

**Severe self-injury**  
**in developmental disorders:**  
*Sensory & immune findings from the periphery*

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*University of Minnesota*

Interagency Coordinating Committee for Autism  
2016

# Disclosures

None

Not an ASD expert

# The Need

Good evening, my name is \_\_\_\_\_. I am typing on a phone, so excuse obvious typing issues. I am a mom to a 9 year old with autism. His repetitive head behaviors in toddler years grew into highly intense head punching a few years ago. The typography of his sibs has evolved and recently has gone back to chin and temple punching. Your name came up a year ago and many things prevented me from reaching out to a complete stranger.

Fast forward to today and I find myself in a crisis. \_\_\_\_\_ was just released from \_\_\_\_\_ on Friday with an ng tube. He refuses to eat solids.....Unraveling this story is interesting, but insanity producing to us, parents. So now I have 2 major issues and depending on the day, he can be very physically aggressive too.

I could tell you so much more, but I reach out to you today in hopes you have ideas. The hospital was at a loss on how to support us as intense behavior issues are not their specialty and the pysch unit seemed really inappropriate for a young, autistic child with a new ng tube.

# Parent Perspective

- Why?
- Help, please.

# Scientific Puzzle & Clinical Paradox

- Why do some people with intellectual and developmental disabilities/disorders self-injure by almost any possible means without regard to the consequences? Actions that should normally be regulated by their outcome become 'out of control' among individuals with chronic self-injury.



# Self-injury & ASD

- **Prevalence:** Estimates vary widely (8% - 72%)
  - Subgroups? (e.g. HFA vs. LFA)
- **Mechanisms:** unknown & understudied
  - We don't understand pathophysiology
- **Interventions:**
  - Established evidence base for behavioral interventions but ...
    - Evidence for more severe cases is limited particularly wrt maintenance
  - Biomedical intervention – no consistent evidence
  - Evidence-vacuum: sad/bad things happen (restraint, sedation, aversives...)
- **Cost / burden of care:** Significant
  - Society: NIH 1998 US estimate ... ~\$3 billion
  - Family: likely far exceeds impact of ASD alone
  - Person: significantly impacts quality of life

# Self-injurious behavior (SIB): Some general conceptual models

- Developmental – Behavioral
  - Communication: SIB develops into a means of expressive communication in non/minimally verbal cases
- Psychological – Psychiatric
  - Linked to essentially all forms of comorbid psychiatric symptoms (irritability, anxiety, OCD, depression, hyperactivity)
- Neurological
  - Sensory / Pain: common assumption is insensitivity to pain or increased pain threshold

# Self-injury & pain: Insights from animal models & pain-related neurologic conditions

- Self-injury is the standard behavioral marker of altered nociception and pain in animal models that involve damage to peripheral nerves.
- Consistent with human cases (e.g. sensory neuropathies) where damage to peripheral nerves can produce:
  - altered sensation at peripheral sites (focal → generalized)
  - “hyperalgesia” (increased sensitivity to pain) & “allodynia”(non-noxious stimuli perceived as painful)
  - self-injury targeted to site where sensation has been altered
- Inflammatory & immune-related mechanisms play a role in the development of altered nociception and neuropathic pain in both animal models and clinical conditions.
- By way of analogy think about scratch → itch or related sensory experiences you have had (e.g., sunburn)
- In all the clinical instances and preclinical models, it seems that SIB is driven by increased sensory sensitivity, NOT decreased sensitivity.



# Our Overall Approach & Focus

- **Pain markers in persons with cognitive / communication deficits with and without SIB**
  - Sensory testing + pain biomarkers
  - **SIB associated with hyperalgesia: increased sensory sensitivity + altered autonomic & immune activity**

# Collaborators

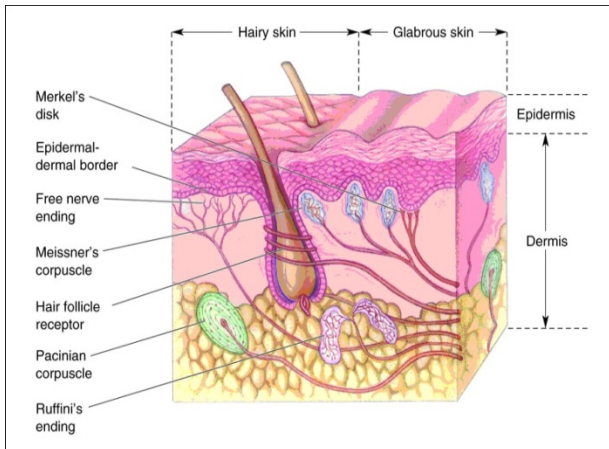
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- **G. Allen Finley**
- **Patrick J. McGrath**
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  - IWK Health Center
- **Laura Stone**
  - McGill University
- **Tim Oberlander**
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  - University of British Columbia
- **Raymond Tervo**
  - Mayo Clinic
- **Elizabeth Gilles**
  - Children's Hospitals St. Paul
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- **Breanne Byiers**
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# Self-Injury - saliva, skin, and sensory mechanisms

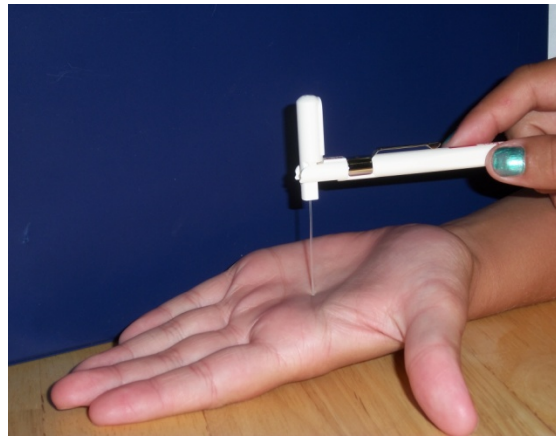
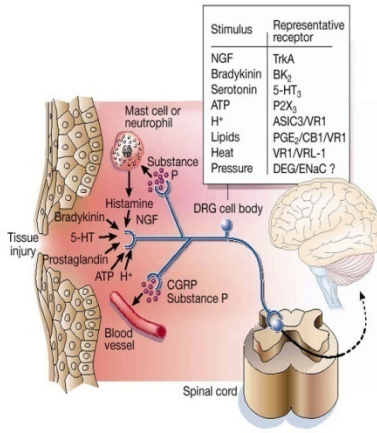


**Saliva:**  
Non-invasive window;  
vulnerable population



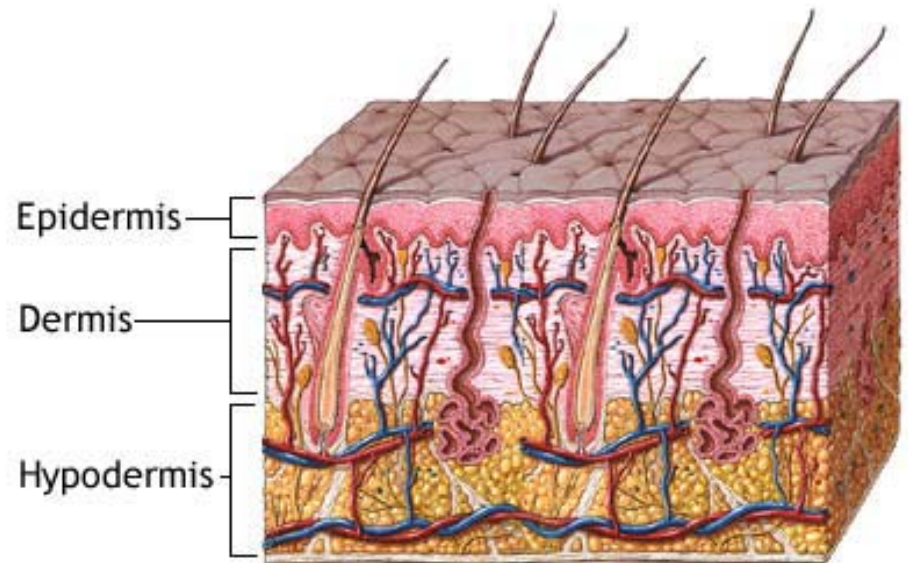
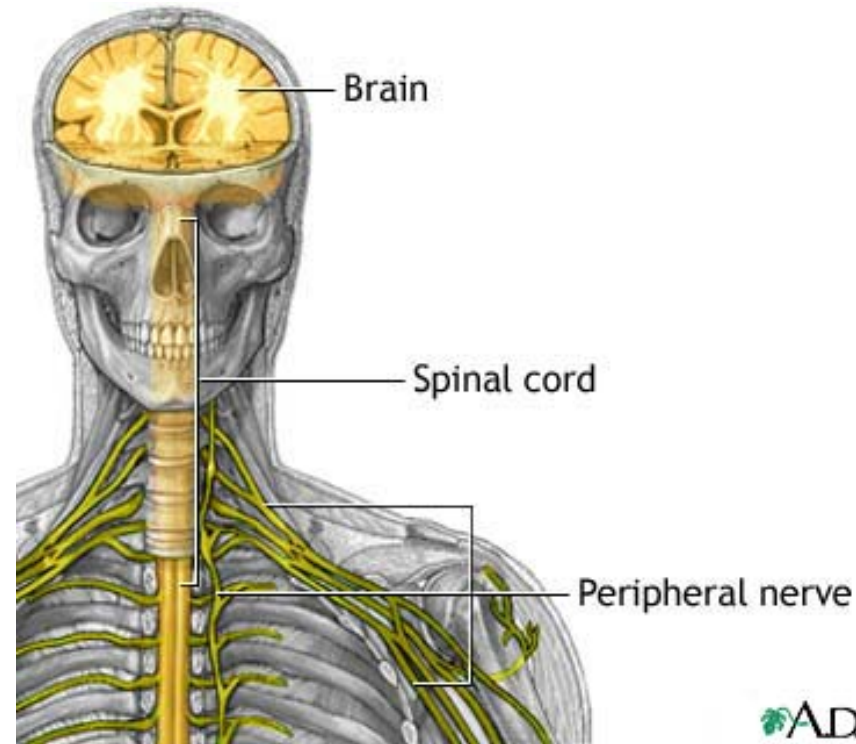
**Skin:**  
Where behavior meets biology

Axons from skin	A $\alpha$	A $\beta$	A $\delta$	C
Axons from muscles	Group I	II	III	IV
Diameter ( $\mu$ m)	15-20	6-12	1-5	0.2-1.5
Speed (m/sec)	80-120	35-75	5-30	0.5-2
Sensory receptors	Proprioceptors of skeletal muscle	Mechanoreceptors of skin	Pain, temperature	Temperature, pain, itch

