

The CT Afferent System: What is it & What is it For?

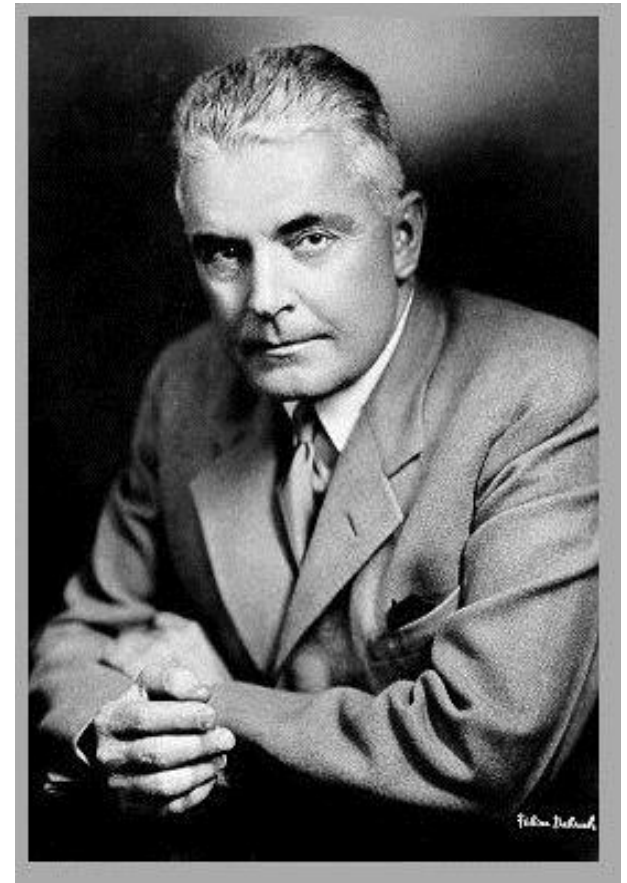
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Visiting Professor, University of Liverpool



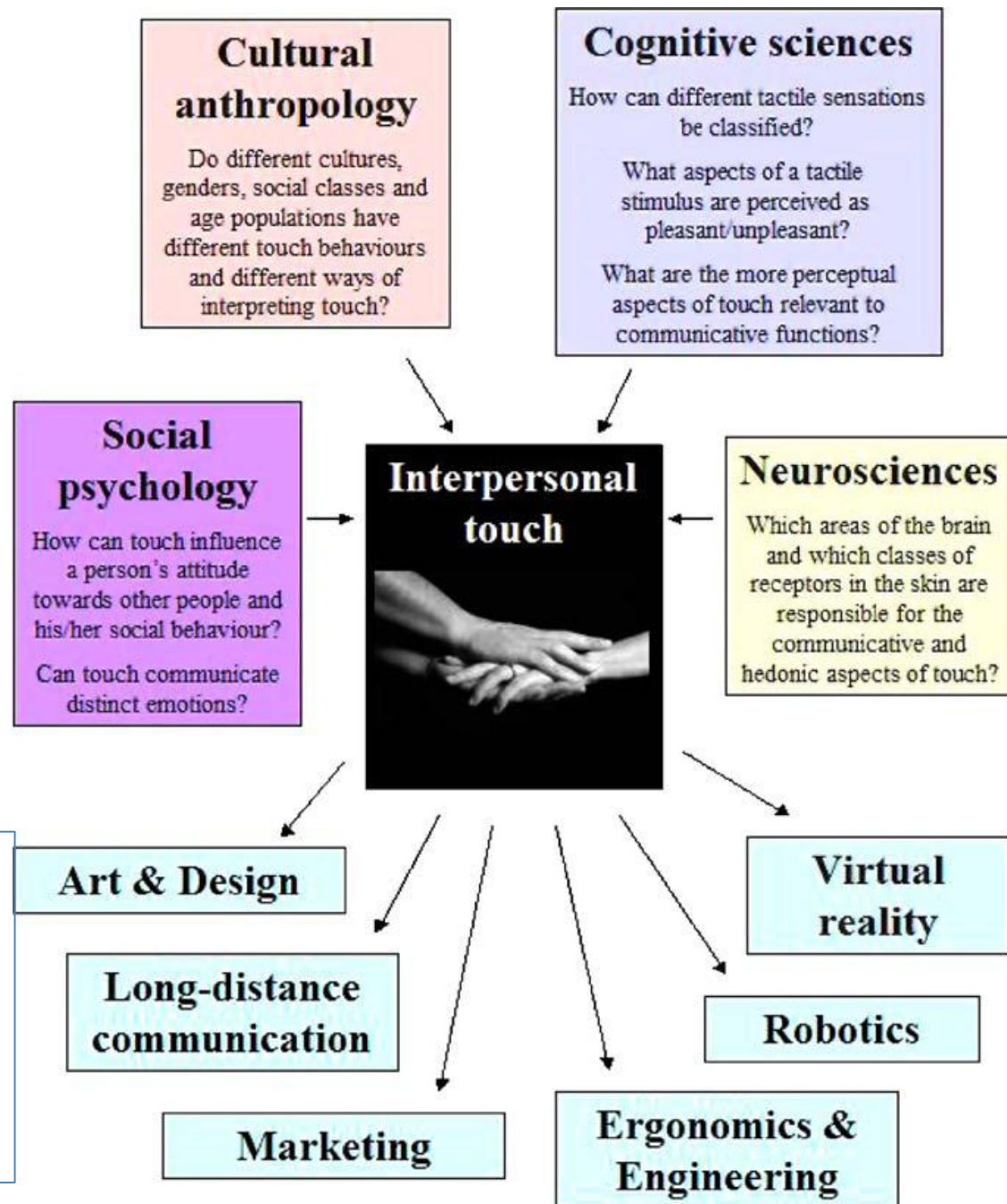
Out of touch.....!!

- John B. Watson, instigator of the Behaviourist School of Psychology, advised parents to “maintain a physical boundary between themselves and their children” and that they should “Never hug and kiss them....shake hands with them in the morning...”
- Watson believed that excessive touching - such as caressing - would create “mawkish” adults.
- He stated that an untouched child would “enter manhood so bulwarked with stable work and emotional habits that no adversity can quite overwhelm him.”



John Broadus Watson
(1878-1958)

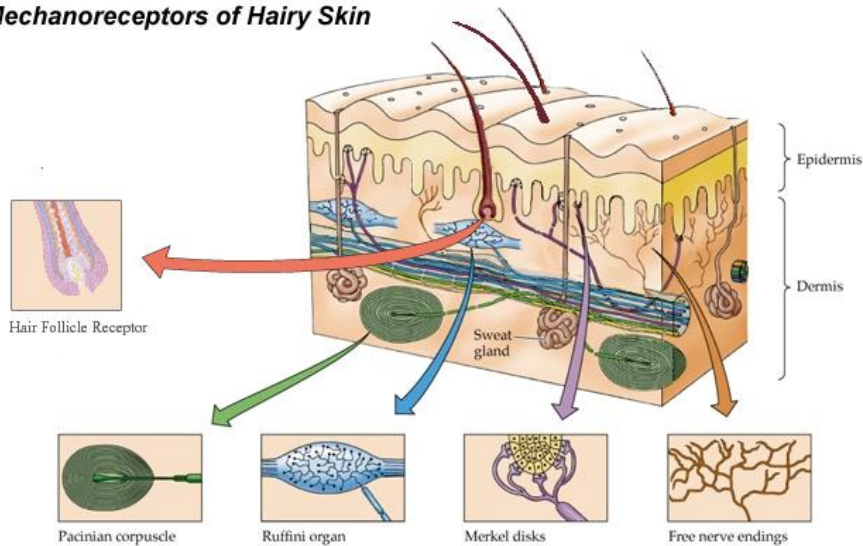
- Disciplines relevant to touch research.....



- *Via nurturing touch, a system of unmyelinated cutaneous afferents shape the destiny of the social brain.....*

Textbook view on sensory receptor units in human skin

Mechanoreceptors of Hairy Skin



courtesy of http://www.hhp.uh.edu/clayne/6397/Unit4_files/image019.jpg

Thick myelinated ($A\beta$)
 $\sim 35-60$ m/s
Mechanoreceptors

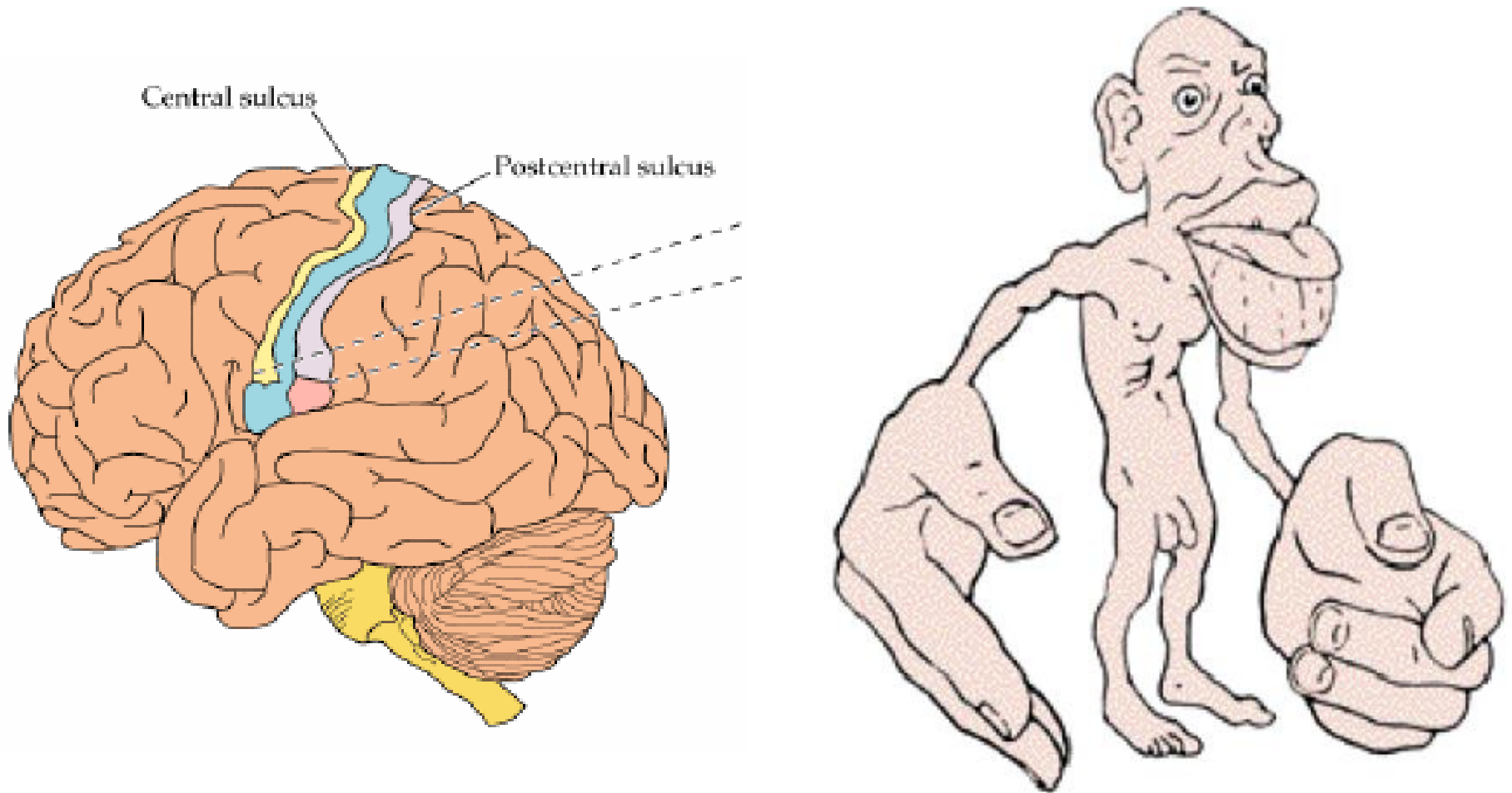
Thin myelinated ($A\delta$)
 $\sim 5-35$ m/s
Temperature: cold
Pain

Unmyelinated (C)
 $\sim 0.4 - 2.0$ m/s
Temperature: warm, cold
Pain

Receptor type	Axon type	Diameter (μm)	Conduction speed (m/s)
Proprioceptors of skeletal muscles	$A\alpha$	13-20	80-120
Mechanoreceptors of skin	$A\beta$	6-12	35-75
Pain, temperature	$A\delta$	1-5	5-30
Temperature, pain, itch	C	0.02-1.5	0.5-2

