarded for saccading to the dot. If the patterns are different than the dot will appear to the right of the fixation point. After learning this task, a dim dot will appear on the opposite side of fixation and gradually this dot will brighten until it is of equal brightness as the dot signifying the correct response. All the while, the animal will only be rewarded for making the correct saccade. After the animal learns to discriminate the whole shape, partial tactile features will be presented to the animal. Animals in experiment E1 perform only task 1, animals in experiment 2 will perform both tasks, and animals in experiment E3 will perform only task 2.

Procedures

Anatomical clustering: Another objective of these experiments is to determine whether neurons cluster into specific groups. One aim of these studies is to determine the roles that the three areas of SII cortex play in representing the size and shape of objects. Recordings will be made with a multi-electrode microdrive that allows us to independently drive 7 microelectrodes, spaced 400 microns apart along a line, into the cortex. Before each penetration, the electrodes are coated with one of 4 fluorescent dyes (Dii, DIO, Dil-C5, and fast blue). These dyes serve as markers so that the location of each penetration can be reconstructed histologically. Detailed records are kept concerning the location and type of dye with which the electrodes are coated. The microdrive is positioned such that for each set of penetrations, the electrode array spans about 2 mm of cortex. In S1 cortex this allows recordings to be made simultaneously from 4 to 5 neurons that span the supra- and infragranular layers of cortex. After recording from both hemispheres, the monkeys will be sacrificed and processed using standard histological techniques (DiCarlo et al., 1996). Each penetration will be reconstructed to determine the anatomical location of every recorded neuron. These locations will then be combined with the neurophysiological data to see whether the responses cluster.

Animal care, training, and surgery: All neurophysiological experiments will be done using rhesus monkeys that weigh 3-4 kg. The animals will be purchased through the Department of Comparative Medicine, which ensures that the animals are B-virus negative, tests the animals regularly for TB and intestinal parasites, and is responsible for their general and veterinary care. During training and recording, animals are under a water restricted diet and are brought to the laboratory 6 days a week for 5-7 hours each day, where they will receive all of their water. It takes about 2 weeks for the animals to learn to perform task 1. We expect that it will take about 8 weeks to train the animals in task 2. The animal's weight and health are carefully monitored throughout the experiments. All of the procedures are approved by the Johns Hopkins animal care and use committee.

Briefly (see section F, Vertebrate animals for details), after an animal is trained to do the task, surgery is performed under sterile conditions to fasten head restraining posts to the skull using stainless steel bone screws and dental acrylic. The animal is then retrained to perform the task(s) with its head restrained. After the animal is fully trained, a hole is trephined through the dental acrylic and a 19 mm diameter recording chamber is positioned over SI and SII cortex and secured to the skull. A small hole (3 mm) is made within the recording chamber to expose the dura covering the hand region over either SI or SII cortex. At the end of each recording day a few drops of 0.1% dexamethasone and gentamicin are put on the dura and the dura is covered with a small piece of Gelfoam. The chamber is then filled with sterile saline and sealed. All of the procedures are approved by the Johns Hopkins University animal care and use committee.
Recording methods: Each morning the animal is taken from the cage, put in a primate chair, and brought to the laboratory. The monkey's head is fixed and the chamber cover removed. The Gelfoam is then lifted off the dura and the chamber is flushed with sterile saline. Mounted to the recording chamber is a sealed plate that contains a 3 mm diameter hole that can be positioned using precision micrometers at any XY location (within 25 microns) within the recording chamber. The center of the hole in the stage is positioned over the center of the recording hole. The multi electrode micro drive (Mountcastle et al., 1991) is then loaded with electrodes made of glass filaments with tungsten-platinum metal cores and the electrodes are then coated with the appropriate dyes. The animal and primate chair are then brought into the recording room and the chair is mounted on a floating table that isolates the animal and stimulator from building vibrations. The micro drive is then centered over the hole in the XY stage and the electrodes are advanced into the cortex. The recordings last 5-6 hours after which the electrodes are removed, the chamber is cleaned, and the animal is returned to its cage.