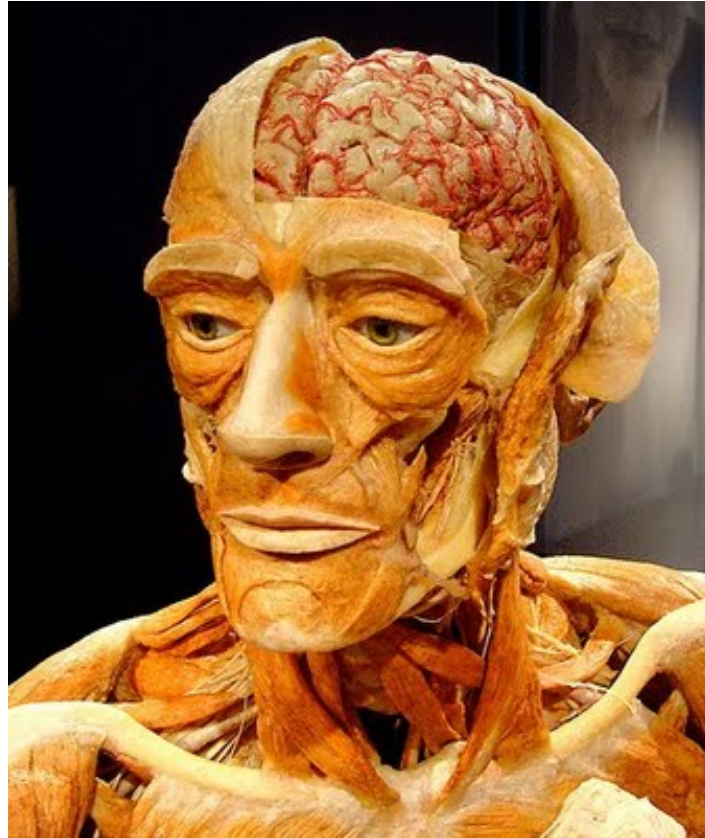


**Sensory Mechanisms:**  
Thresholds – intact, altered?

# Nervous System & Skin



## How Does Experience Get Under the Skin?



# Direct Route

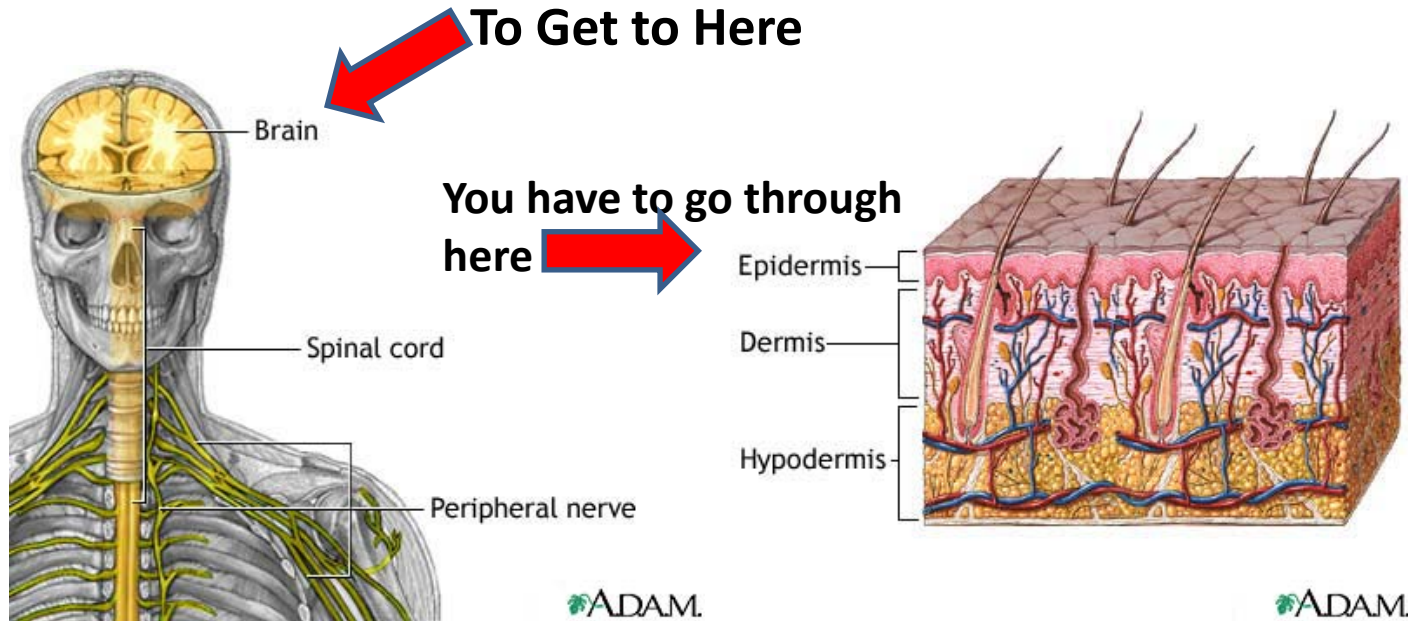


“Whoa! *That* was a good one! Try it, Hobbs — just poke his brain right where my finger is.”

Experience gets 'under the skin' .....through the skin

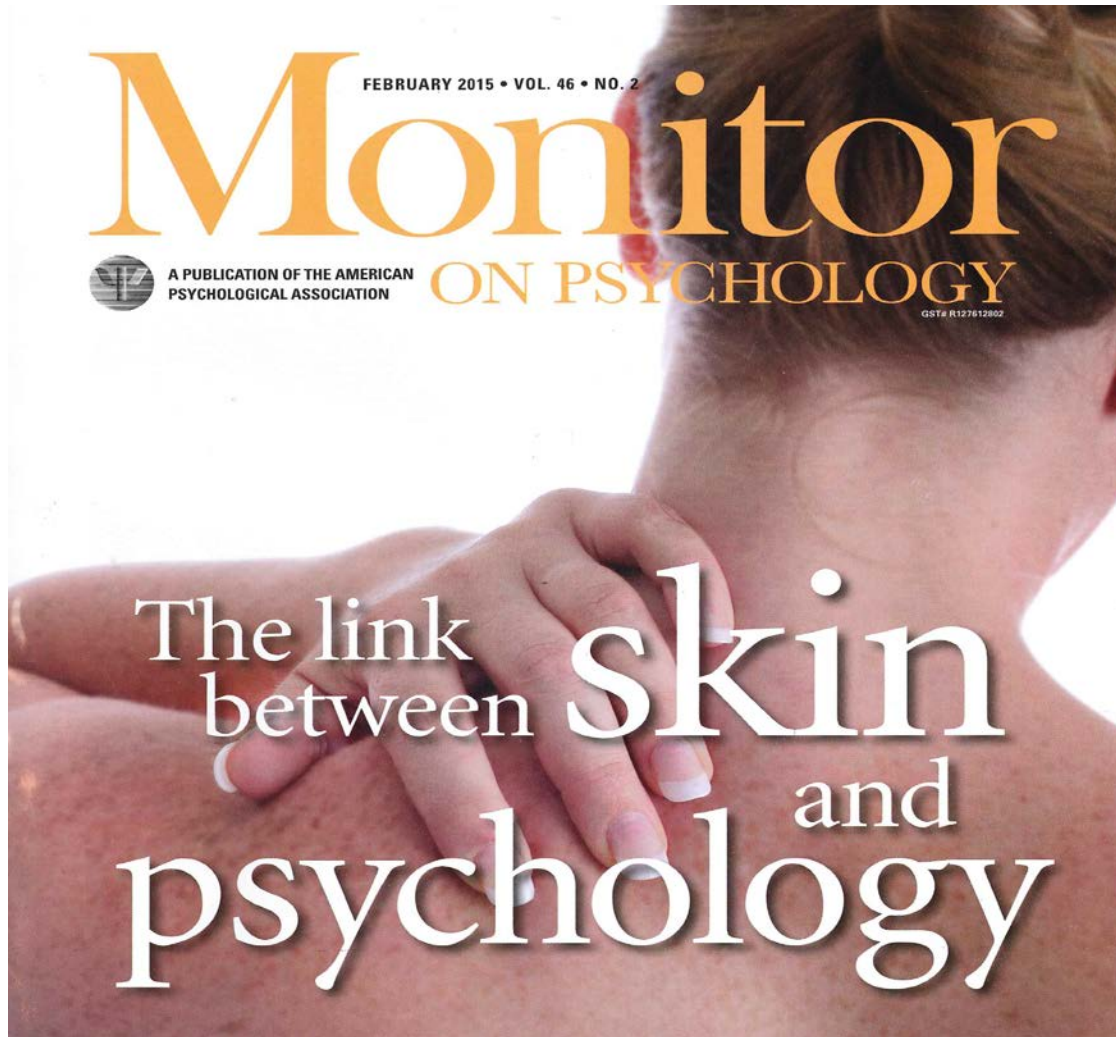


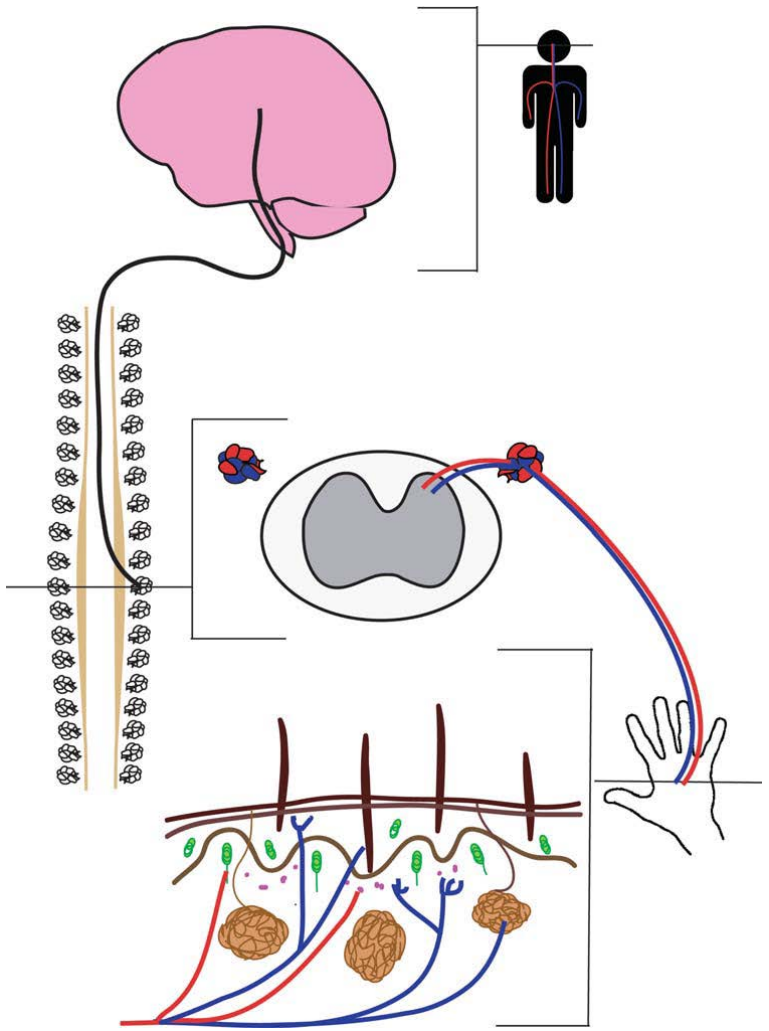
# Peripheral Nervous System & Skin ...for touch/tactile and pain/nociception...