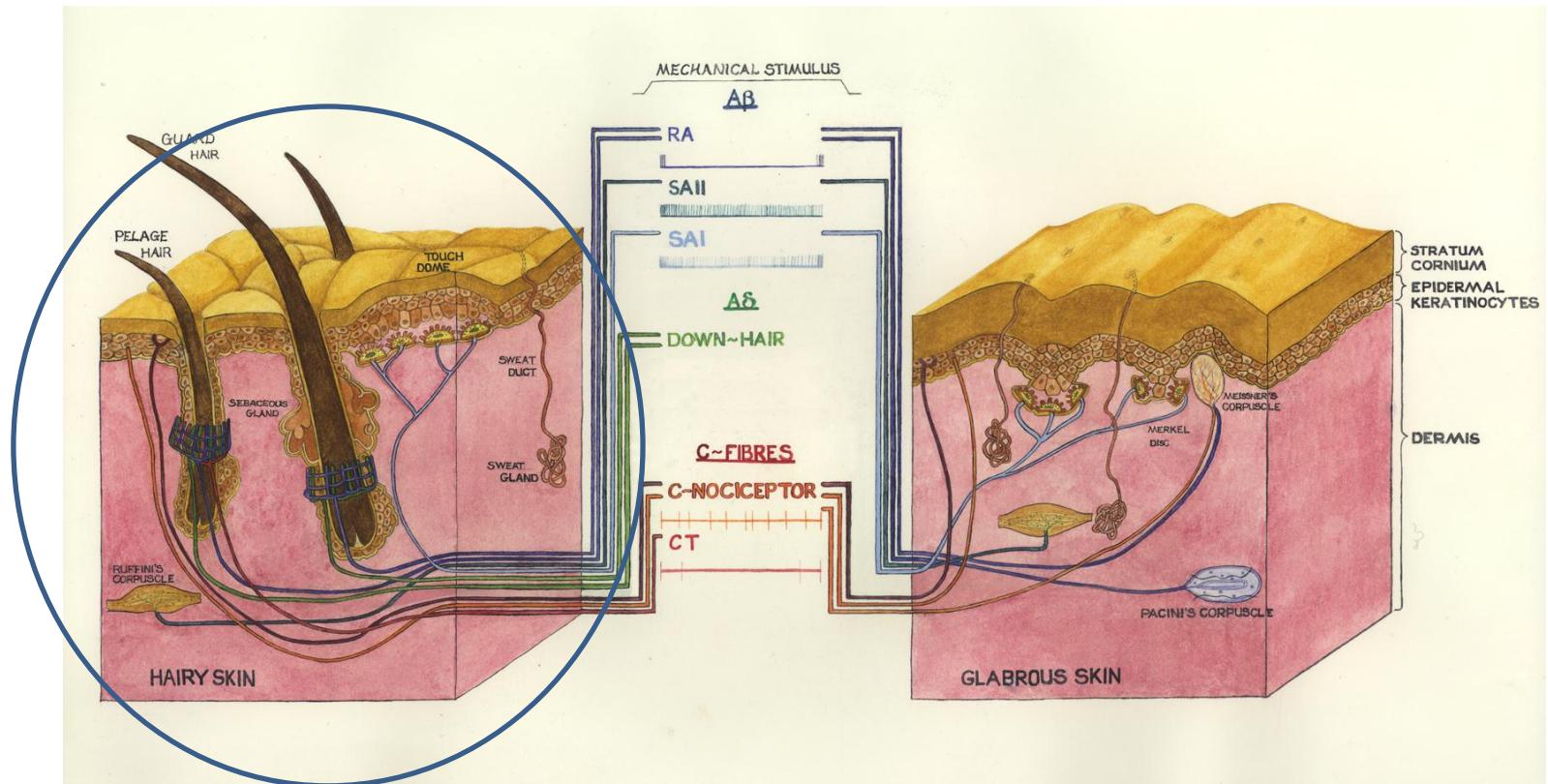
The somatosensory (discriminative) homunculus

- Touch cortex has a topographic map of body surface



Techniques & Tools for Tactile Research

- Behavioural measures
- Psychophysics
- A lexicon for touch
- Microneurography
- Neuroimaging



Unmyelinated (C) mechanoreceptors with low touch thresholds?

- Found in cats, rodents and primates

Zotterman, 1939

Douglas & Ritchie, 1957

Iggo, 1960

Bessou & Perl, 1969

Kumazawa & Perl, 1977

- Humans:

Tactile sensation is lost when myelinated afferents are experimentally blocked (pressure 1

C afferents are *slow* –

Unmyelinated tactile afferents lost during evolution?

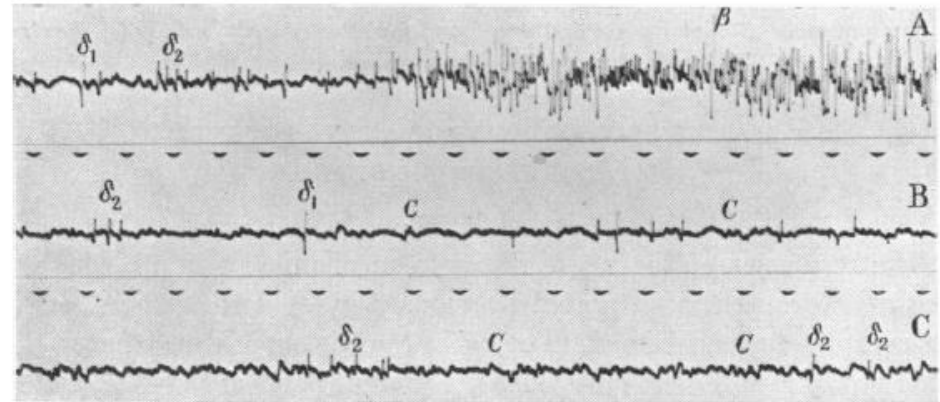
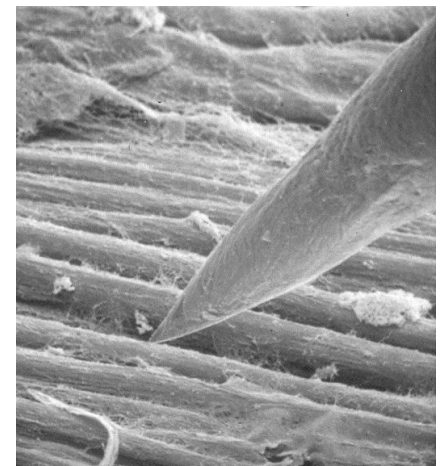
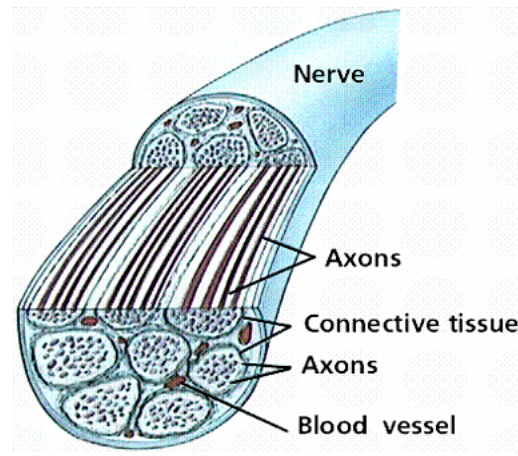
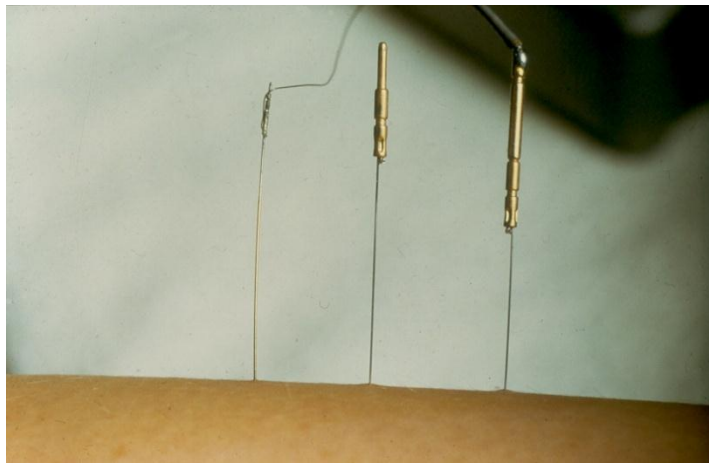
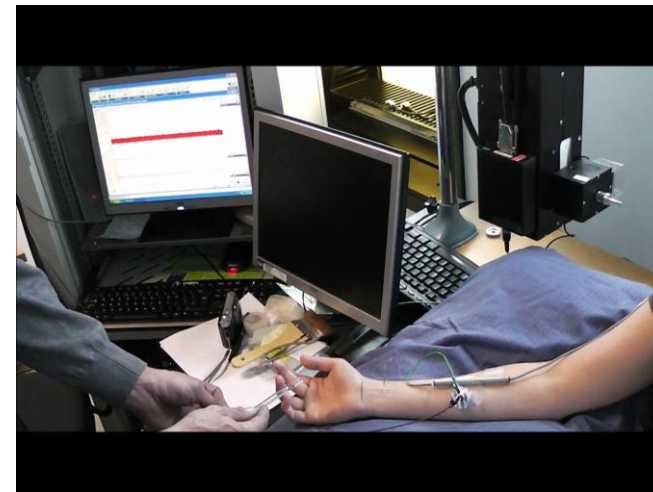


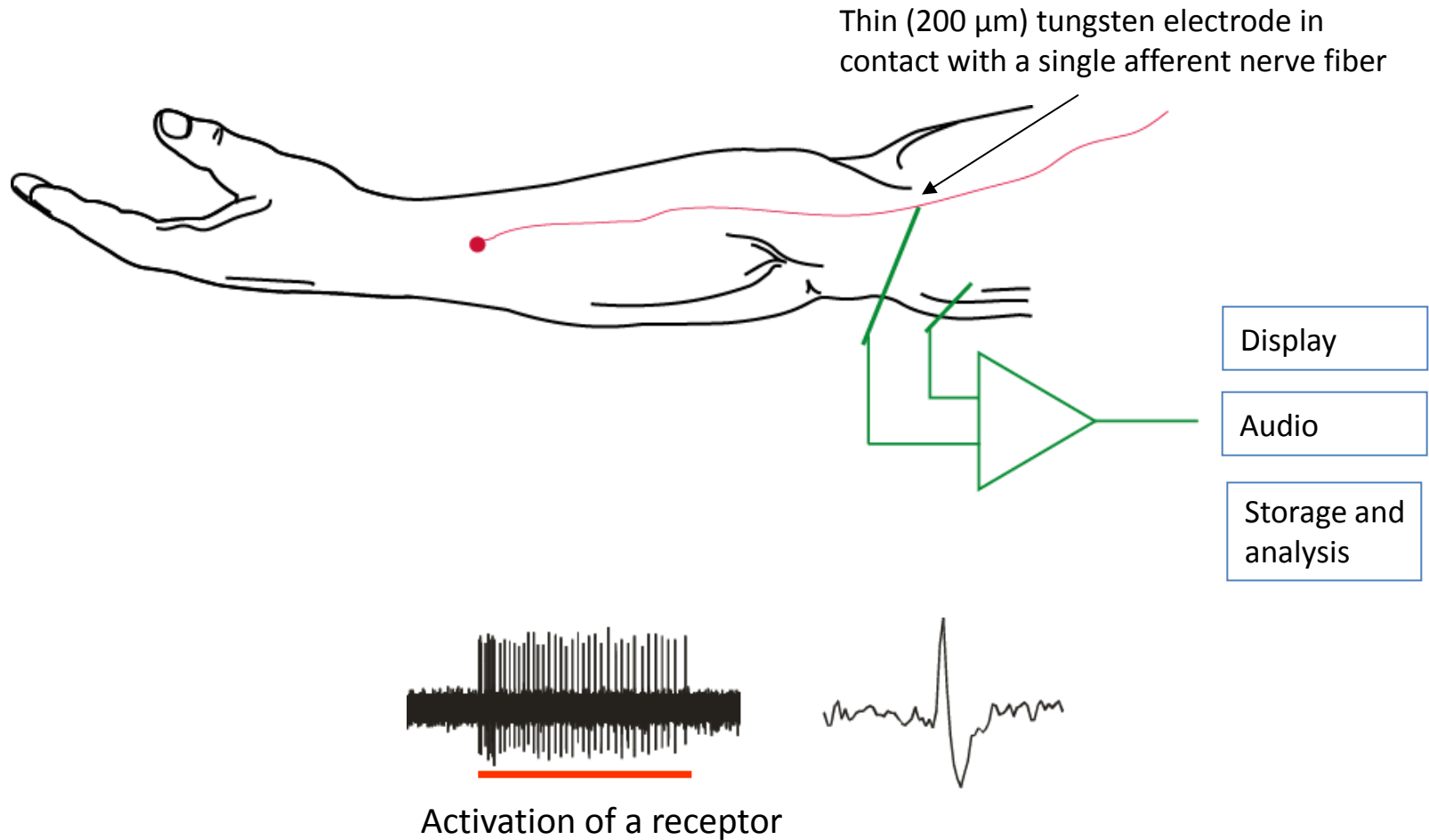
Fig. 3. To be read from right to left. A, shows the end of a firm stroke with a wooden pin; B, from the same record 3 sec. later; C, light burning. Time 1/50 sec.