As the seven electrodes are advanced into the cortex, detailed notes are kept in a computer database about the neural responses to hand held stimuli. When the electrodes reach the desired cortical depth, single unit responses are isolated on each electrode and recordings for that set of neurons begin. Neurons can be held for an hour and usually longer. After finishing with one set of neurons, the electrodes are advanced and another set of neurons are isolated. We typically record from three sets of neurons per day, with each set containing four to five well-isolated neurons. Recordings for each area of cortex usually last about 20-25 days (a total of about 140-175 penetrations) with about 300 to 400 neurons per experimental series. We plan to record from SII and then SI cortex and perform a total of 40-50 recording sessions per hemisphere (seven electrodes per session).

Data collection and analysis: The experiments are controlled by several PC computers. One computer is devoted to running a database program that records all of the details about the experiments including penetration locations, comments, neuron depths and types, and stimulus parameters. Two computers are devoted to: 1) controlling the animal's behavior by monitoring the location of the stimulus, detecting when the animal responds, and turning on a solenoid to give the animal a liquid reward; 2) collecting the occurrence times of the action potentials and behavioral and stimulus events; 3) displaying raster plots of the raw data; and 4) controlling the stimulators. Another computer is devoted to sorting action potentials from the seven electrodes (Alpha Omega Corporation) and providing TTL pulses indicating the occurrence times of the action potentials to the collection computer. Times of events are recorded with a resolution of 10 microseconds. The data are stored on another PC computer that is also used for offline analysis. The times of occurrences of action potentials, behavioral events, and stimulus events are converted into stimulus, behavioral, and spike rate arrays that are analyzed using Matlab and SPSS.

Stimulator: Experiments E1 and E2 employ the same basic

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Figure 27 Stimulator showing a stimulus assembly (right) suspended from the platen.
strategy of positioning the hand in a predefined configuration and then presenting statically indented stimuli to one or more digits. Stimuli will be presented using six linear motor assemblies (Figure 27). At the bottom of each assembly is a magnetic chuck that allows the stimuli to be changed rapidly, either automatically, where the motor assembly moves to a stimulus holder and drops off the old stimulus pattern and picks up a new one, or manually. The six motor assemblies are mounted on a force/platen system that allows each motor assembly to be positioned at any x, y location over the animal’s hand.

**Hand holding/monitoring:** A critical aspect of all the experiments is being able to accurately monitor the positions of the fingers. In experiments E1 and E2 the hand will be held flat against a holder that restrains the arm and palm from moving; the fingers (D2-5) are then extended and held securely against moveable mounts. The mounts for D2-4 will be motorized such that a computer can control finger flexion and extension. The hand holder for experiment E3 is a compromise between allowing the animal to freely grasp the object and having the fine movements of the fingers under computer control. This hand holder restrains the animal’s arm and wrist and has tether lines attached to the back of the fingers. The other ends of the tether lines are wrapped around spools that are under computer control. To disengage a finger from the object the tether line will shorten, and will be allowed to lengthen when the finger is supposed to contact the object. Hand position will be monitored using a cyberglove that accurately monitors joint angle and finger position.

**Possible difficulties** The main problem that we expect to have is training animals to perform the tactile–visual matching tasks proposed in experiments E2 and E3 (i.e. task 2). In earlier studies we have trained animals to perform similar tasks that required animals to match embossed letters of the alphabet scanning across the finger pads with letters presented visually. Animals have also been trained to perform a delayed match-to-sample task that required it to indicate whether the orientation of a bar presented one second after a sample bar was the same or different. The tactile tasks that we propose here are potentially more difficult to perform since they require the animal to make discriminations of objects from limited points of view. The sparse inputs may make the task too difficult to learn. If this is so, we will restrict the number of target shapes and make the task easier by increasing the number of contact points.

A second possible difficulty is that the technology for the cyberglove has yet to be developed for monkey-sized hands. We have been working with the company for the last five months and have purchased the first version of the glove to use in human studies. The company has assured us that they will have an improved version of the glove in a few months and that they will produce a small version for us in the near future. If this does not happen then we will be forced to use other ways of monitoring hand conformation. One possibility, which we are presently pursuing, is to mount optical reflectors on the back of the fingers and to track finger movements using video cameras.