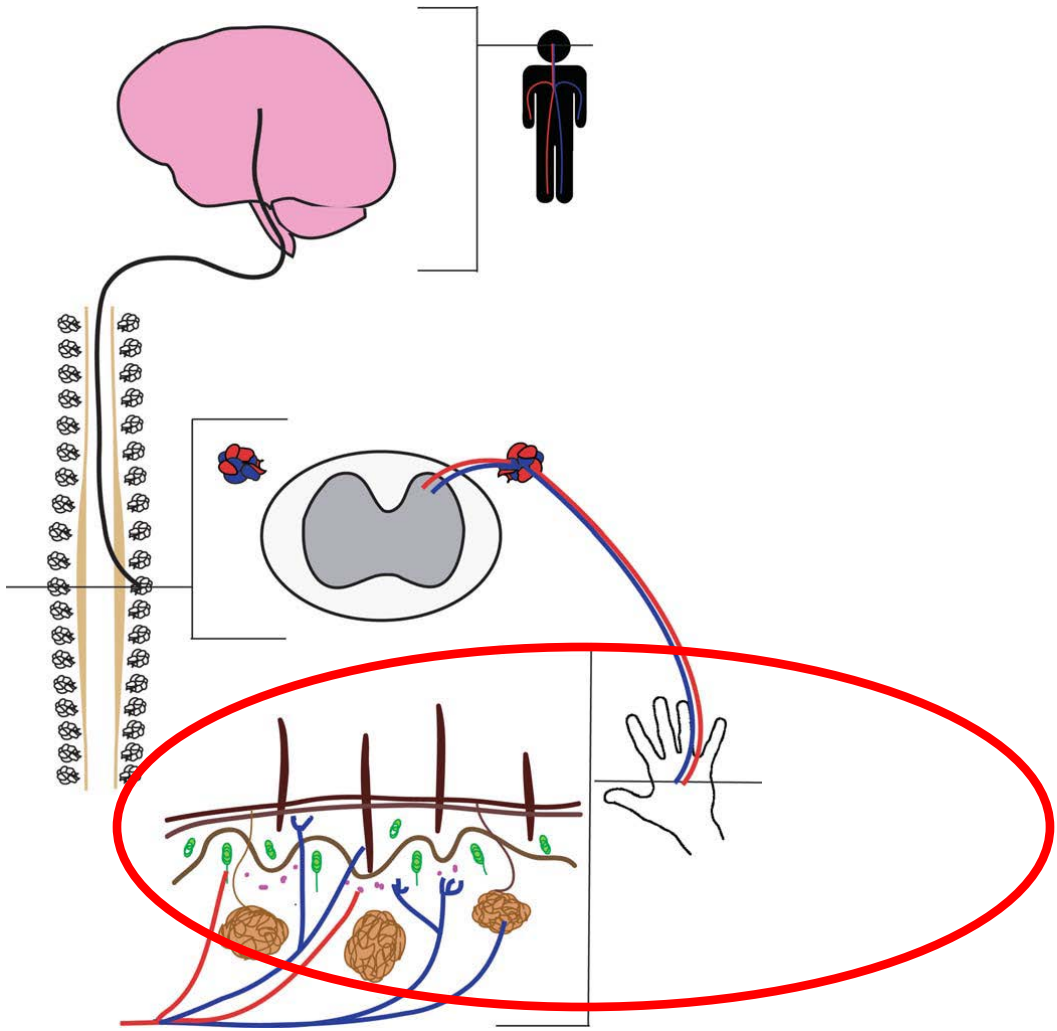




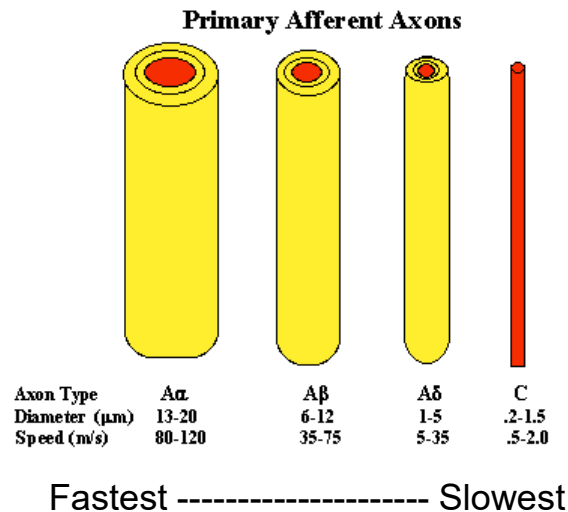
The skin is our body's largest sensory organ – comprised, in part, by an array of different specialized nerve endings.....







# Background – Sensory Fibers



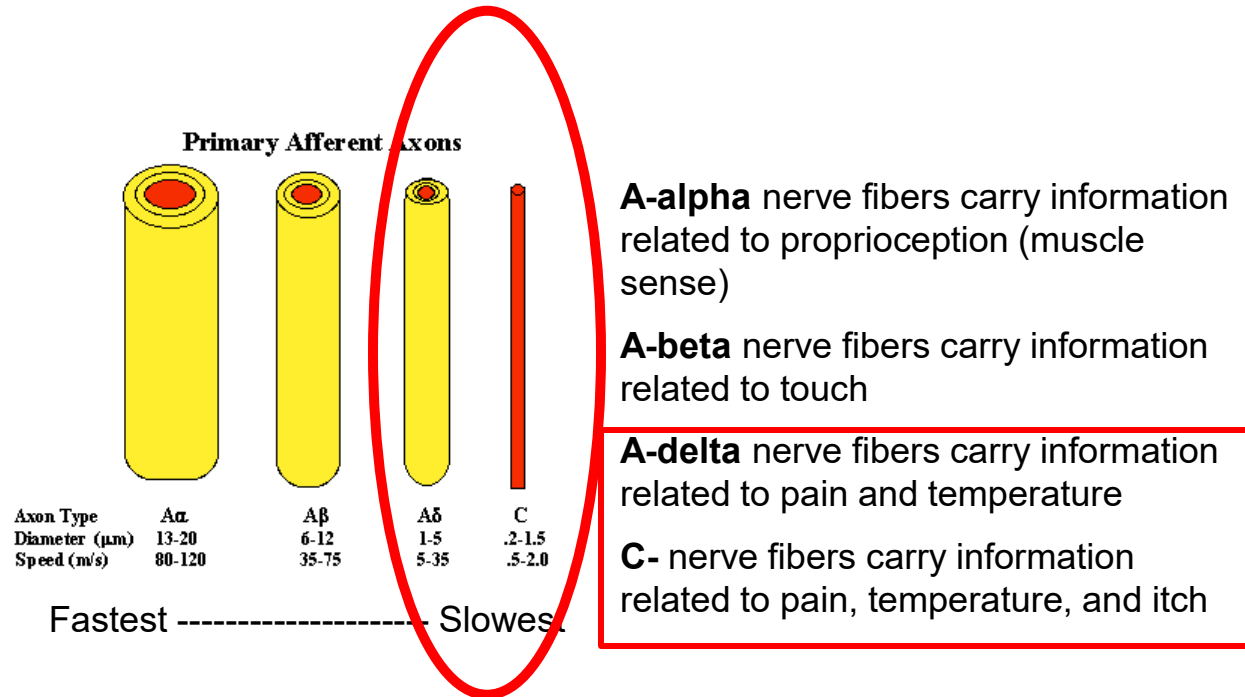
**A-alpha** nerve fibers carry information related to proprioception (muscle sense)

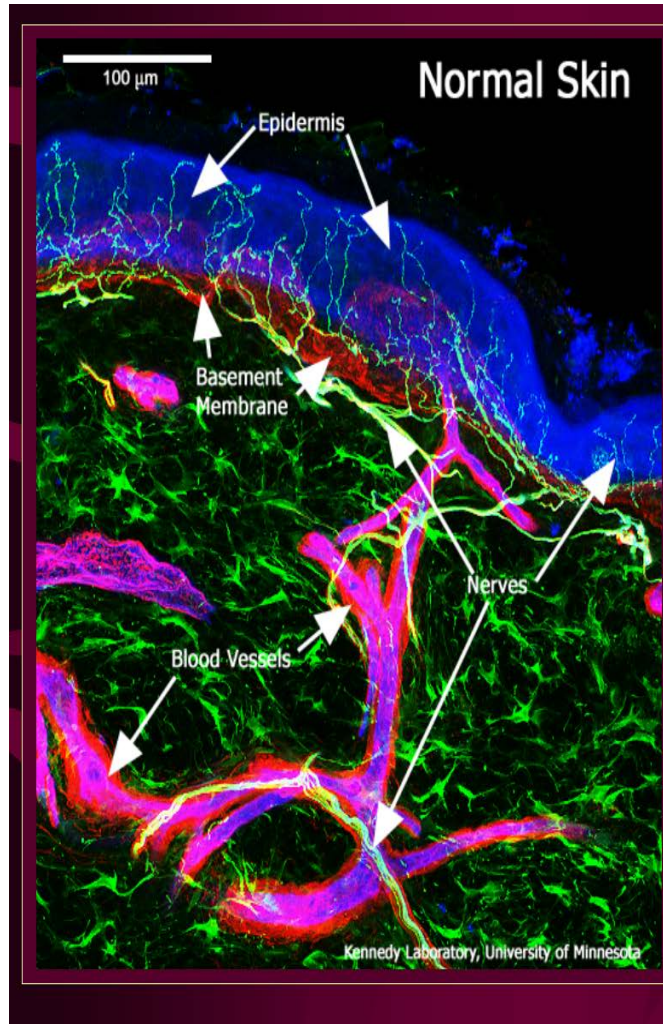
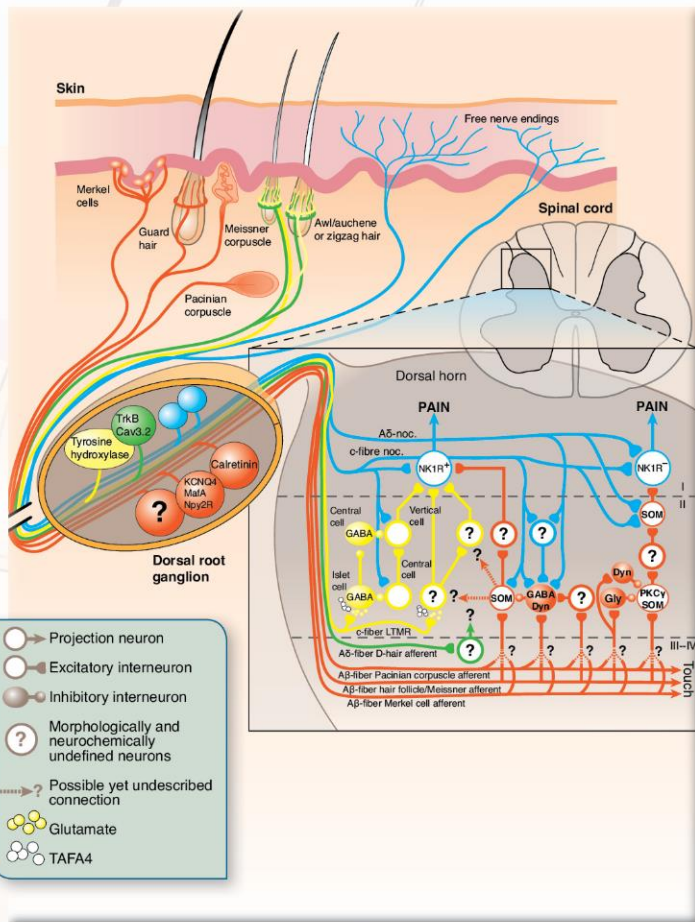
**A-beta** nerve fibers carry information related to touch