Microneurography

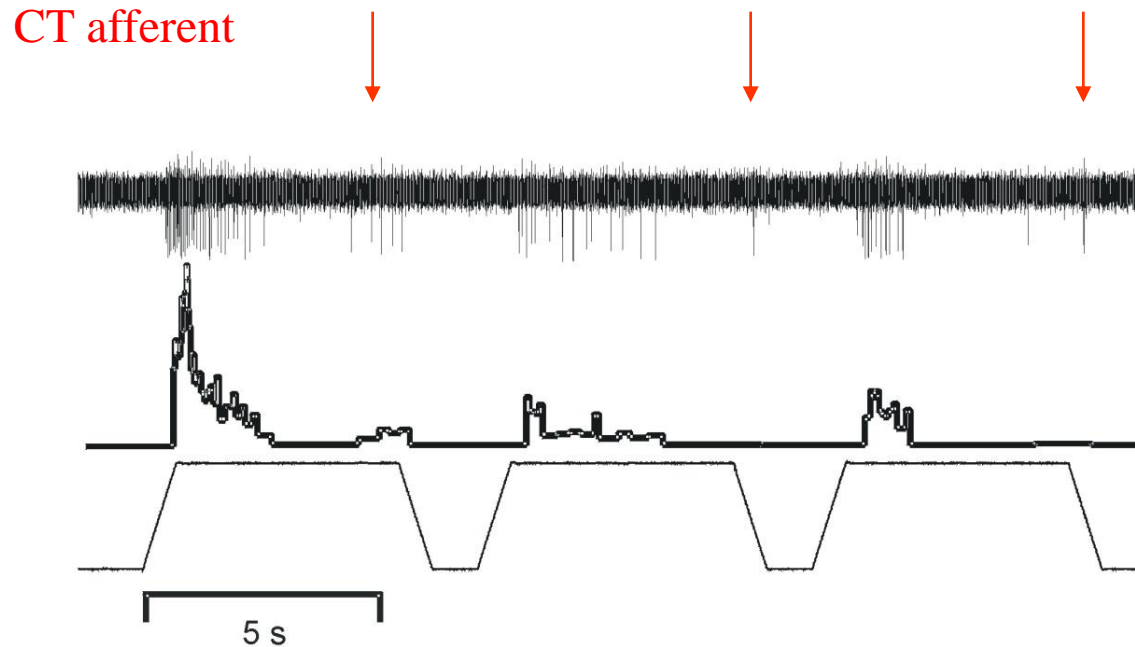
- Records electrical activity from single touch nerves using tungsten microelectrodes (shaft diameter 0.2 mm; tip 5 μm), inserted percutaneously into a nerve.
- Physiologically characterised MRA's can be electrically micro-stimulated to produce a percept (distinct sensations specific to the skin territory, and type of stimulated afferent).



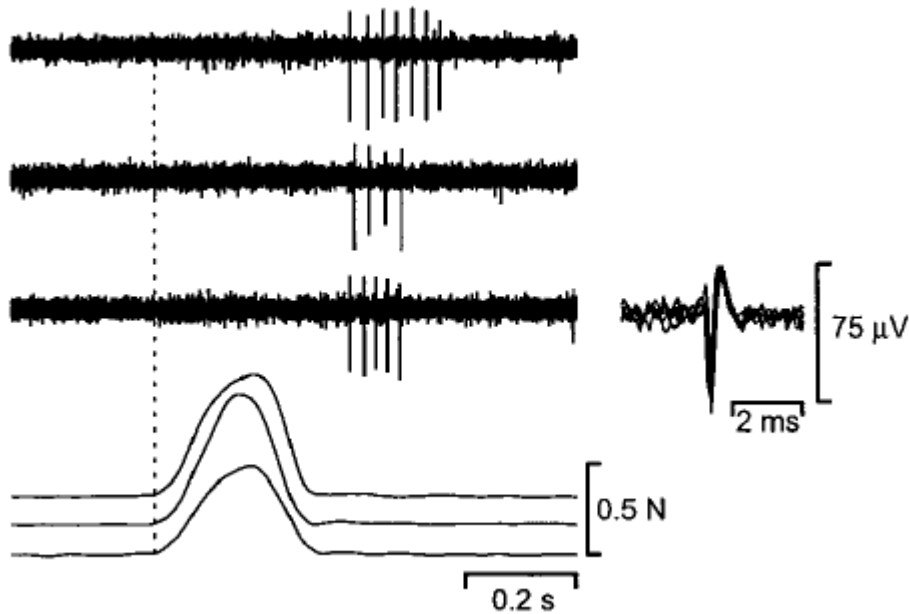
The microneurography technique



Response properties of C-tactile afferents to a stationary indentation, showing adaptation, off response and fatigue

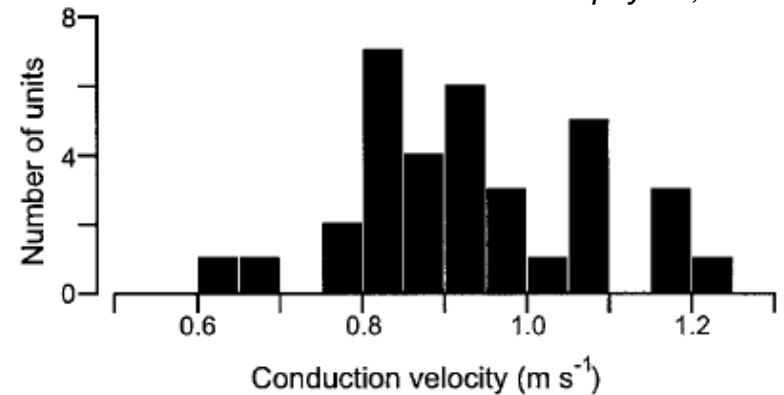


Results from microneurography

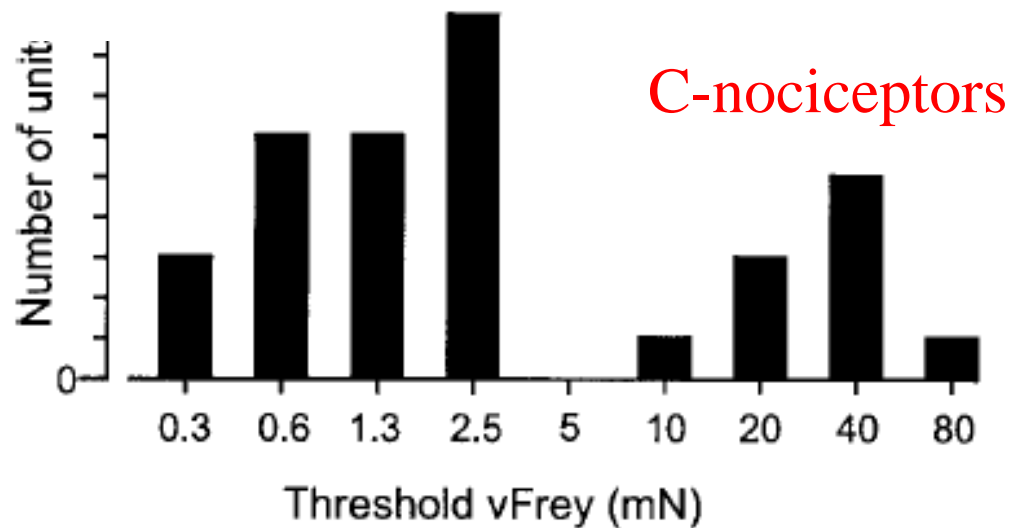


Vallbo, et al, J Neurophysiol 1999

Wessberg et al., *J Neurophysiol*, 2003



C-tactile

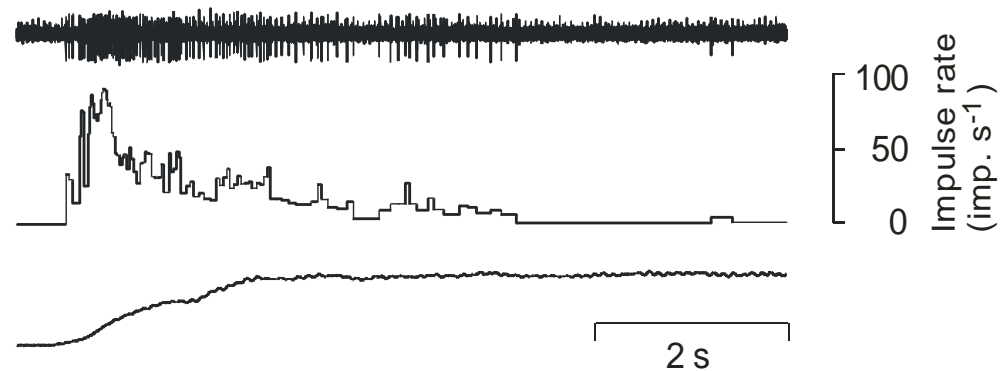


C-nociceptors

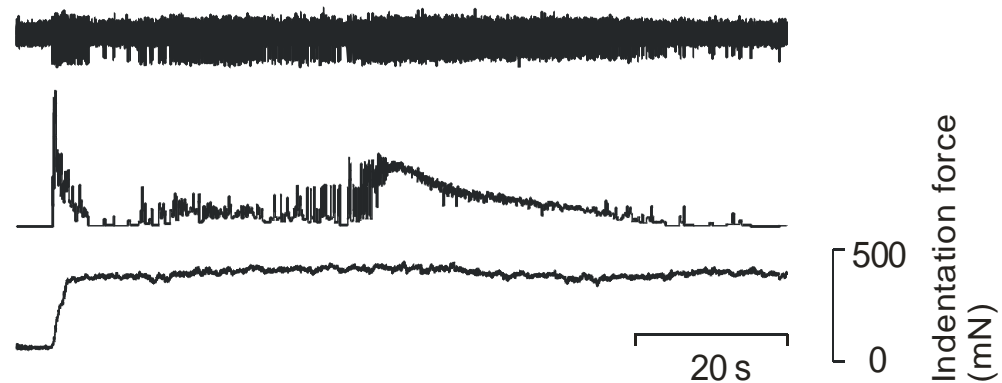
CTs are capricious.....