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The anatomical studies will be done after the recordings are completed for each monkey. It is estimated that about 3 monkeys will be used in each experiment.
E. Human Subject Research

Although we did not explicitly describe experiments that involve human subjects in the Research and Design section of the proposal, we regularly perform psychophysical experiments on human subjects to assess their ability to perceive tactile stimuli (see progress report and preliminary results section for examples). As such we include here information about the protections that we provide to human subjects.

**Purpose of the study:** The aim is to study tactile perception and how it is processed in the brain. In this part of the study human participants will be presented with simple shapes or textures to their finger pads and will be asked to make judgments about the roughness, shape, or orientation of the presented surfaces. The surfaces model the experience people have in their everyday lives. Moreover, the stimuli and tasks are entirely innocuous. The purpose is to determine how information is integrated between digits on the same or opposite hand. Approximately 10-20 subjects will participate in each study.

**Procedures:** Subjects are asked to participate in either an active or passive tactile task. The passive tasks entail the following: subjects are asked to sit in a quiet room and will place their hand in a support with their arm and fingers behind a curtain. A soft plastic mold is placed around the subject’s fingers to hold them stationary. The stimuli consist of smooth plastic shapes such as oriented bars, curved surfaces, or textured surfaces. When the experiment begins, subjects are presented with one or more of the surfaces. Subjects are then asked to make judgments about the different surfaces. The supports for the fingers are designed such that the subjects can easily pull their hand out of the apparatus at any time. In active tasks, subjects will reach through a curtain and actively scan one of the stimulus surfaces. Each session lasts no more than one hour.

**Risks to the subjects:** Participation in the passive task presents minimal risks of injury to the fingers. To ensure that the stimulus does not push into the skin with excessive force, we have built-in mechanical stops, which act as limit detectors and restrict the amount that the surface can be pushed into the skin. The device also has force detectors, which will be used to limit the forces that are applied to the skin. The hand support is designed such that subjects can pull their fingers free at any time. To avoid fatigue subjects are given regular breaks during each session. The risks associated with participation in this study are no greater than those encountered in daily life. Only healthy adult males and females (21-60) participate in these experiments. Children are not included because their hands are generally too small.

**Adequacy of protection against risks:** Subjects are recruited by posting e-mails to undergraduate and graduate students and by placing fliers around the campus. All subjects are required to sign a consent form, which contains the following statements:

**Benefits:** There are no direct benefits to you from participating in this study. This study will benefit society by providing a better understanding of how the brain processes tactile information.

**Voluntary participation and right to withdraw:** Your participation in this study is entirely voluntary. You choose whether you want to participate. You may quit the project any time you like. There are no penalties, and you will not lose any benefits to which you would otherwise be entitled. If you choose to participate in the study, you can stop your participation at any time, without any penalty.

**Confidentiality:** Any study records that identify you will be kept confidential to the extent possible by law. The Homewood Human Subjects Review Board of the Johns Hopkins University which is responsible for making sure that your participation in the research is kept confidential may review the records from your participation. Otherwise, records that identify you will be available only to people working on the study, unless you give permission for other people to see the records. We will use code numbers or initials rather than participants’ names on data sheets.
**Targeted/Planned Enrollment Table**

This report format should NOT be used for data collection from study participants.

**Study Title:**  Attention and tactile processing in Somatosensory cortex

**Total Planned Enrollment:**  80

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* The "Ethnic Category: Total of All Subjects" must be equal to the "Racial Categories: Total of All Subjects."
Inclusion Enrollment Report

This report format should NOT be used for data collection from study participants.

Study Title: Attention and tactile processing in somatosensory cortex
Total Enrollment: 54
Protocol Number: M1091
Grant Number: NS24086-09

PART A. TOTAL ENROLLMENT REPORT: Number of Subjects Enrolled to Date (Cumulative) by Ethnicity and Race

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Racial Categories

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<tr>
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<td>36</td>
<td>0</td>
<td>54</td>
</tr>
</tbody>
</table>

Racial Categories: Total of All Subjects* 18 36 0 54 *

PART B. HISPANIC ENROLLMENT REPORT: Number of Hispanics or Latinos Enrolled to Date (Cumulative)

<table>
<thead>
<tr>
<th>Racial Categories</th>
<th>Females</th>
<th>Males</th>
<th>Unknown or Not Reported</th>
<th>Total</th>
</tr>
</thead>
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</tr>
<tr>
<td>White</td>
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<tr>
<td>More Than One Race</td>
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</tbody>
</table>

Racial Categories: Total of Hispanics or Latinos** 2 2 0 4 **

* These totals must agree.
** These totals must agree.
F. Vertebrate Animals

1. Animals: Four rhesus monkeys, B-virus negative animals that weigh between 3-4 kg (either sex), will be used per year with about three animals used in each of the above experiments.