**A-delta** nerve fibers carry information related to pain and temperature

**C-** nerve fibers carry information related to pain, temperature, and itch

# Background – Sensory Fibers





## Normal Skin

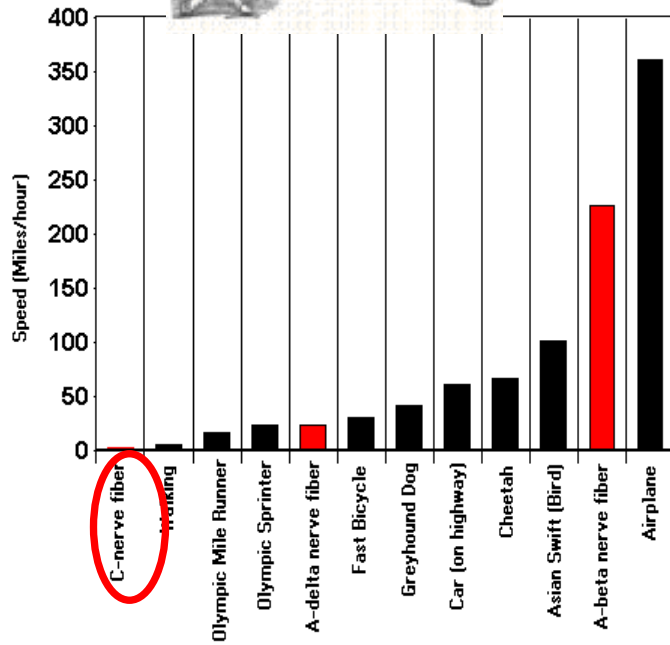
Sensory Nerves:  
Nerve Bundles  
Sub Epidermal Neural Plexus  
Epidermal Nerve Fibers

Nerve Fiber Assessment  
Epidermal Nerve Fibers  
Basement membrane  
Branch points and length

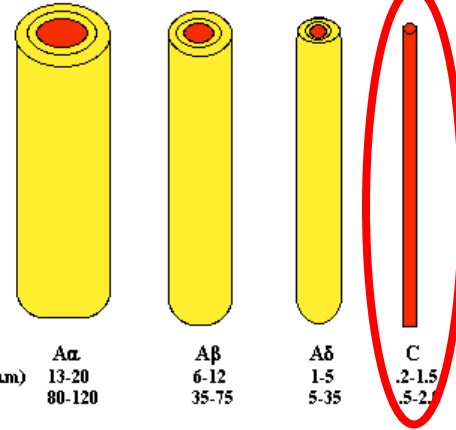
Epidermal Nerve Fiber Density  
Accurate  
Objective  
Quantifiable

## Bio-Behavioral Analysis of SIB, Sensory Mechanisms, and Pain

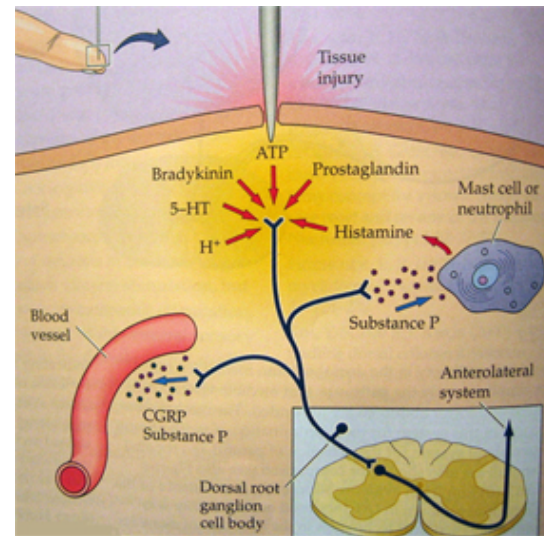




### Primary Afferent Axons

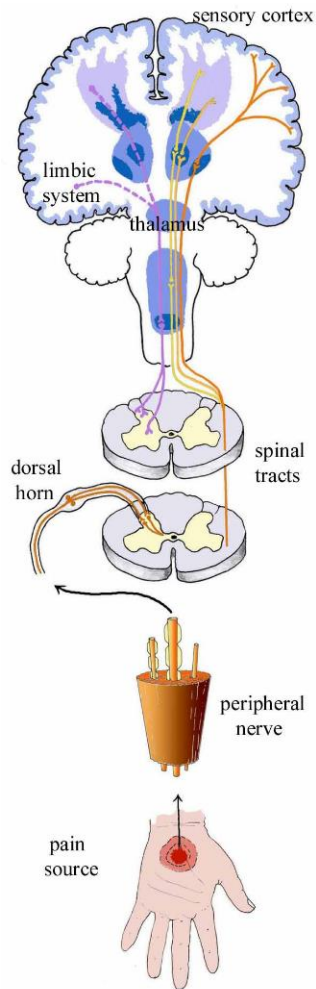


Axon Type	A $\alpha$	A $\beta$	A $\delta$	C
Diameter ( $\mu\text{m}$ )	13-20	6-12	1-5	.2-1.5
Speed (m/s)	80-120	35-75	5-35	5-2.5



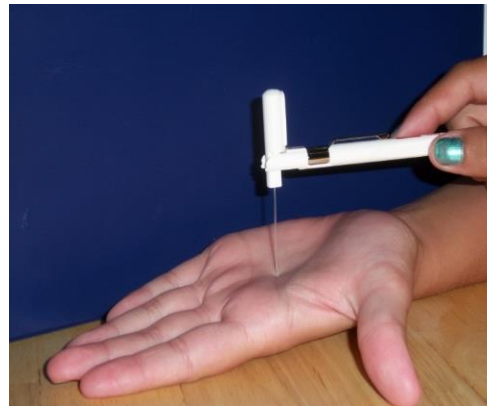


## (m) Quantitative Sensory testing



Pain perception depends on the functioning of the peripheral nerves and their ability to transmit the pain **signal** to the central nervous system (Ji & Woolf, 1999).

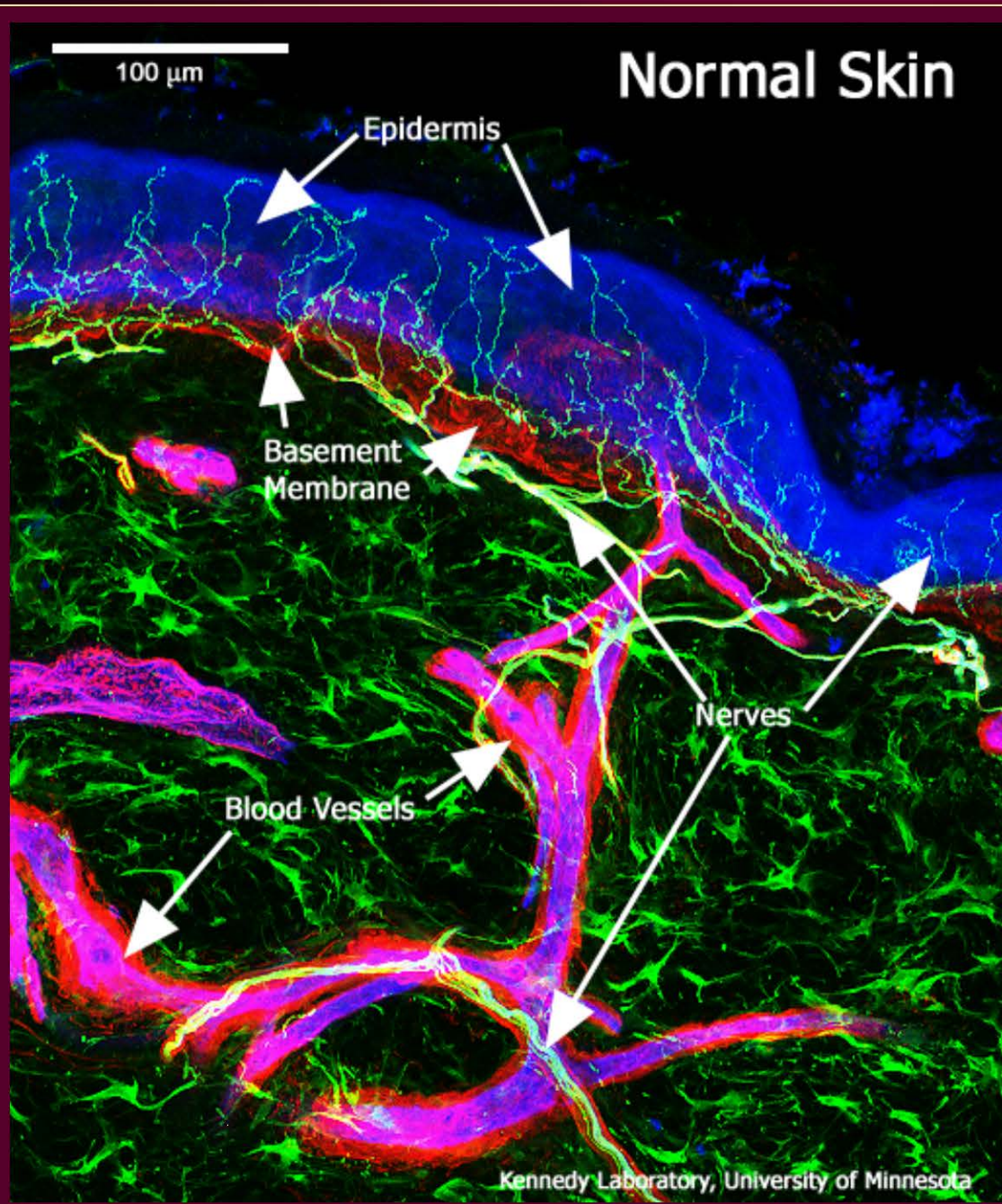
Quantitative sensory testing provides an opportunity to study **indirectly peripheral nerve functional integrity** (Greenspan, 2001).





# Skin Biopsy Approach/Methods

- Sample to Date
  - SIB cases
    - 25 adult [80% profound cognitive impairment]/Residential
    - 5 pediatric [100% profound cognitive impairment]/Outpatient
    - 13 pediatric [global developmental delay]/Outpatient
  - No SIB with developmental disability/delay controls (N = 16/10)
  - No SIB with no developmental disability controls (N = 45 [but adult])
- 3 mm punch skin biopsy
  - SIB Group: non-self-injurious body site
  - Control: site-matched normal skin samples
  - No known primary chronic illness (e.g., diabetes) or genetic condition associated w/SIB (e.g., LNS).
- Dependent measures
  - Epidermal nerve fiber (ENF) structure: coefficient of variation (CV)
  - Peptide content: SP, CRGP, VIP
  - Immune activity: mast cell granulation