Delayed acceleration of unit response
during sustained and uniform indentation

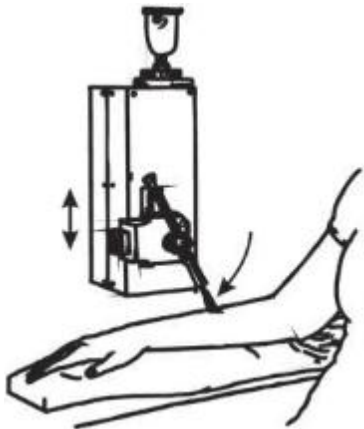
A Initial 8 seconds



B

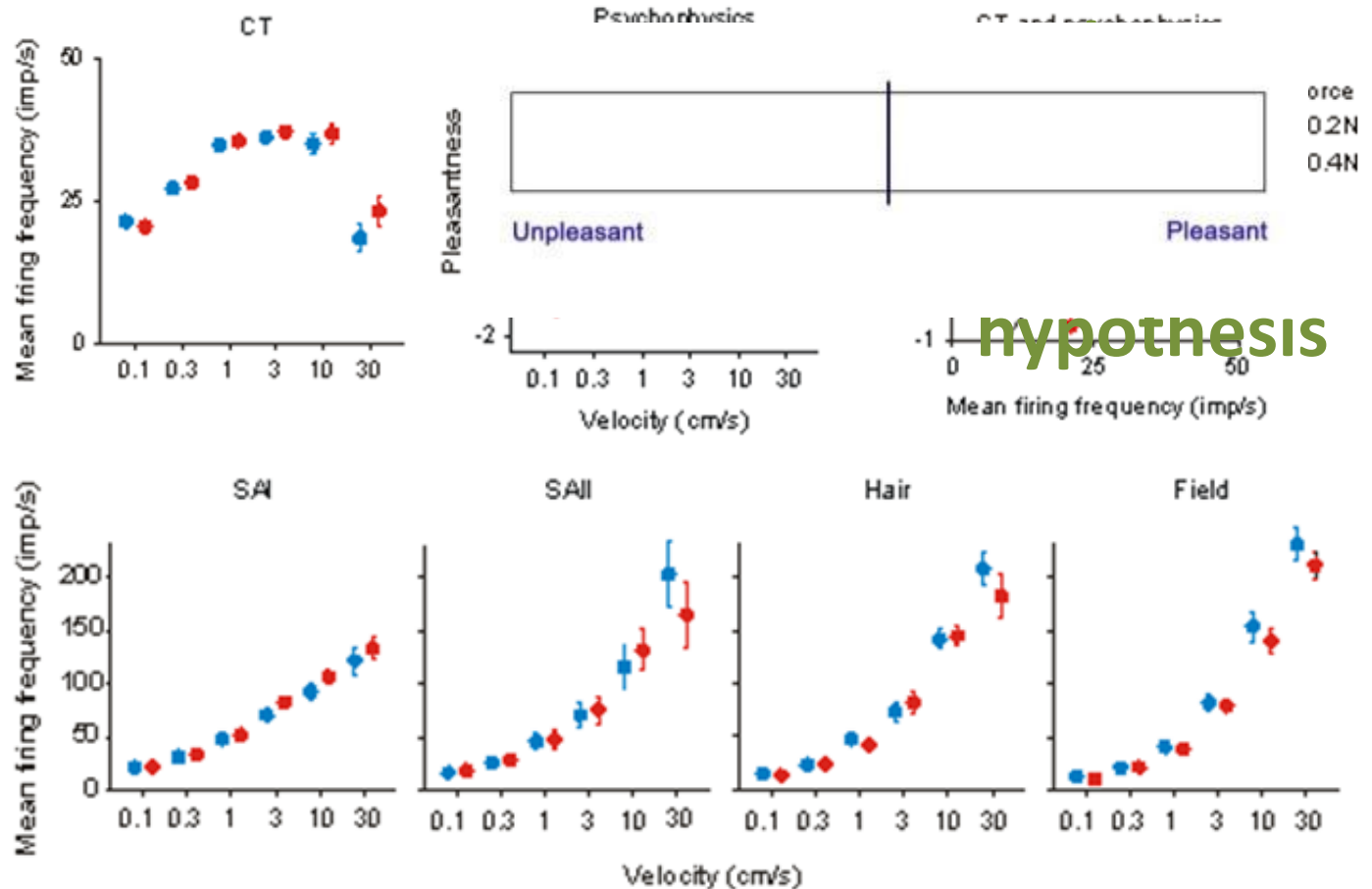


Microneurography and psychophysics



Rotary Tactile Stimulator (RTS) provides well-controlled stroking velocity and force.

(Developed at the University of North Carolina, Chapel Hill and by Dancer Design.)



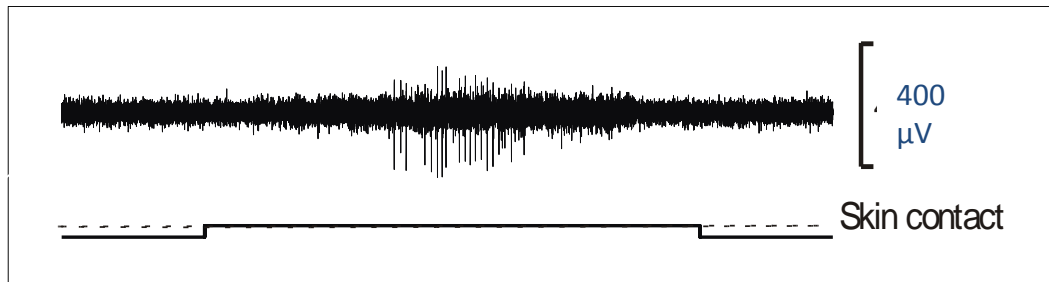
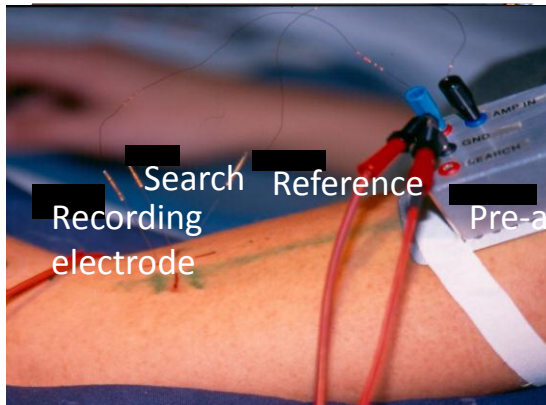
Listen to the two types of touch.....



1st Touch (A-beta nerves) : cognitive, discriminative processing of touch



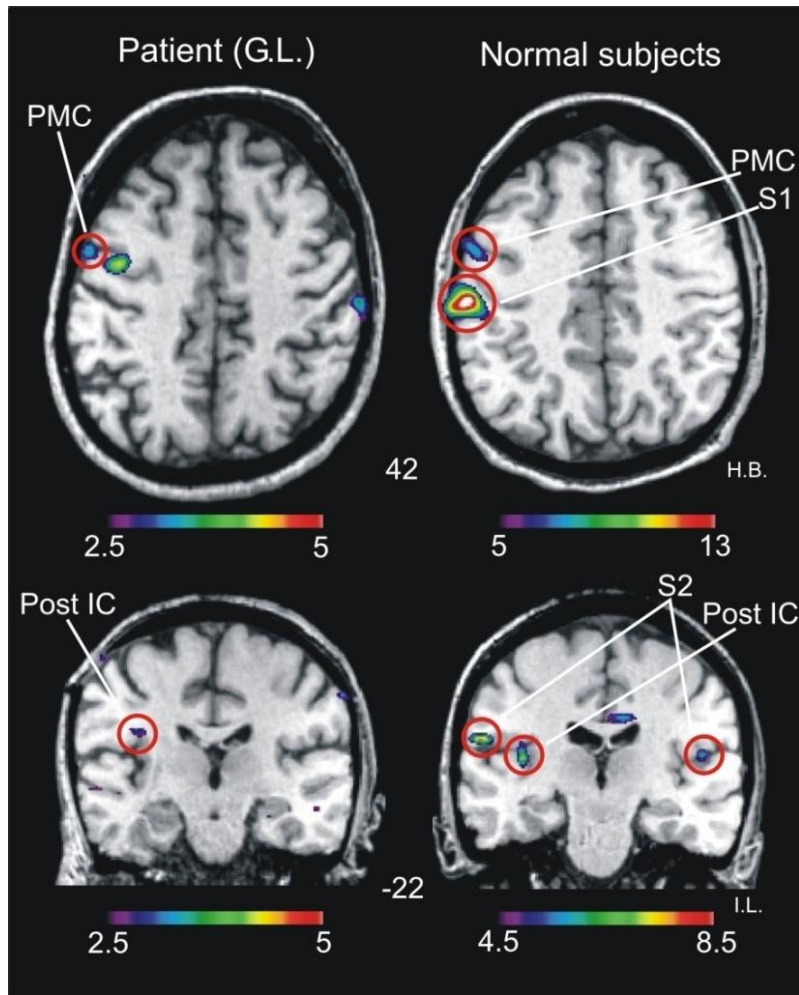
2nd Touch (CT-fibres): non-cognitive, emotional processing of touch ?



Selective CT stimulation: deafferented subjects G.L. & I.W.

- Selective degeneration of large myelinated (A-beta) afferents with C-afferents intact
- G.L. and I.W. both around 60 years old. Developed sensory ganglionopathy, at age 30 and 19 respectively.
- Unique opportunity to study effects of pure CT activation.

fMRI: Selective CT stimulation

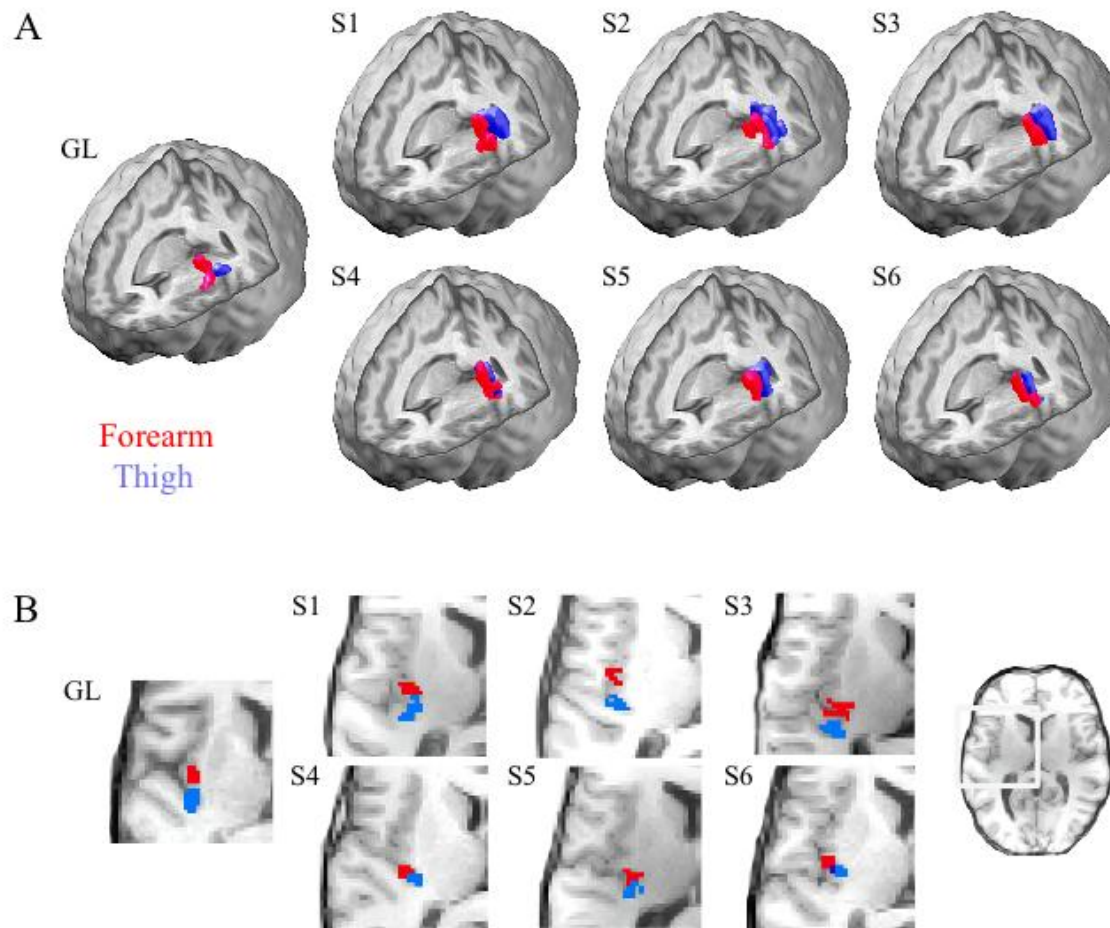


- GL and IW, sensory ganglionopathy
- Complete and selective loss of A-beta afferents – No “touch”!
- Later, in 2-afc they can detect stimuli which effectively activates C-tactile afferents

“Weak but clearly pleasant”



fMRI: C-tactile afferents project somatotopically to insular cortex



C-denervated subjects

- 11 subjects with congenital sensory neuropathy (hereditary sensory neuropathy type V, mutation in the nerve growth factor beta gene), HSAN-V.
- Severe loss of C-fibers, moderate loss of A-delta fibers (sural nerve biopsy)
- A-beta fibers intact
- Reduced sensitivity to pain and temperature
- Painless fractures and joint deformations