2. Justification: Rhesus monkeys are used because they are one of the few species that can be used to study the neural mechanisms of tactile perception from the hand. Only rhesus monkeys have hands and fingers that are like those of humans and can be trained to perform the complex behavioral tasks described above. We have been working with these animals for many years and know how to train them to do the tasks specified in the proposal. We record from each hemisphere of each animal for about a month. Three animals per year is reasonable since it means that we can record for about half of the year.

3. Veterinary care: All animals will be purchased through the Department of Comparative Medicine who insure that the animals are B-virus negative, test the animals regularly for tuberculosis and intestinal parasites, and are responsible for their daily care and well being. All of the animals are caged in specially designed animal quarters in the Mind/Brain Institute, which is staffed by caretakers of the Department of Comparative Medicine. All procedures used are reviewed and approved by the Johns Hopkins Animal Care and Use Committee.

4. Procedures to minimize discomfort: During surgery: All surgical procedures are performed under sterile conditions with the animals under general anesthesia using sodium pentobarbital. To implant the head holding device, the animal is first sedated with ketamine (20 mg/kg IM) and then anesthetized with either sodium pentobarbital (25mg/kg IV) or with isoflurane (inhalation). Recently we have started using isoflurane to do these surgeries since we have found that the animals recover more quickly and seem to show fewer aftereffects of the anesthesia. We plan to use sodium pentobarbital as a backup method of anesthetizing the animals. Typically, the entire operation lasts 2-3 hours during which time the anesthetic is administered as necessary. After surgery the animal is allowed to recover under continuous observation by Dr. Hsiao or one of the technicians. A topical anesthetic (Xylocaine, 2%) is applied and infiltrated into the margins of the wound. After the surgery, the animal is given doses of Buprenex (0.03 mg/kg IM buprenorphine) for several days or as needed and a single large dose of penicillin (40,000 IU/kg). When the animal is sufficiently alert and has regained muscular control it is returned to the cage.

During training and recording: All of the procedures are designed to minimize discomfort and pain. Training and recordings are performed six days a week from Monday through Saturday, and throughout these sessions both the animal's fluid intake and weight are carefully controlled and monitored. Animals are given a minimum daily dose of about 35 ml/kg body weight of water per day either through rewards or by a supplement at the end of the day. If the animal happens to work for more than 35 ml/kg during the training session then it is allowed to do so. In addition to the water, animals are fed raisins and other fruits throughout the day and on a regular basis are fed "monkey mash", which consists of crushed monkey chow biscuits and mashed banana. On Saturdays after training, the animals are allowed to drink as much water as they like. On Sundays the water intake is restricted to 100-120 ml to insure that the animals are motivated to work on Mondays. The amount 35 ml/kg is an average based on experience and is only approximate. The actual amount varies according to the individual needs of the animal and is determined to be the amount appropriate to prevent dehydration and weight loss. During the entire training and recording periods animals are monitored for signs of dehydration such as weight loss, constipation, lethargy; or lack of interest in performing their task. If there is any indication of discomfort or distress the animals are given a few days off from the experiment and are given an increased amount of water when the training is restarted. Except for the period just before surgery (see below), the animals receive as much food as
they like. The mild water restriction that we impose on the animals is necessary because we require that the animals be motivated to work for a reward in the experiments. There is no other way of motivating the animal to work for the many trials that are required in a single day. Thus, food is not useful because the animals become sated too quickly.

5. **Method of euthanasia:** After approximately 30 recording days in each hemisphere, the animals are euthanized by a large IV dose of sodium pentobarbital (150 mg/kg/IV). This is one of the recommended methods for euthanizing animals as specified in the 2000 report of the AVMA panel on euthanasia. The brain is then removed from the animal, sectioned, and the electrode penetrations are located under a microscope.
G. Reference List


Craig JC (1985) Attending to two fingers: two hands are better than one. Percept Psychophys 38: 496-511.