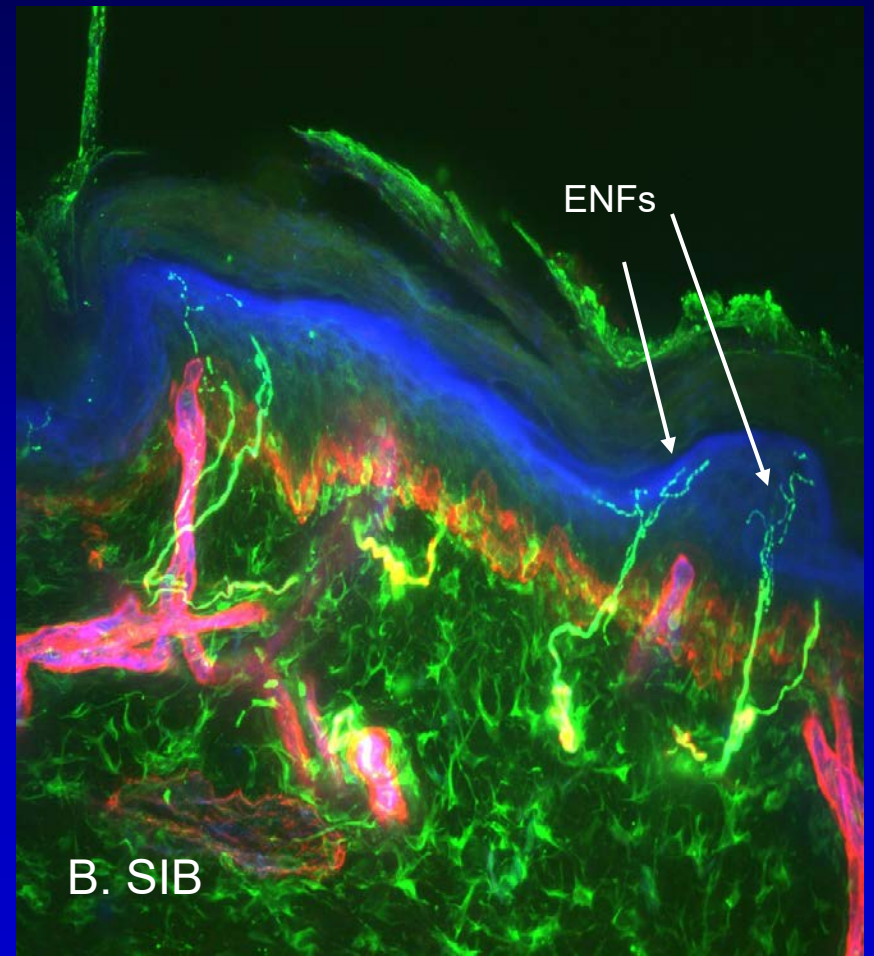
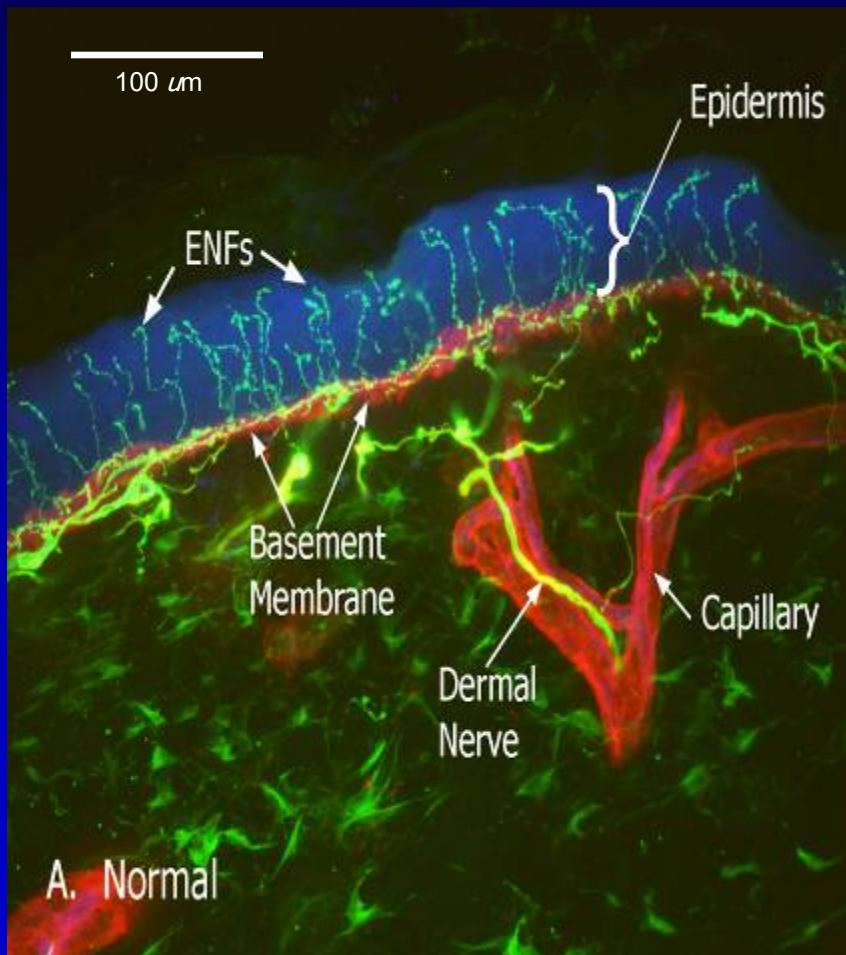
## Normal Skin

Sensory Nerves:  
Nerve Bundles  
Sub Epidermal Neural Plexus  
Epidermal Nerve Fibers

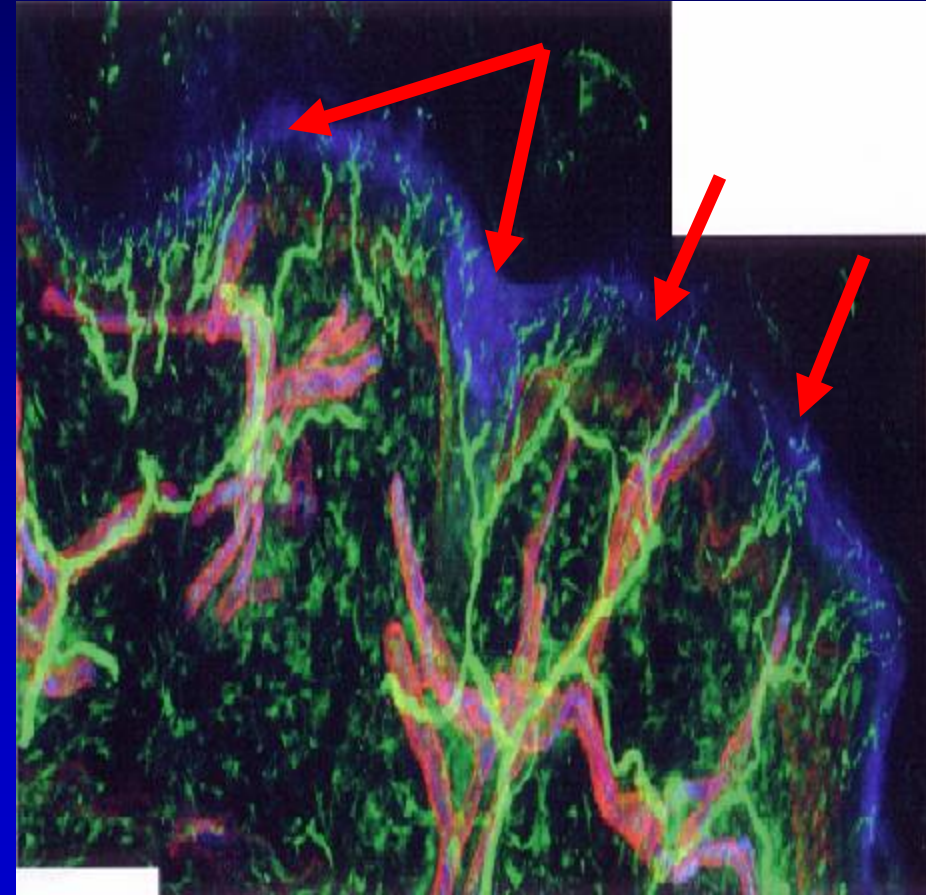
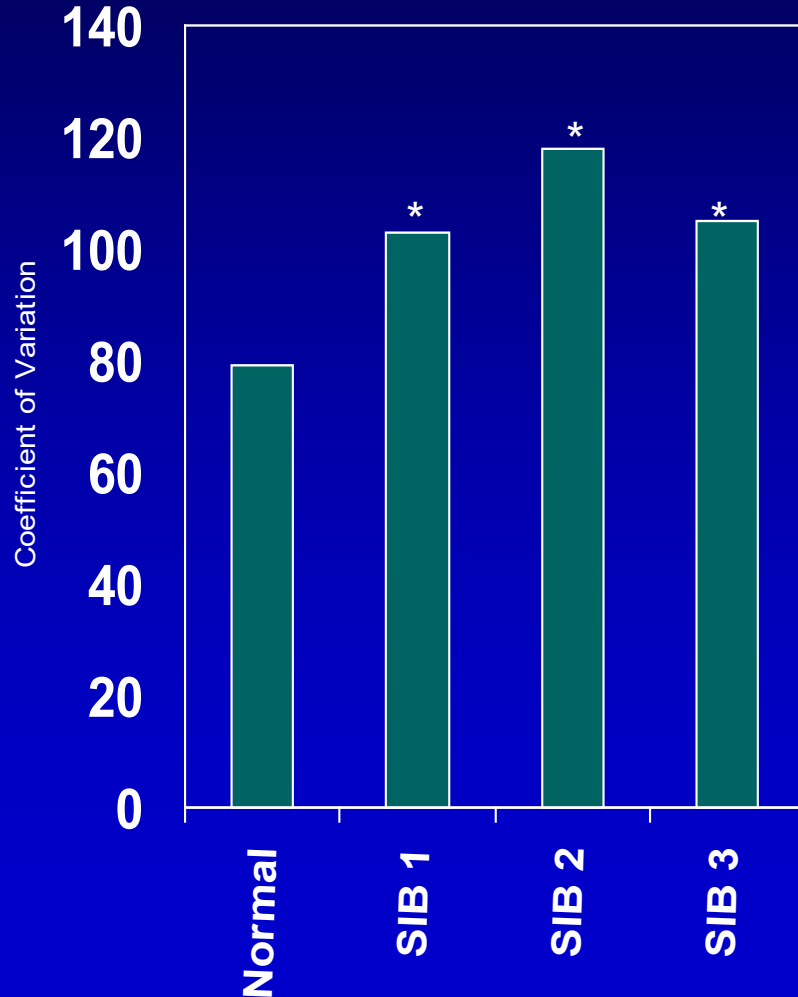
Nerve Fiber Assessment  
Epidermal Nerve Fibers  
Basement membrane  
Branch points and length

Epidermal Nerve Fiber Density  
Accurate  
Objective  
Quantifiable

# Altered Peripheral Nerve Morphology



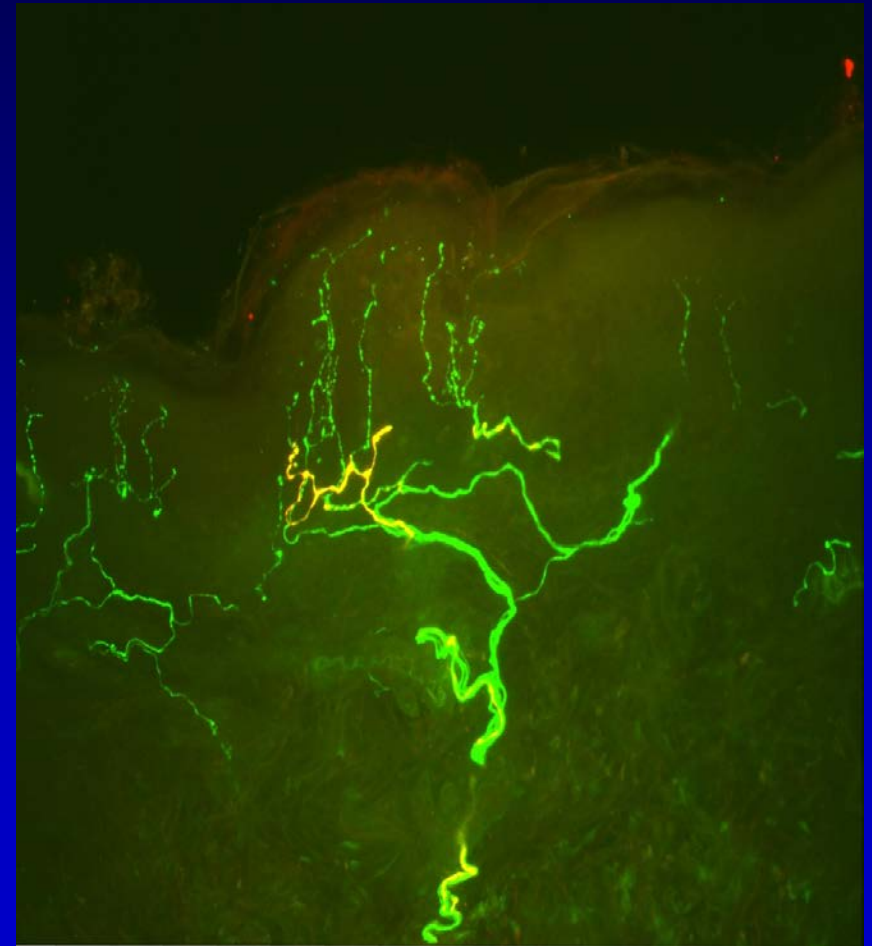
# Epidermal nerve fiber (ENF) density: Coefficient of variation (CV)