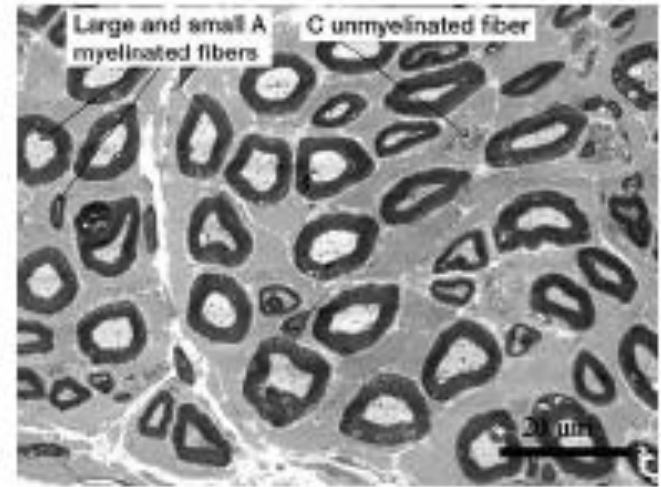
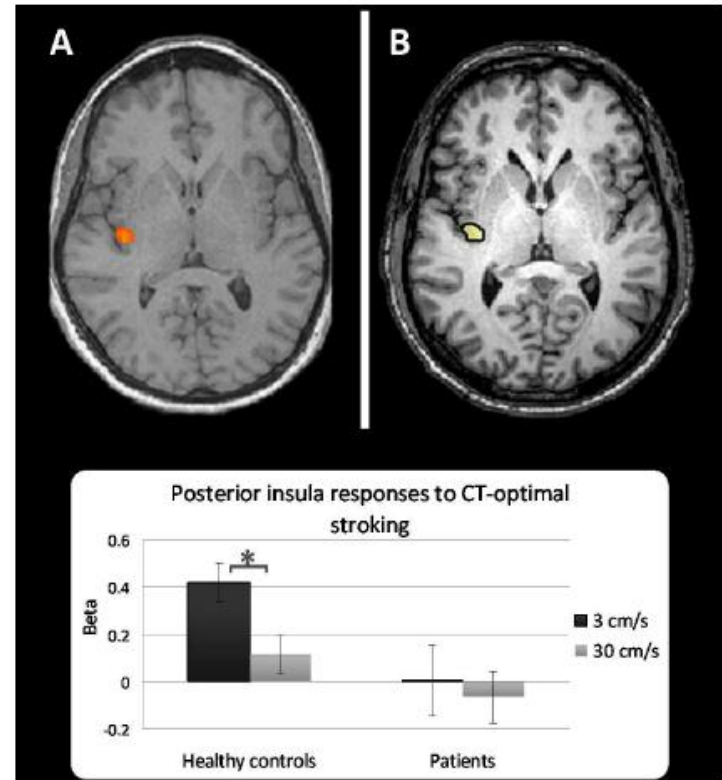
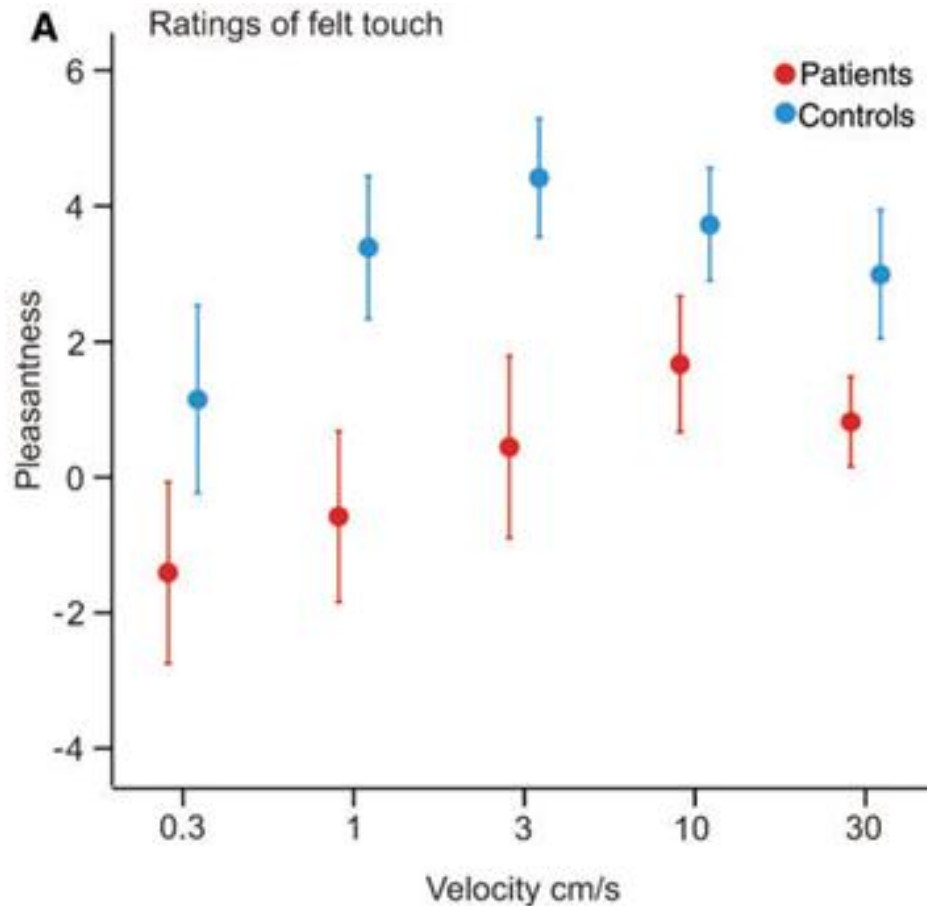


Figure 7. Electron microscopy from the sural nerve (case 1) showing severe reduction in number of C fibers.



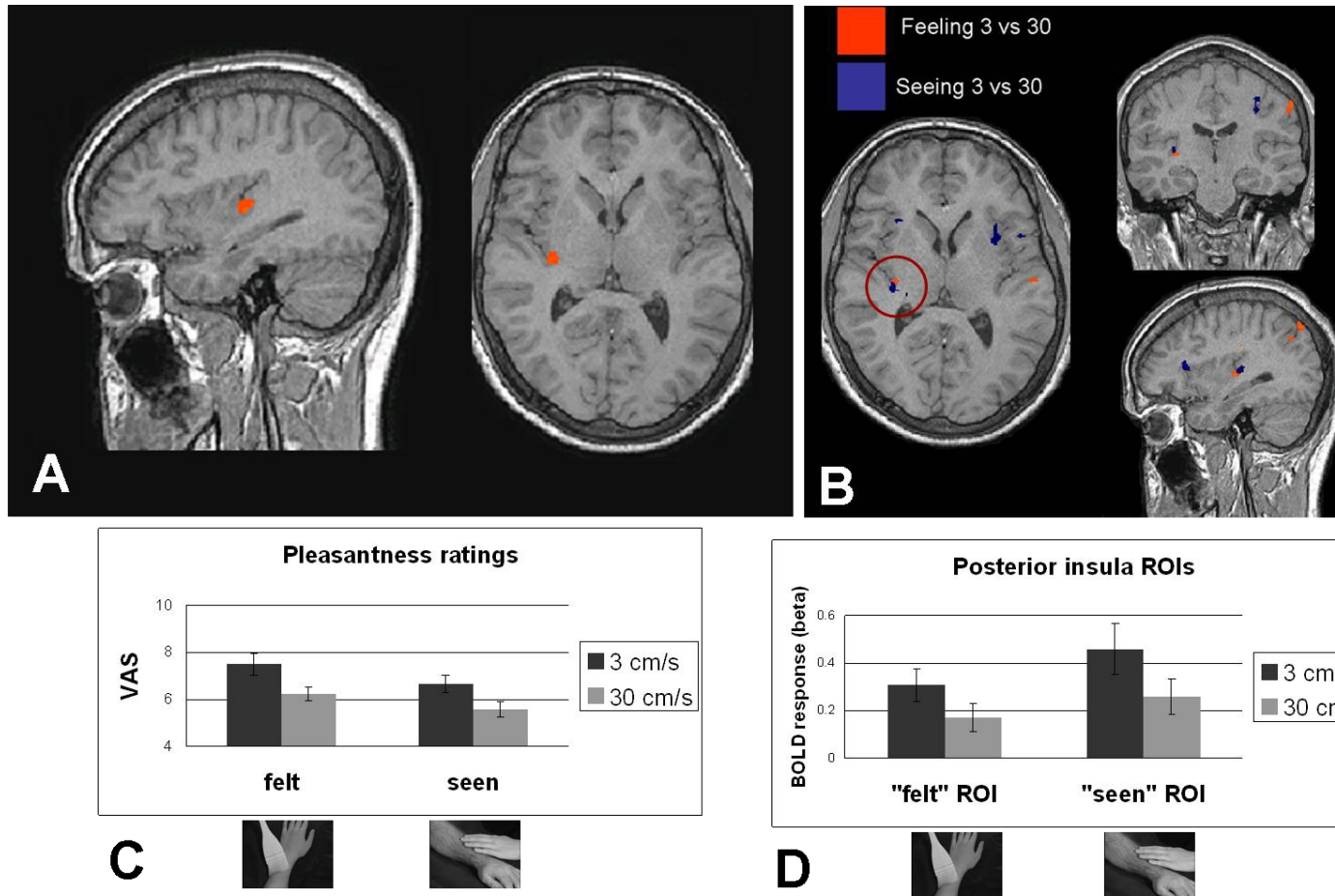
CT denervation affects perceived pleasantness of touch

10 patients 10 controls.



Morrison et al., Brain (2011)

Feeling or viewing pleasant touch activate the same insular region



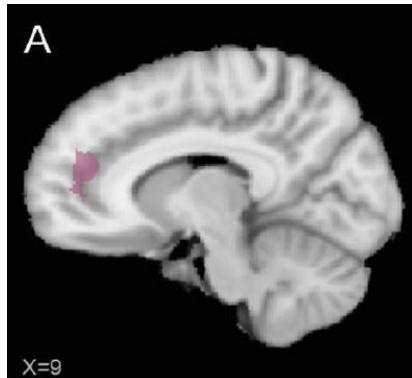
Beyond the insula

♦ Human Brain Mapping 00:000–000 (2011)

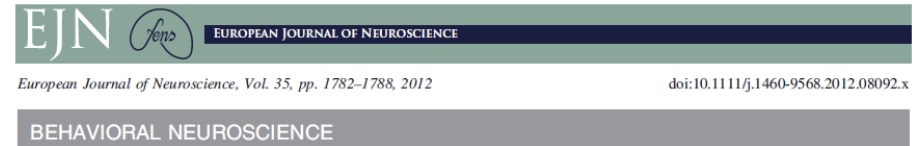
Brain Mechanisms for Processing Affective Touch

Ilanit Gordon, Avery C. Voos, Randi H. Bennett, Danielle Z. Bolling,
Kevin A. Pelphrey, and Martha D. Kaiser*

Yale Child Study Center, Yale University School of Medicine



- Medial Prefrontal Cortex
- Dorso Anterior Cingulate Cortex
- Posterior Superior Temporal Sulcus
- Posterior insula



Touching and feeling: differences in pleasant touch processing between glabrous and hairy skin in humans

F. McGlone,¹ H. Olausson,² J. A. Boyle,³ M. Jones-Gotman,³ C. Dancer,⁴ S. Guest⁵ and G. Essick⁵

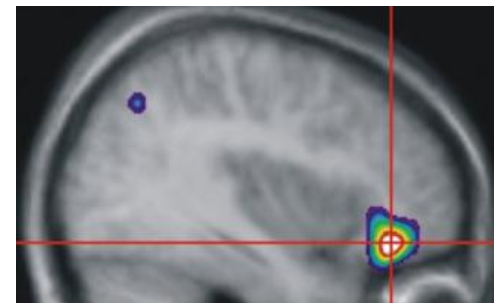
¹School of Natural Sciences & Psychology, Liverpool John Moores University, Liverpool, UK

²Department of Clinical Neurophysiology, Sahlgrenska University Hospital, Göteborg, Sweden

³Montreal Neurological Institute, McGill University, Montreal, Canada

⁴DancerDesign, St Helens, UK

⁵Department of Prosthodontics and Center for Neurosensory Disorders, School of Dentistry, University of North Carolina, Chapel Hill, NC, USA