H. Consortium/Contractual Arrangements
None.

I. Consultants
None.

Personal Info
Principal Investigator/Program Director (last, First, Middle): Hsiao, Steven S

**CHECKLIST**

**TYPE OF APPLICATION** (Check all that apply.)

☐ NEW application. (This application is being submitted to the PHS for the first time.)

☐ SBIR Phase I ☐ SBIR Phase II: SBIR Phase I Grant No. ☐ SBIR Fast Track

☐ STTR Phase I ☐ STTR Phase II: STTR Phase I Grant No. ☐ STTR Fast Track

☐ REVISION of application number:

(This application replaces a prior unfunded version of a new, competing continuation, or supplemental application.)

☒ COMPETING CONTINUATION of grant number: NS034086

(This application is to extend a funded grant beyond its current project period.)

☐ No ☐ Previously reported

☐ Yes, if "Yes," ☐ Not previously reported

☐ SUPPLEMENT to grant number:

(This application is for additional funds to supplement a currently funded grant.)

☐ CHANGE of principal investigator/program director.

Name of former principal investigator/program director:

☐ FOREIGN application or significant foreign component.

**1. PROGRAM INCOME** (See Instructions.)

All applications must indicate whether program income is anticipated during the period(s) for which grant support is requested. If program income is anticipated, use the format below to reflect the amount and source(s).

<table>
<thead>
<tr>
<th>Budget Period</th>
<th>Anticipated Amount</th>
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</table>

**2. ASSURANCES/CERTIFICATIONS** (See Instructions.)

The following assurances/certifications are made and verified by the signature of the Official Signing for Applicant Organization on the Face Page of the application. Descriptions of individual assurances/certifications are provided in Section III. If unable to certify compliance, where applicable, provide an explanation and place it after this page.

☒ Human Subjects; ☒ Research Using Human Embryonic Stem Cells; ☒ Research on Transplantation of Human Fetal Tissue; ☒ Women and Minorities Inclusion Policy; ☒ Inclusion of Children Policy; ☒ Vertebrate Animals Participation.

Debarment and Suspension; ☒ Drug-Free Workplace (applicable to new Type 1 or revised Type 1 applications only); ☒ Lobbying; ☐ Non-Delinquency on Federal Debt; ☒ Research Misconduct; ☒ Civil Rights (Form HHS 441 or HHS 690); ☒ Handicapped Individuals (Form HHS 641 or HHS 690); ☒ Sex Discrimination (Form HHS 639-A or HHS 690); ☒ Age Discrimination (Form HHS 680 or HHS 690); ☒ Recombinant DNA and Human Gene Transfer Research; ☒ Financial Conflict of Interest (except Phase I SBIR/STTR) ☒ STTR ONLY: Certification of Research Institution Participation.

**3. FACILITIES AND ADMINISTRATIVE COSTS (F&A) INDIRECT COSTS.** See specific instructions.

☒ DHHS Agreement dated: September 17, 2004 ☐ No Facilities And Administrative Costs Requested.

☐ DHHS Agreement being negotiated with Regional Office.

☐ No DHHS Agreement, but rate established with Date

**CALCULATION** (The entire grant application, including the Checklist, will be reproduced and provided to peer reviewers as confidential information.)

a. Initial budget period: Amount of base $396,209 x Rate applied 63.00 % = F&A costs $249,612

b. 02 year Amount of base $408,092 x Rate applied 63.50 % = F&A costs $259,138

c. 03 year Amount of base $447,919 x Rate applied 64.00 % = F&A costs $286,688

d. 04 year Amount of base $461,362 x Rate applied 64.00 % = F&A costs $295,272

e. 05 year Amount of base $475,202 x Rate applied 64.00 % = F&A costs $304,129

**TOTAL F&A Costs** $1,394,819

*Check appropriate box(es):

☐ Salary and wages base ☒ Modified total direct cost base ☐ Other base (Explain)

☐ Off-site, other special rate, or more than one rate involved (Explain)

Explanation (Attach separate sheet, if necessary):

**4. SMOKE-FREE WORKPLACE** ☒ Yes ☐ No (The response to this question has no impact on the review or funding of this application.)