# Altered Neuropeptide Content

Density, Spacing, and Neuropeptide Content of SIB and Control Biopsies

Forearm Biopsy	ENF Density	Gap CV	SP	CGRP	VIP
SIB 1	27.6	105	5	12	0
SIB 2	31	118	9	10	0
SIB 3	37.2	103	7	12	0
Control	36.4 5% = 17.8 N=45	79 N=32	2.0 N=32	10.3 N=32	0



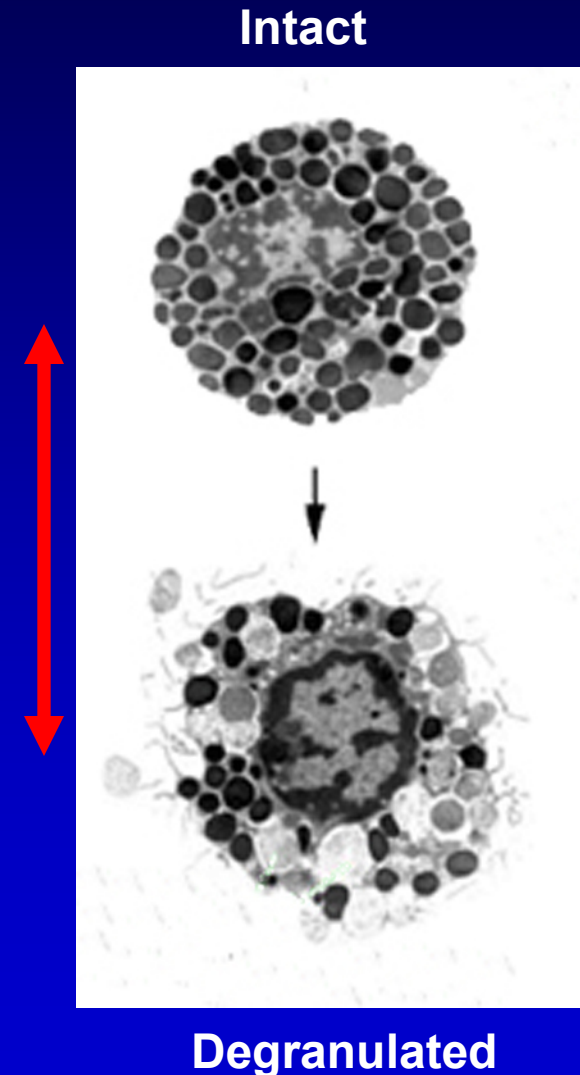
# Immune Activity: Mast Cell Degranulation



Degree of granulation = Degree of Immune activity

## SIB vs No SIB Controls

- $p$  (SIB/dm) = 0.75
- $p$  (CTL/dm) = 0.23
- $X^2 = 4.99 < 0.05$

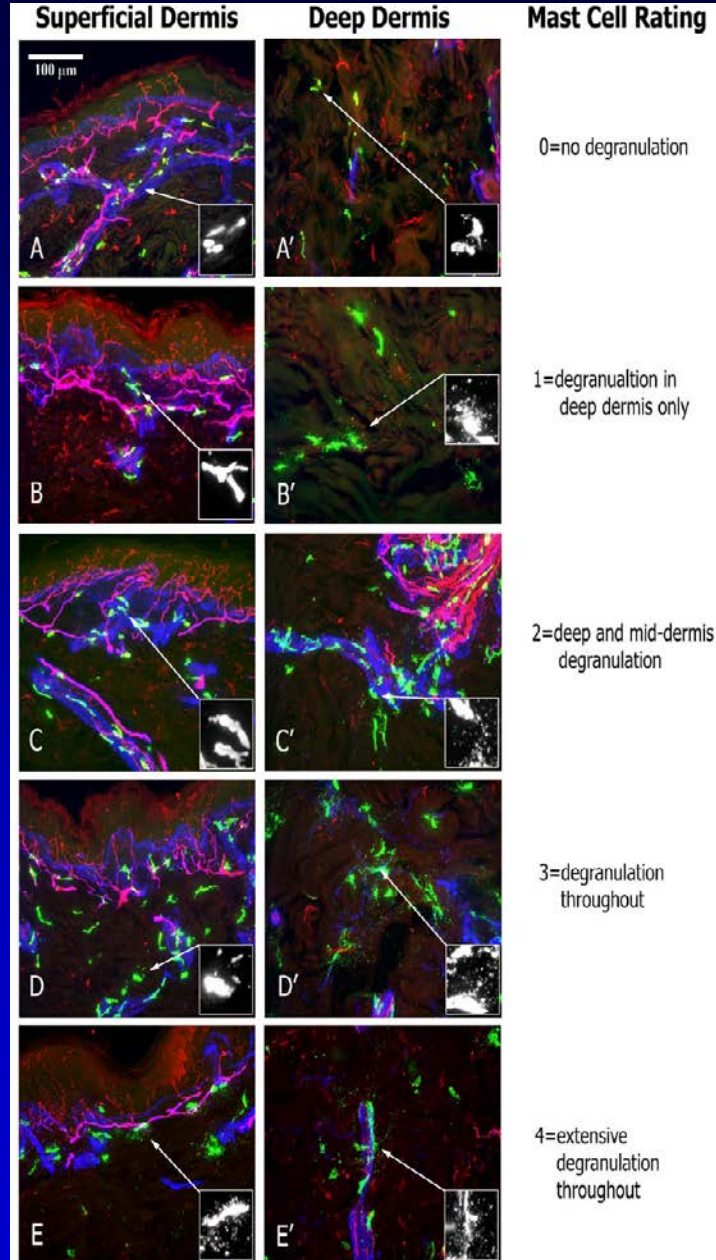
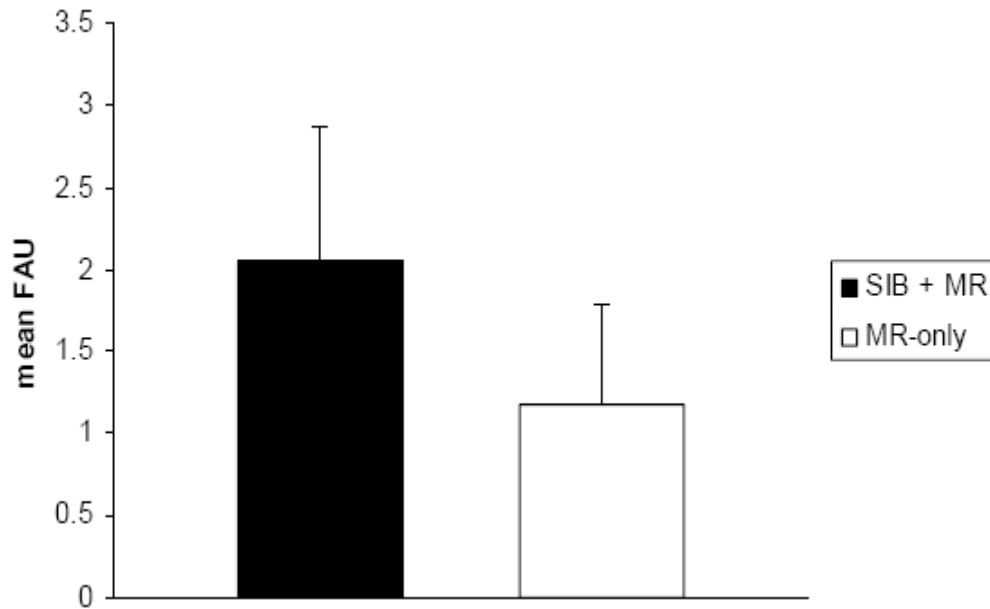
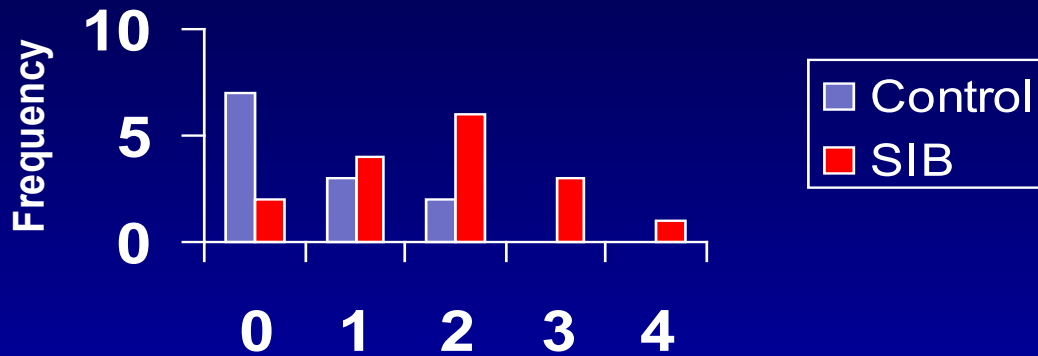