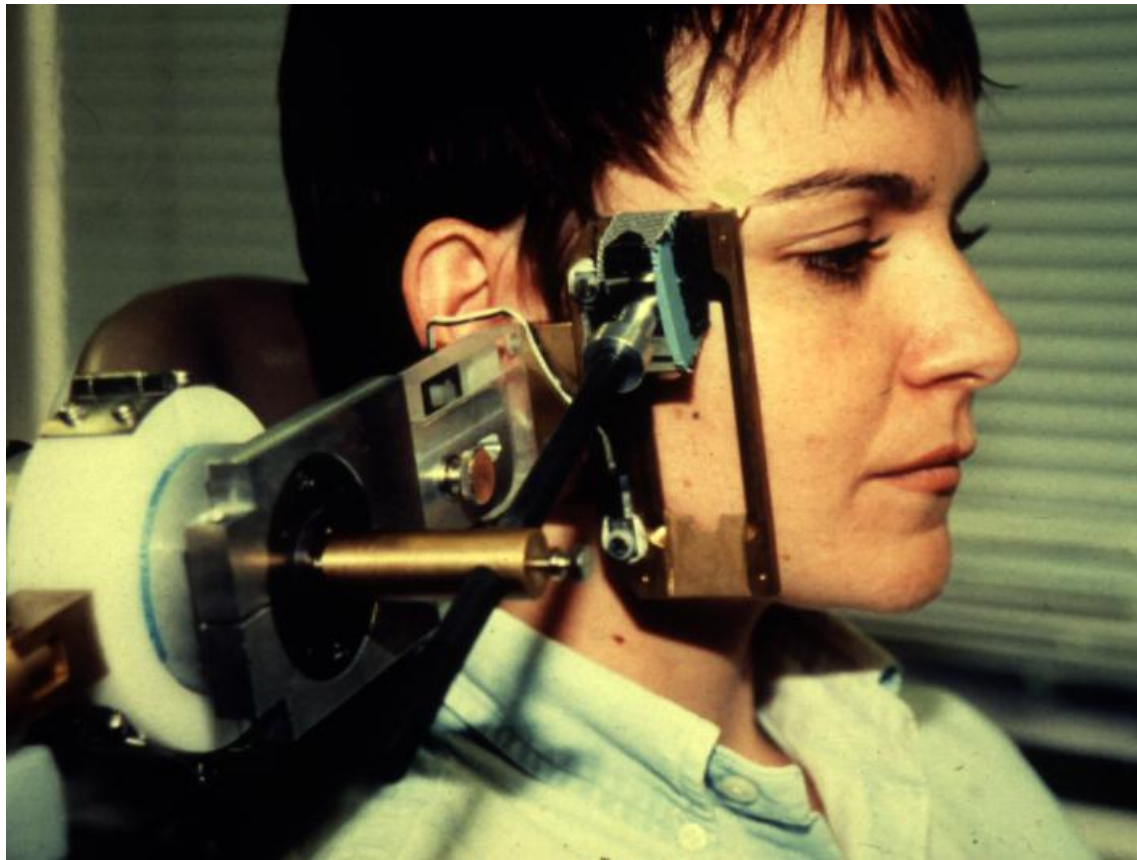
- Mid-Anterior Orbitofrontal Cortex
- Posterior insula

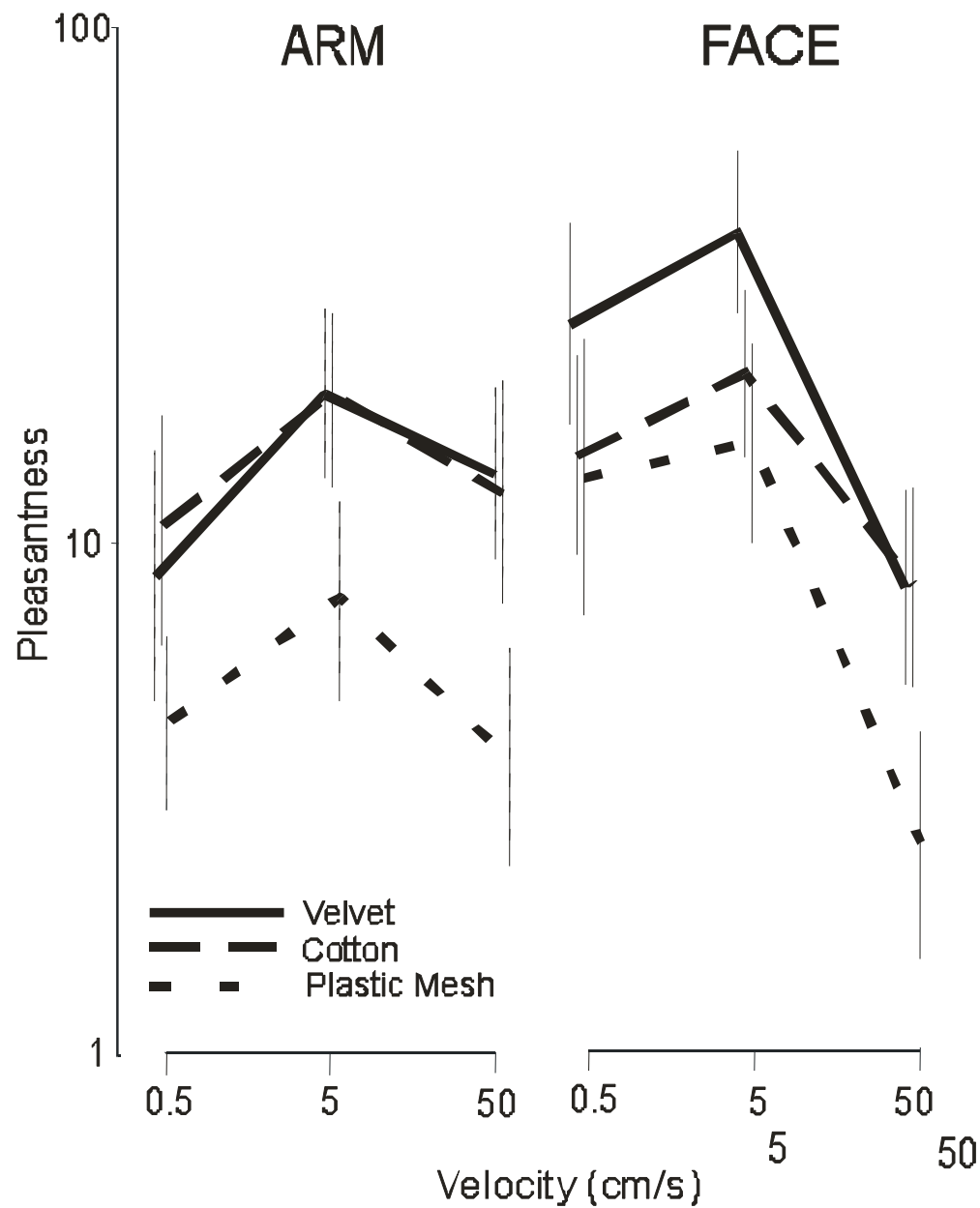
Behavioural measures...

- Aim: we set out to establish if:
 - The pleasant components of touch can be systematically and substantially manipulated during the passive delivery of moving tactile stimuli.
 - The affective (emotional) components of touch can be characterized using a Visual Analogue Scale (VAS) that measures peoples level of liking / disliking of the stimulus.

First Study

- Computer-interfaced servomotor used to stroke stimuli across subjects' skin.
- Region tested: face, ventral arm
- Materials: cotton, velvet, plastic mesh
- Velocities: 0.5, 5, 50 cm/s
- Direction of movement: two opposing





Main effects of Site, Textured Surface, and Velocity and all 2nd order interactions were significant.

(p-values < 0.006)

Figure modified from: Essick & McGlone Neuroreport (1999).

Second Study

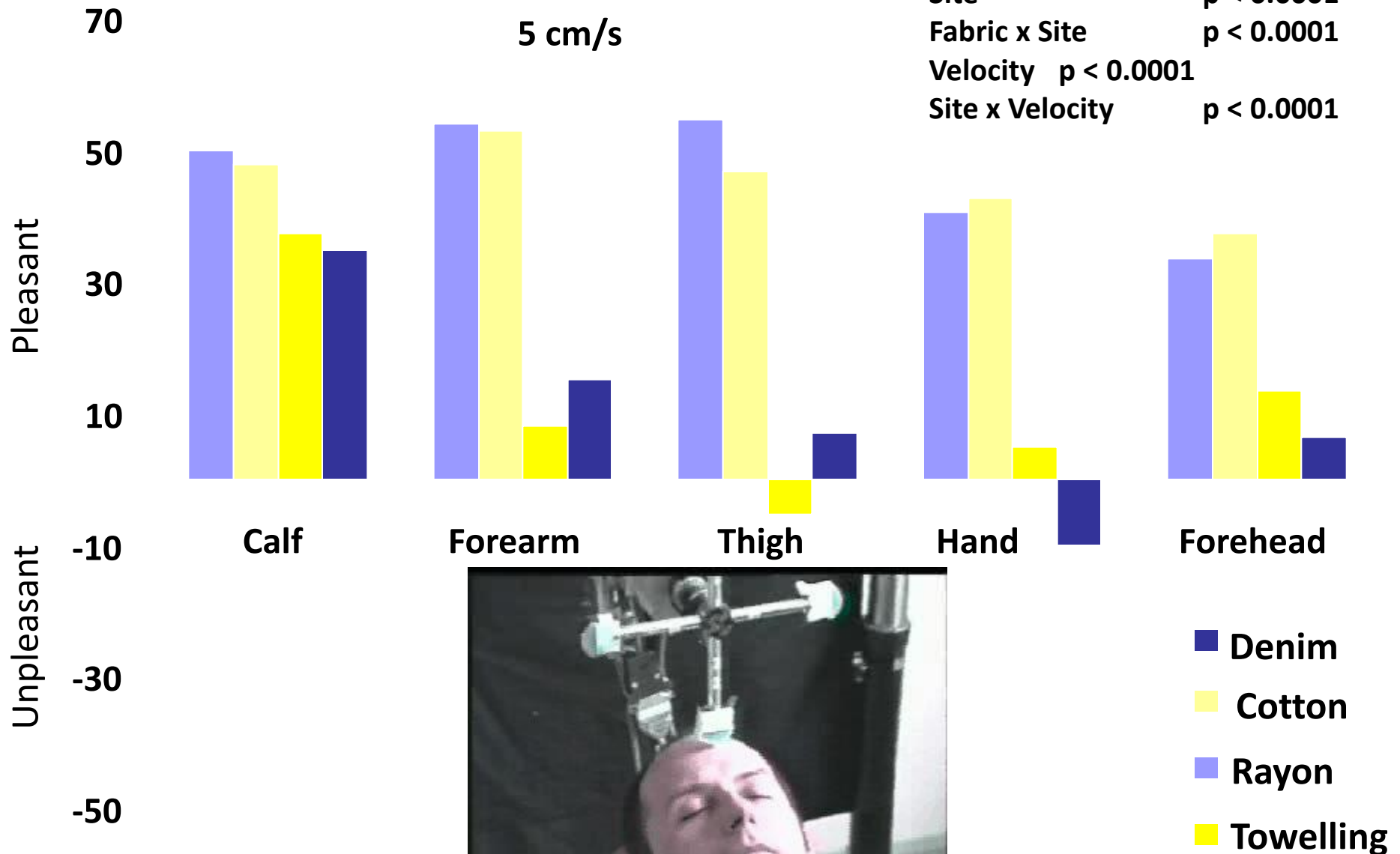
- Designed and built a computer-interfaced Rotary Tactile Stimulator with:
 - Force control
 - Velocity control
 - Position control
 - Four probes



Factors Affecting Pleasantness

Fabric	$p < 0.0001$
Site	$p < 0.0001$
Fabric x Site	$p < 0.0001$
Velocity	$p < 0.0001$
Site x Velocity	$p < 0.0001$

5 cm/s

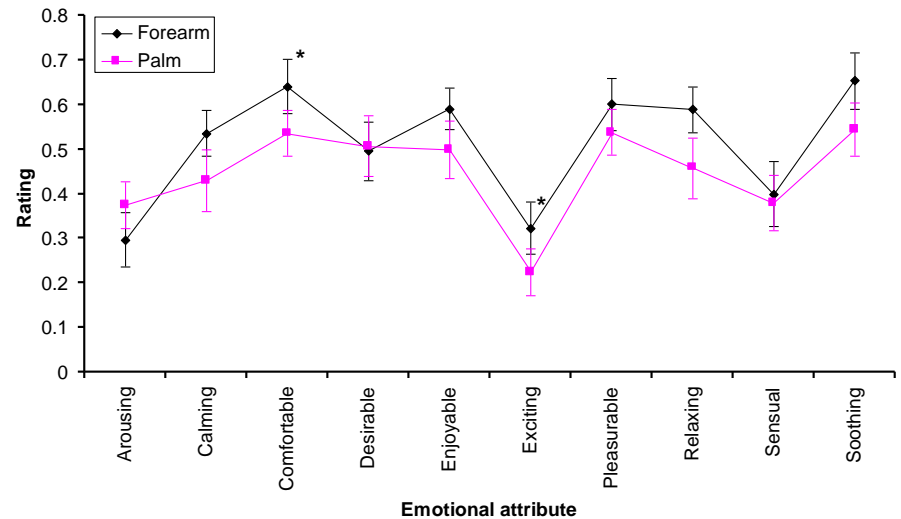


Touch Lexicon

- Emotional Attributes:

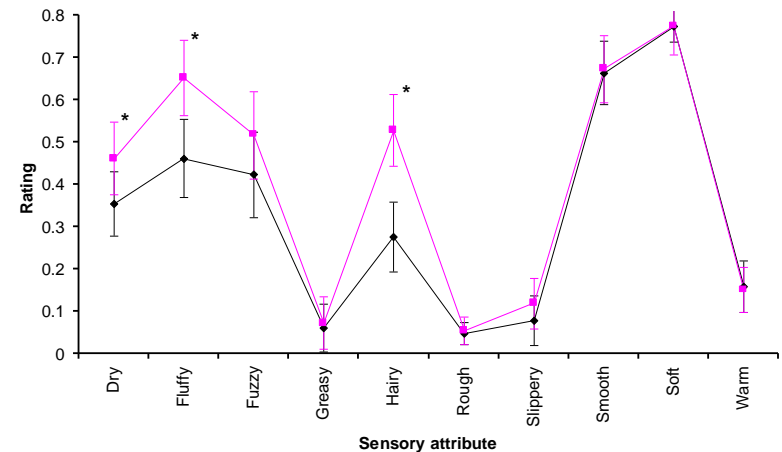
Ratings made of 10 ‘emotional’ tactile attributes for brush stroking against forearm and palm

($n = 15$; $* = P < 0.05$; the attributes ‘enjoyable’ and ‘relaxing’ approached significance, $p \sim 0.08$)



- Sensory Attributes:

Ratings made of 10 ‘sensory’ tactile attributes for brush stroking against forearm and palm.