# Neuro-Immune Crosstalk:

## Sensory Behavioral Effects?

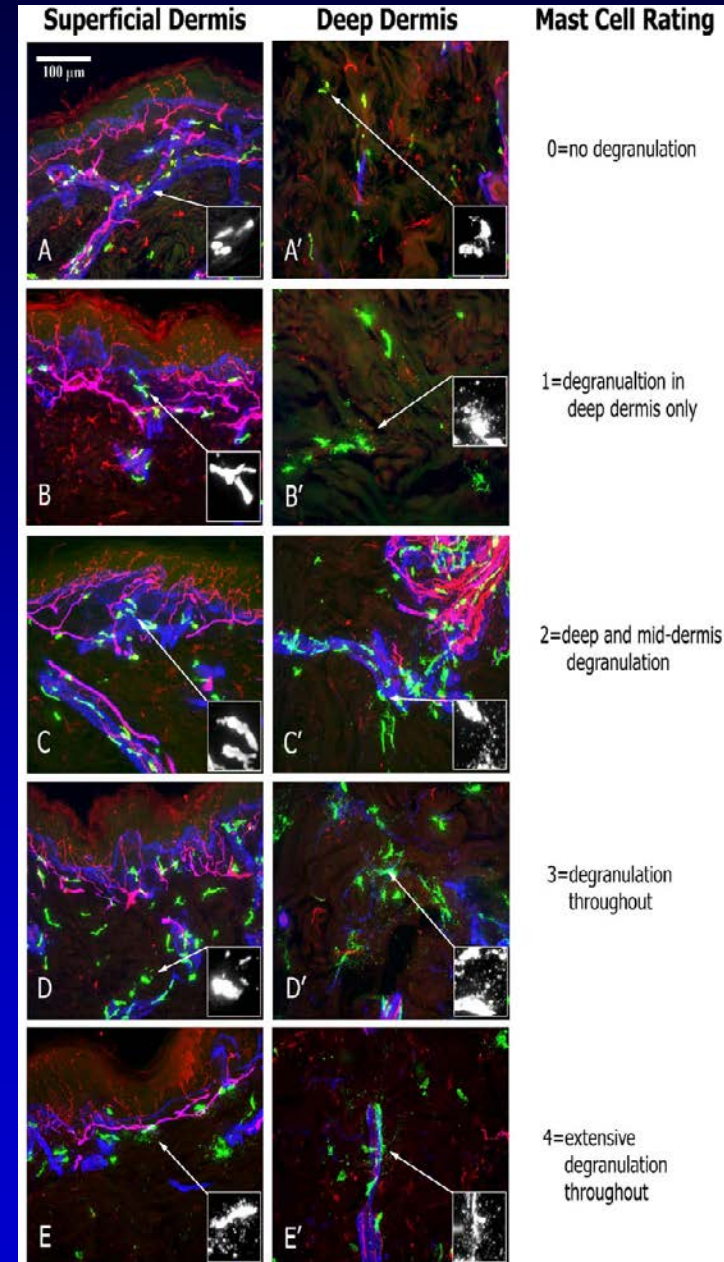
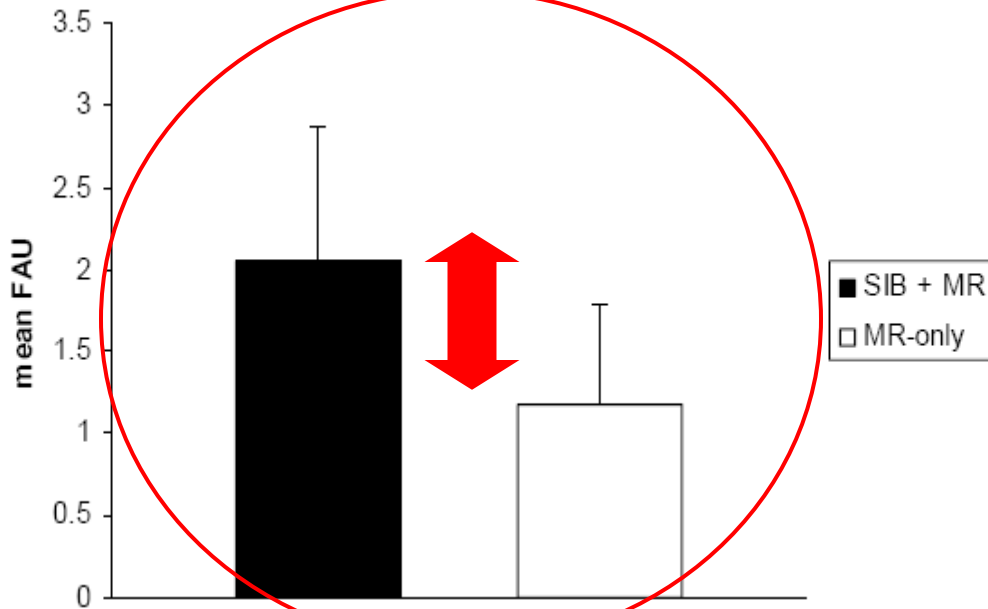
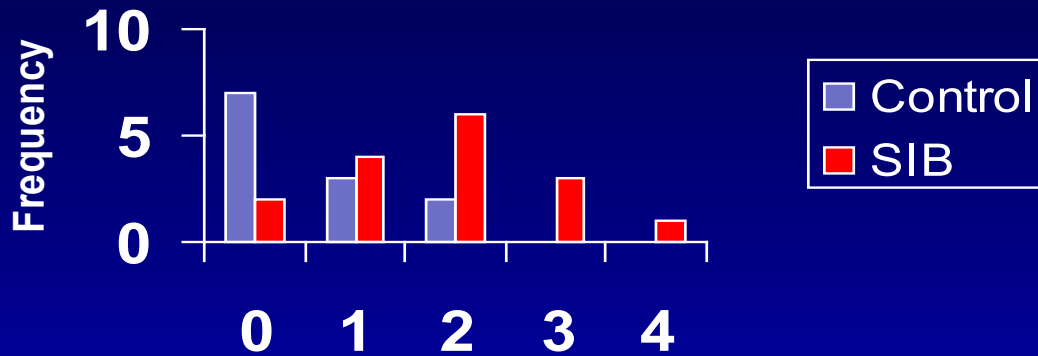
Symons et al (2009) *Brain, Behavior, & Immunity*, 23:365-370



# Neuro-Immune Crosstalk:

## Sensory Behavioral Effects?

Symons et al (2009) *Brain, Behavior, & Immunity*, 23:365-370



So What?

# Peripheral ‘pain’ biomarkers = SIB risk markers?

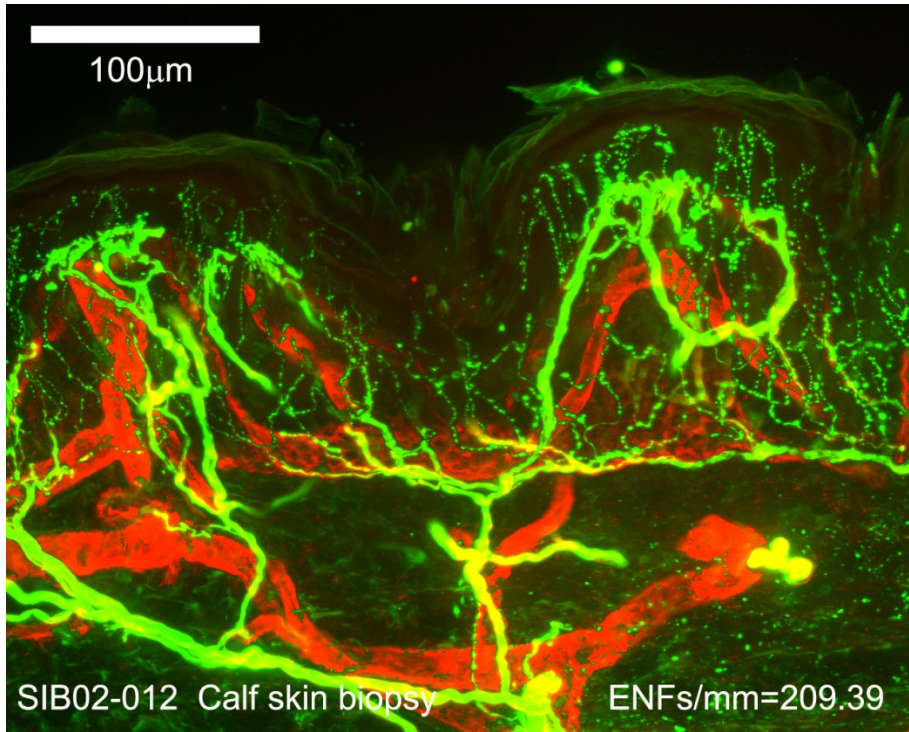
- initial observations of altered intra-epidermal nerve density differences in adult sample with chronic SIB (no controls)

*Pain 134, 232-237.*

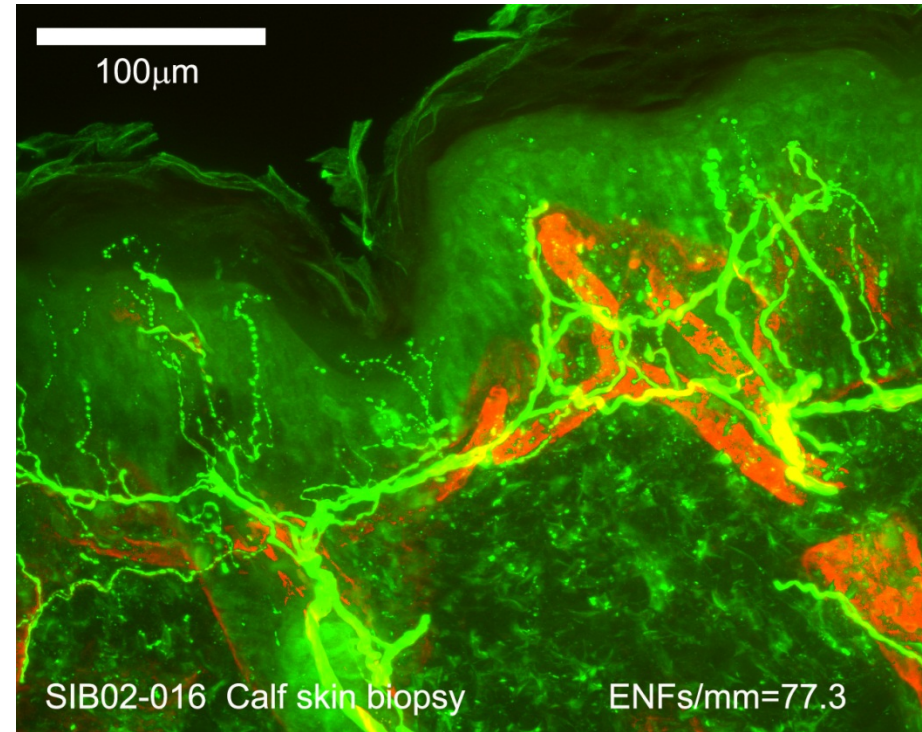
- replicated finding with a larger sample of adult SIB cases relative to matched controls *Brain, Behavior, & Immunity, 23, 365-370.*
  - observed increased SP-positive fiber counts in some but not all samples
  - observed extensive mast cell degranulation (consistent with immune mediated inflammatory response)
- also observed that adult individuals with SIB and altered peripheral markers (relative to matched controls) were more (not less) responsive during a modified quantitative sensory testing protocol *The Journal of Pain, 11, 773-781.*

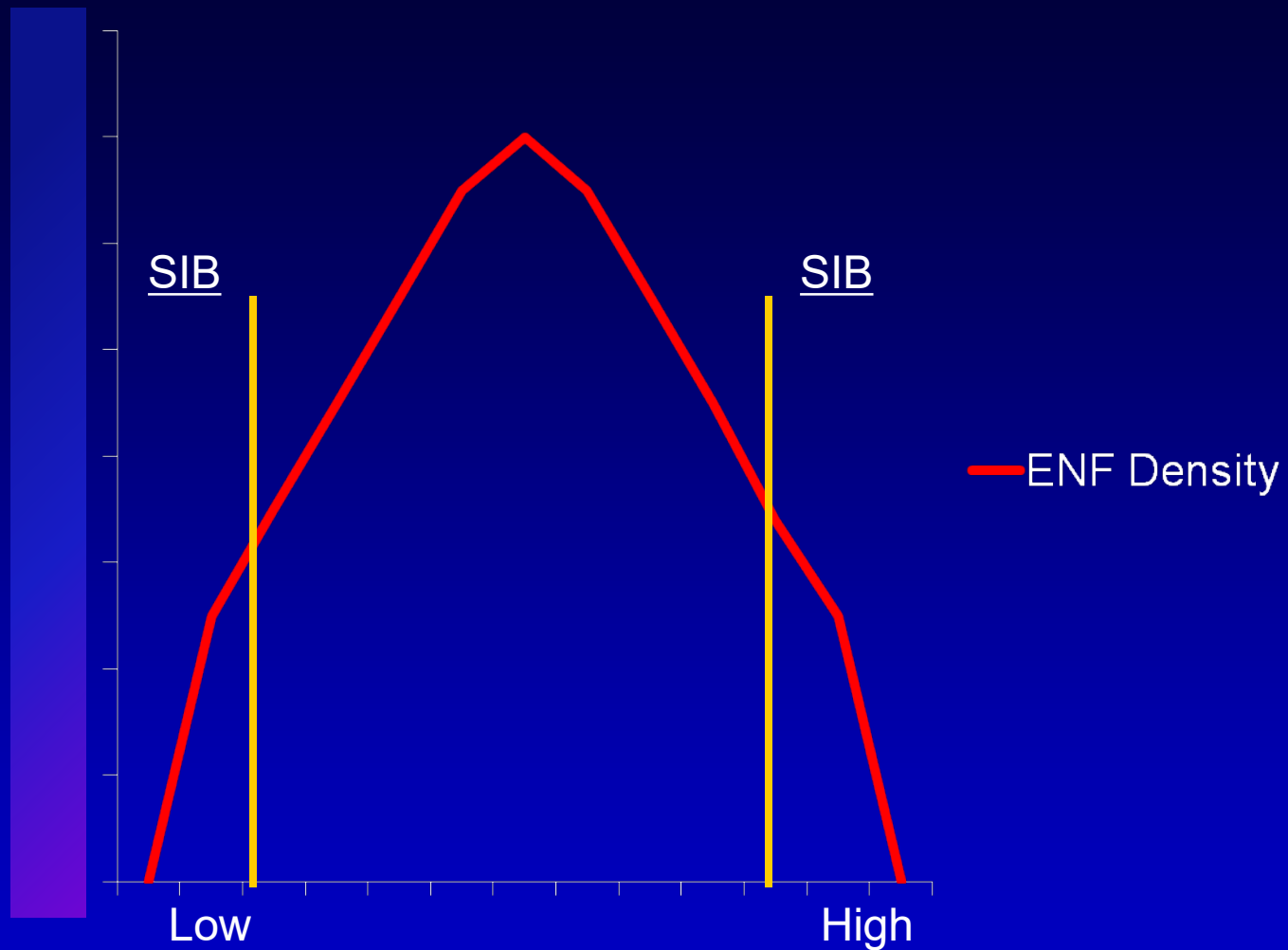
# Early ENFd variation w/ 'At Risk' sample

At Risk: 'High' (?) ENFd



At Risk: 'Normal' (?) ENFd





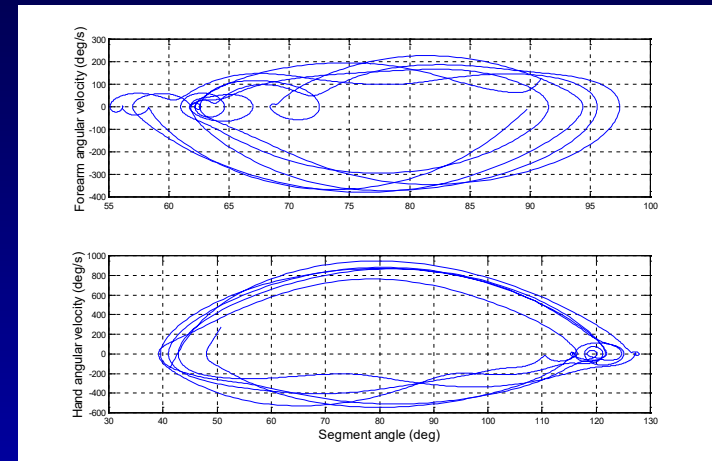
## Hypothetical Plot of ENF Density Histogram

Evidence to date for extreme low and high density ENF innervation among SIB cases

(Symons et al., 2008 *Brain, Beh, & Immunity*, 23; Symons et al, 2008, *Pain*, 134.)

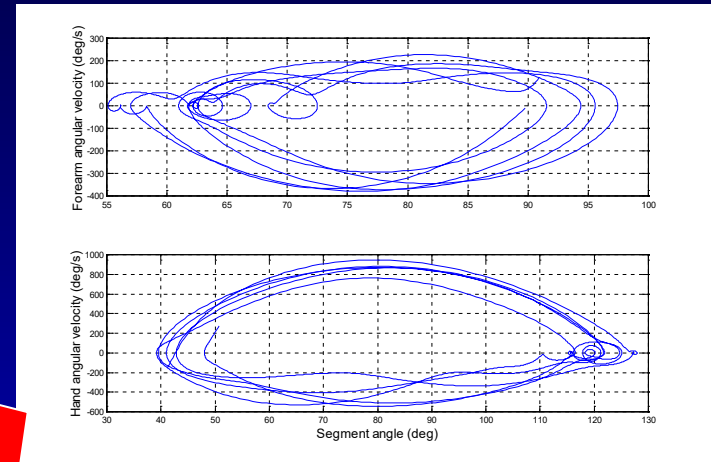
# Closing Thoughts on Long-Term Effects of Chronic Tissue Damaging SIB

Coupling the impact forces with the frequency of blows during a single bout of self-injury would essentially be the equivalent of dropping a 48-oz (3-lb) hammer on your forehead every second for up to a half an hour.



# Closing Thoughts on Long-Term Effects of Chronic Tissue Damaging SIB

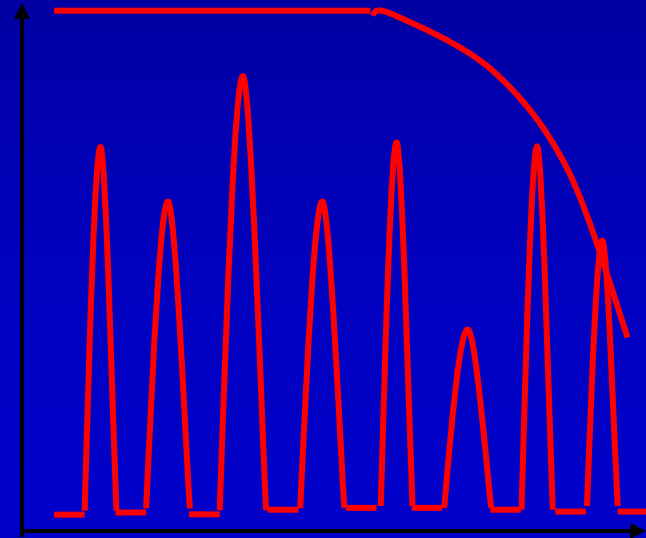
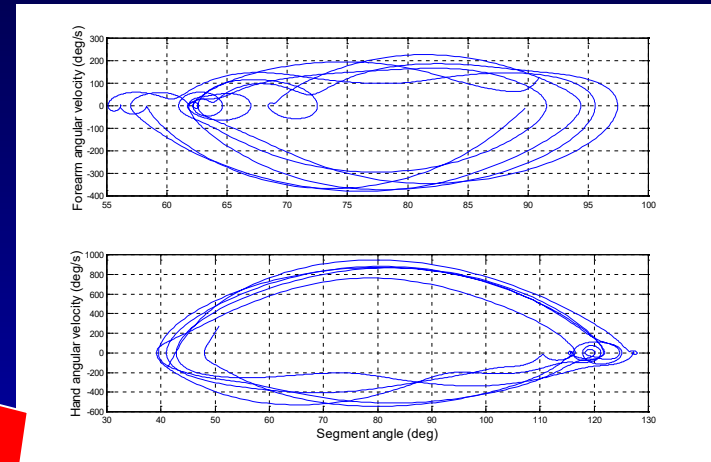
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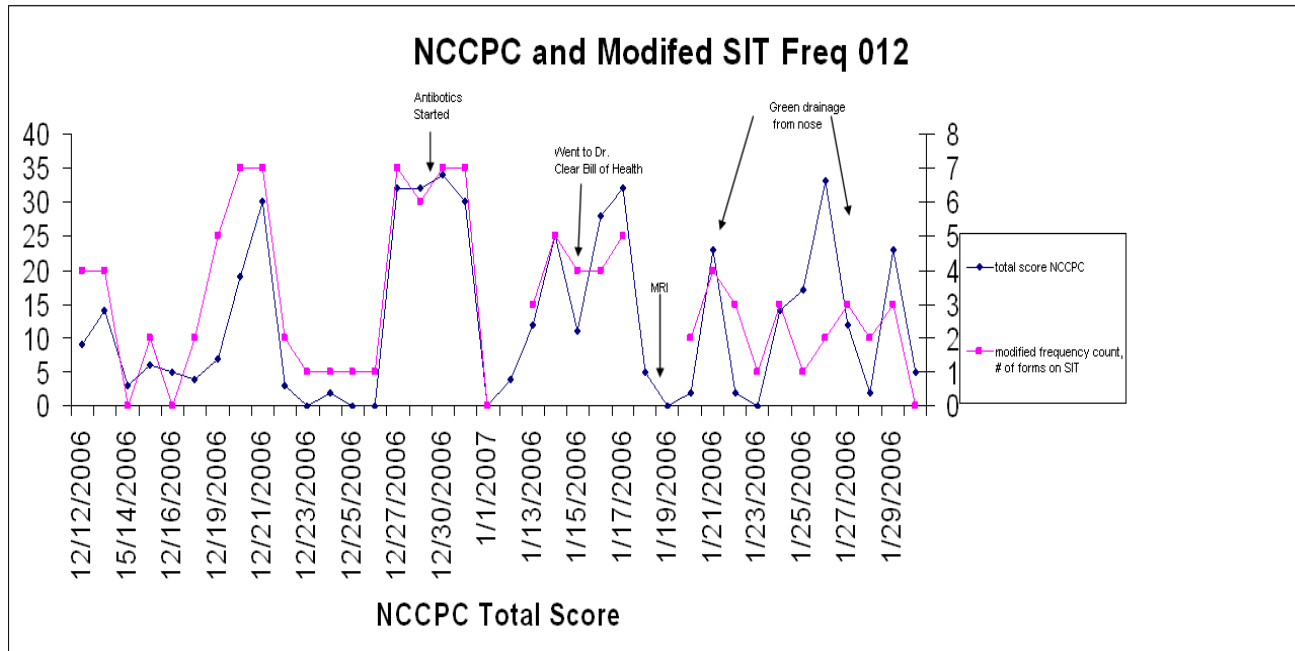


# Summary of findings

- **ASD subtype** (ASD with or without IDD)
  - Clear differences in SIB phenotype
  - Severe & persistent SIB common in ASD+IDD
- **Objective methods** for measuring nociception in persons who are nonverbal
  - Quantitative Sensory Testing + FACS
  - Biomarkers
- **Altered nociceptive function** SIB in ASD+IDD findings consistent with allodynia / hyperalgesia
  - ↑ response to multiple sensory modalities suggesting that non-noxious stimuli might be perceived as painful (e.g. touch, temperature changes, etc).
  - Alterations in ENFs that could disrupt sensory/pain signaling
  - Alterations in immune-mediated inflammatory response

# Clinical implications:

- **Assessment:** SIB & nonverbal pain signs
- **Intervention:** Tx pain, Tx SIB?



# Research implications

*from mechanism to treatment target*