Guest et al 2011. The development and validation of sensory and emotional scales of touch perception. APP 73(2),

Affective touch



- Elderly, touched during mealtimes consumed more calories and protein (Eaton et al 1986).
- Physical touch expresses more emotion and social communication than can be relayed in language/speech. (Dunbar, 2010)
- Children who spent long periods of time in hospital died through lack of physical touch (Marasmus, a serious protein-energy malnutrition).
- Touch decreases stress activated cortisol production - lower levels allows for increased cell development in the hippocampus, impacting on both short and long-term memory function (Miles et al 2006).
- Field (1999) compared American and French teenagers, observing their interactions in a fast food restaurant. Touch interactions were monitored.
 - American teenagers self touched more and displayed more aggressive behaviours
 - French teenagers spent more time kissing, stroking and hugging each other.





- In Harlow's experiments baby monkeys were separated from their mothers a few hours after birth and raised with 'surrogate' mothers made either of heavy wire or of wood covered with soft terry cloth.
- Both types of surrogates were present in the cage, but only one was equipped with a nipple from which the infant could nurse.
- Even when the wire mother was the source of nourishment, the infant monkey spent a greater amount of time clinging to the cloth surrogate.

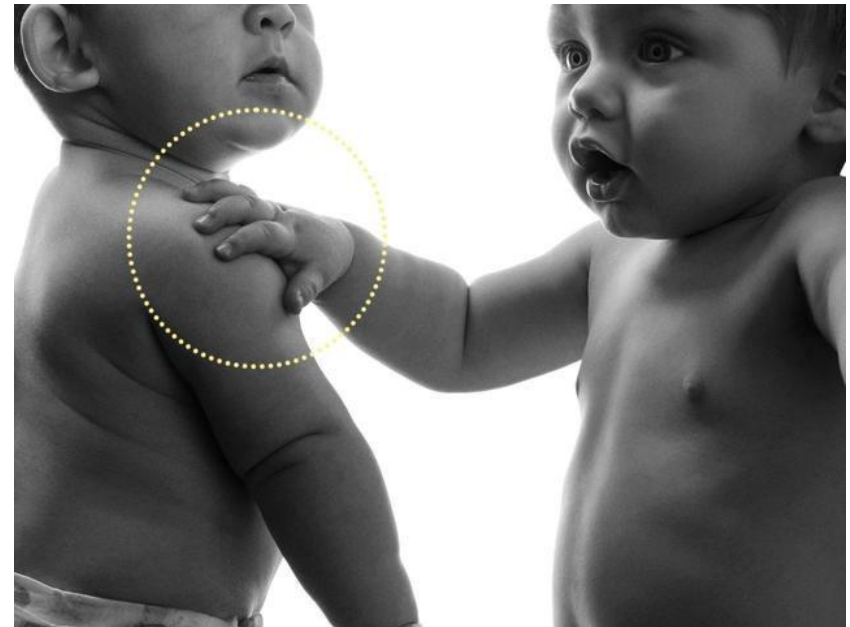


- This study opened the doors to research concerning the necessity of touch in normal human development.
- Touch has been found to be particularly important during the early stages of life. Specifically, touch in the form of massage has been shown to have profound medical benefits for premature infants.
- These positive effects include:
 - improved weight gain
 - improved sleep/wake states,
 - decreased stress
 - improved skin integrity
 - increased development of the sympathetic nervous
 - enhanced parent-infant bonding



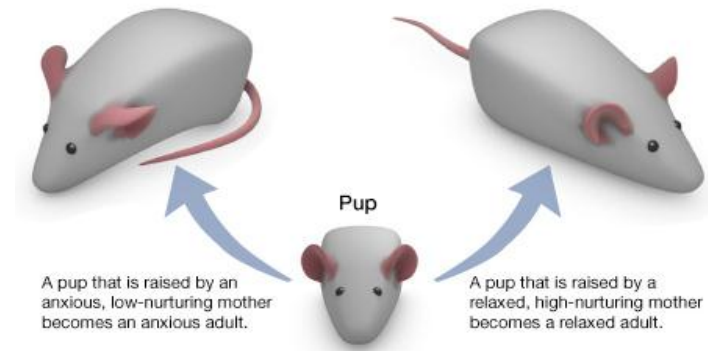
Touch Matters.....

- Across the lifespan social tactile interactions have been shown to benefit an individual's physical health and psychological well-being.
- Therapeutic tactile interventions have proven potential in a range of clinical settings.
- However, to date, little attention has been paid to the neurobiological basis of these effects.



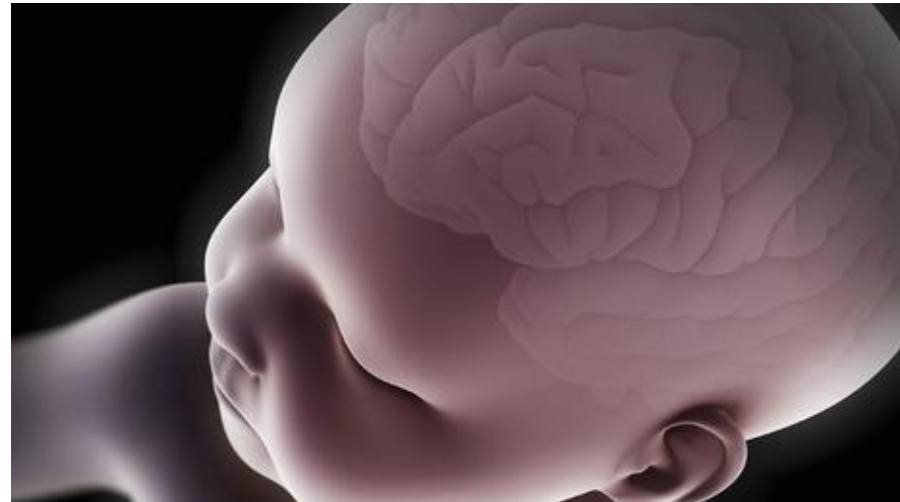
Nurture and Nature

- Some mother rats spend a lot of time licking, grooming and nursing their pups whilst others seem to ignore their pups.
- Highly nurtured rat pups tend to grow up to be calm adults, while rat pups who receive little nurturing tend to grow up to be anxious.
- The difference between a calm and an anxious rat is not genetic - it's epigenetic.
- Nurturing behaviour during the first week of life shapes the pups' epigenomes and the epigenetic pattern that has been established shapes the adult *social/antisocial* behaviour.



Maternal Touch

- Powerful suppressor of HPA-axis activity.
- Increases in CRH, ACTH and corticosterone after separation of pups is reduced by stroking touch.
- High frequency 'licking grooming' produces a more adult 'beneficial phenotype':
 - Reduced HPA responsivity to stress
 - Reduced hypothalamic CRH content
 - Reduced CRH receptor expression in amygdala
 - Increased glucocorticoid receptors in hippocampus
- In human infants gentle touch reduces pain responses and reactivity to stress
- Increased vagal activity
- Increased growth and immune system



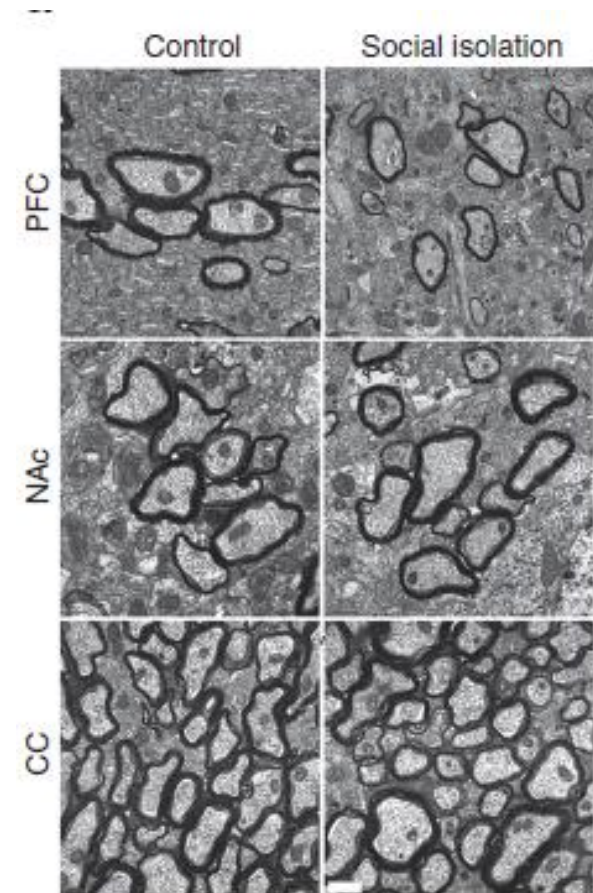
bdnf gene: essential in brain development and synaptic plasticity.

- There are critical (sensitive) periods during early prenatal and postnatal development during which the developing brain demonstrates an unparalleled level of plasticity.
- Environmental influences e.g. caregiving, nurturing - *essentially tactile interactions* – during these periods shape neural circuits that influence life-long structural and functional aspects of brain and behaviour
- Bdnf - key mediator of activity-dependent processes with profound influence on neural development and plasticity.
- Maltreatment alters bdnf DNA methylation in mPFC, hippocampus and amygdala.
- Brief and repeated experiences with a nurturing foster dam have been shown to have long-term effects on methylation even though this manipulation that did not produce any obvious behaviour difference in infants.
- Such studies provide support of DNA methylation modifications as biological consequences of caregiving environments.

Impaired adult myelination in the prefrontal cortex of socially isolated mice

- PFC integrates external stimuli and controls complex behaviours. Myelin changes in PFC are present in a wide range of psychiatric illnesses - autism, anxiety, schizophrenia and depression.
- Models of juvenile social isolation result in myelination changes that mimic conditions related to neurodevelopmental disorders.
- These myelination changes have been reported to be stable and partially explain the long-term consequences of early childhood experience on the development of psychiatric disorders in adulthood.

Liu et al (2012) *Nat. Neuro.* 15(12):1621-1624



Prolonged social isolation induces hypomyelination in PFC – note, no changes in nucleus accumbens or corpus callosum.

Neonatal handling reduces stress induced enhancement of chronic mechanical hyperalgesia

- Neonatal handling of rat pups induces resilience to the negative impact of stress and pain by:
 - increasing the quality and quantity of maternal care
 - attenuating mechanical hyperalgesia produced by water-avoidance stress
- Decrease in mechanical pain threshold in skeletal muscle exposure to water-avoidance stress, was significantly attenuated by neonatal handling. It also attenuated the mechanical hyperalgesia produced by intramuscular pronociceptive mediator, prostaglandin E2 in rats exposed as adults to water-avoidance stress.
- Neonatal handling induces a smaller corticosterone response in adults exposed to a stressor as well as changes in central nervous system neurotransmitter systems.

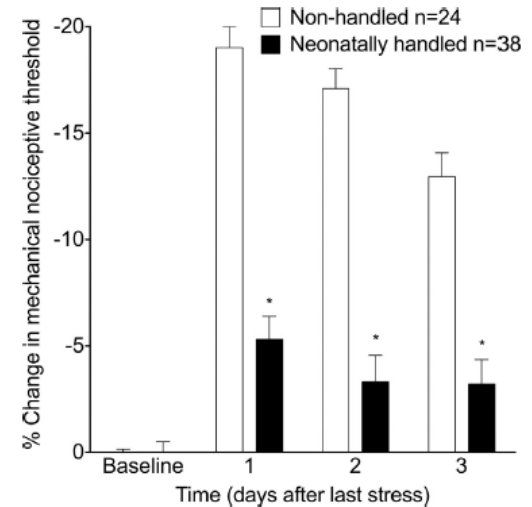


Fig. 1. Neonatal handling attenuates stress-induced muscle hyperalgesia in adult rats. Water-avoidance stress produces a significant decrease in nociceptive threshold in the gastrocnemius muscle (3 d after the last exposure to the stressor). Water-avoidance stress induces reduction in nociceptive threshold that is markedly attenuated in neonatally handled rats. * $p < 0.05$.

Delayed Gratification in Children

- This study tested the effect of touch on children's compliance behaviour in a modified delay-of-gratification task ($M = 59$ months) randomly assigned to a Touch or No Touch group.
- Intervention condition received a friendly touch on the back while being told that they should wait for permission to eat a candy.
- Children in the Touch condition waited an average of 2 min longer to eat the candy than children in the No Touch condition.
- This finding has implications for the potential of using touch to promote positive behaviours in children.

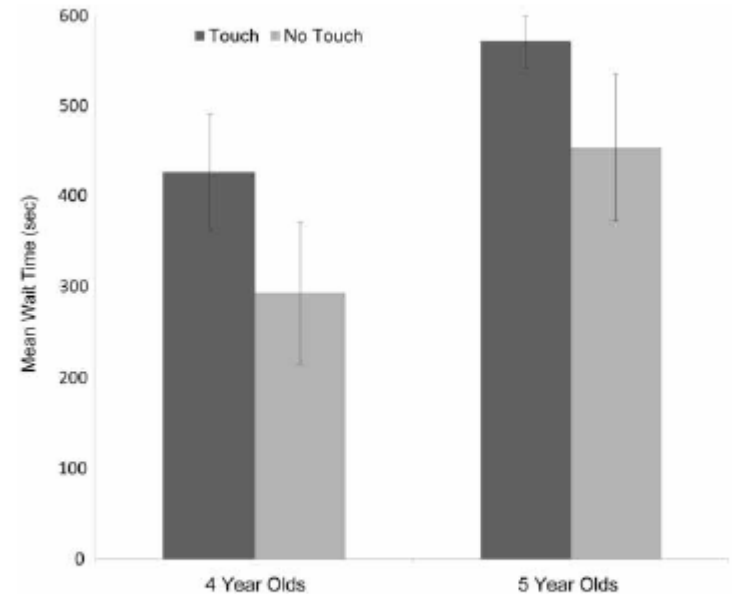


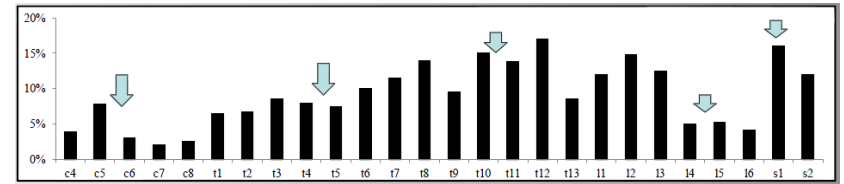
Figure 1. The effects of touch and age on mean waiting times in a delay-of-gratification task

Affiliative Touch

- Examples are courtship, gentle stroking and grooming, and certain maternal patterns such as breastfeeding, all of which include caressing tactile behaviours (Polan & Hofer 1998). Indeed, rat pups find physical contact with the mother inherently rewarding (Hofer et al. 1989).
- In human mothers the pleasurable feelings resulting from interactions with their infants (e.g., nursing) inform them that these behaviours are benefiting their offspring (Panksepp et al. 1994).
- Whereas appetitive approach processes bring an individual into contact with unconditioned incentive stimuli, consummatory processes bring behaviour to a gratifying conclusion (Hilliard et al. 1998).

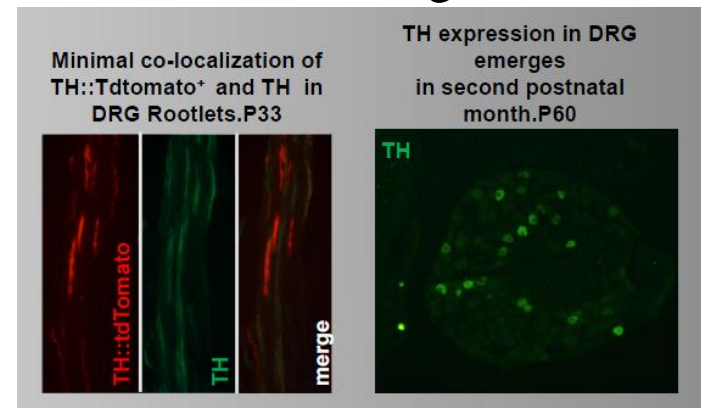
Expression of C-LTMRs in DRGs during postnatal development.

- A population of C-LTMRs can be identified by selective expression of tyrosine hydroxylase (TH) which have the highest incidence of expression in thoracic and sacral spinal DRGs. (Li et al Cell 147, 2011).
- C-LTMR stimulation associated with pleasurable touch and its apparent full emergence in adulthood in this study supports a role in prosocial behaviours such as mating and bond formation, rather than maternal grooming interactions as a pup!
- Are there more than one population of CLTM/CTs?



Percentage of c-LTMR cells in each DRG calculated by counting tdTomato labelled cells. Spinal cord sections and skin samples taken to observe the distribution of this TH+ population.

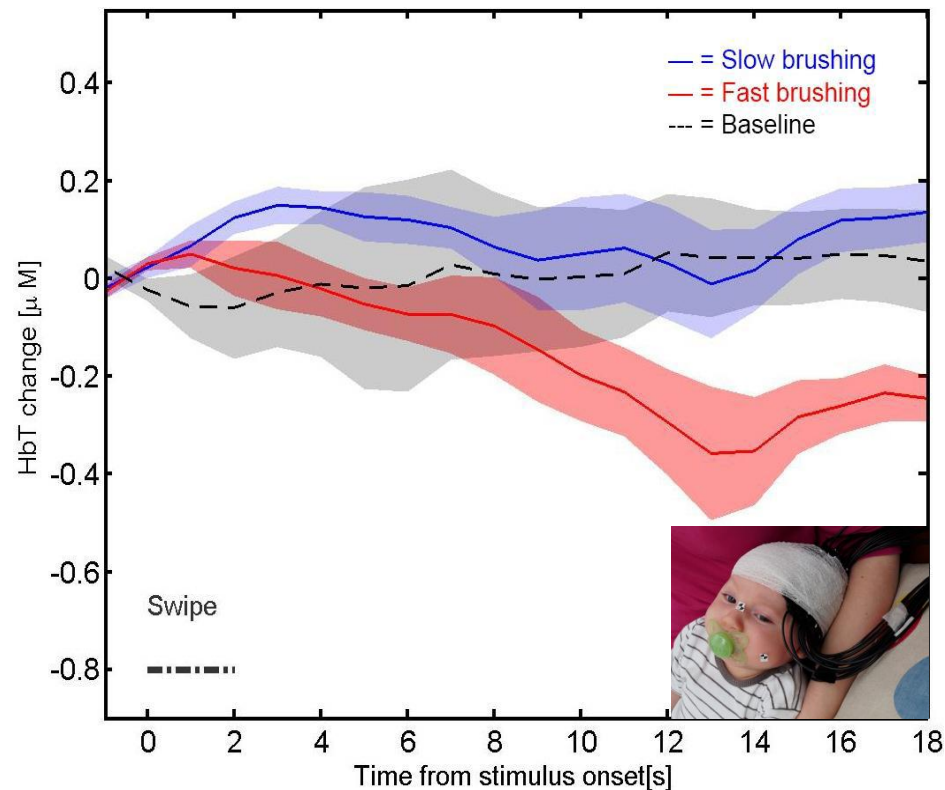
DRG labelling



Lower Incidence of C-fibre LTMRs found during early postnatal development.

Affective touch processing in infancy -fNIRS study

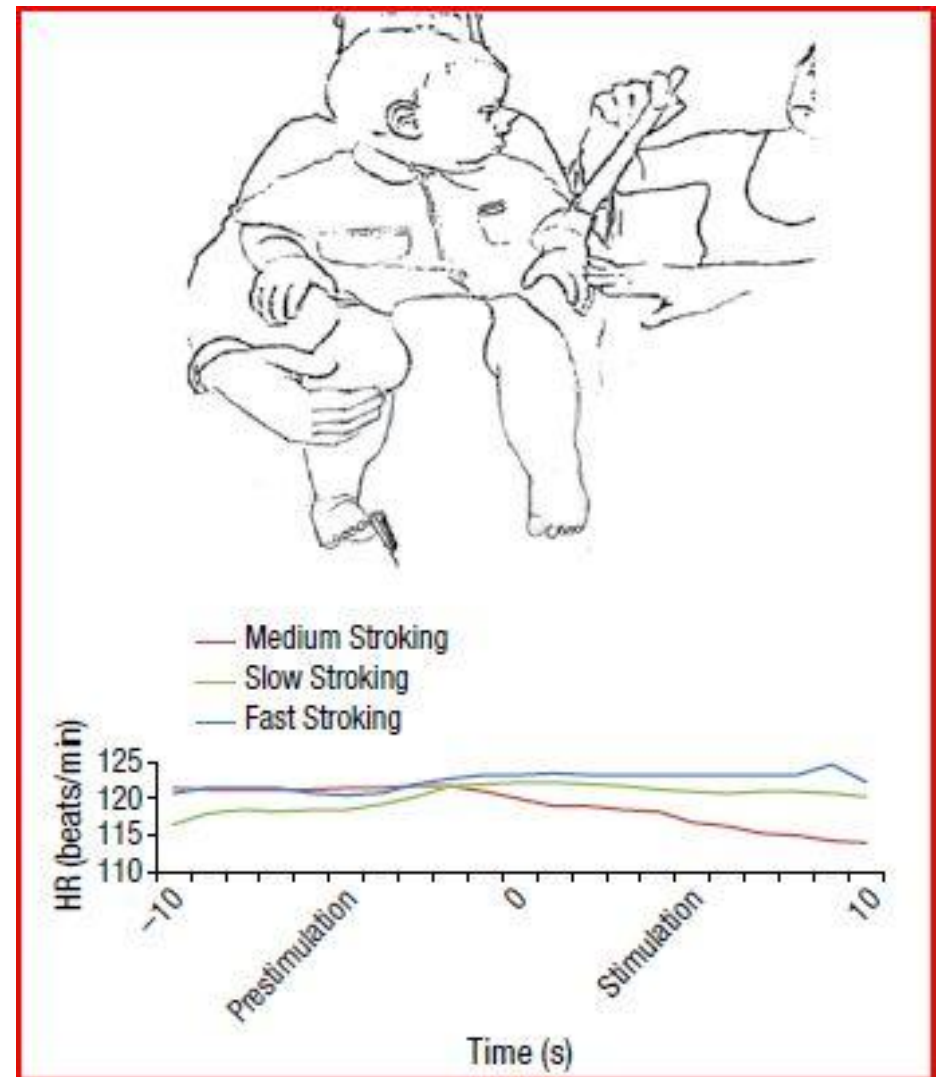
- fNIRS probe was attached to the left side of the infant's head.
- Soft brush stroking forearm at slow and fast velocity's.
- Statistically significant difference in ΔHbT for slow touch compared to fast touch in the frontal part of the probe for the time window 3-6 seconds after stimulus onset.
- **Already at a very early stage of development, the human brain has different ways of processing affective, CT-targeted touch compared to fast, non-affective touch to the hairy skin**



Jönsson et al University of Gothenburg, Sweden,

Infants' Sensitivity to Pleasant Touch

- Infant (~9 months) was stroked on the dorsal forearm with a soft brush at one of three velocities - slow: 0.3 cm/s, medium: 3 cm/s, fast: 30 cm/s.
- Arousal measured by pulse-oximeter.
- Graph shows an individual infant's heart rate (HR) during the 10 s before stimulation and the 10 s during stimulation as a function of stroking velocity.



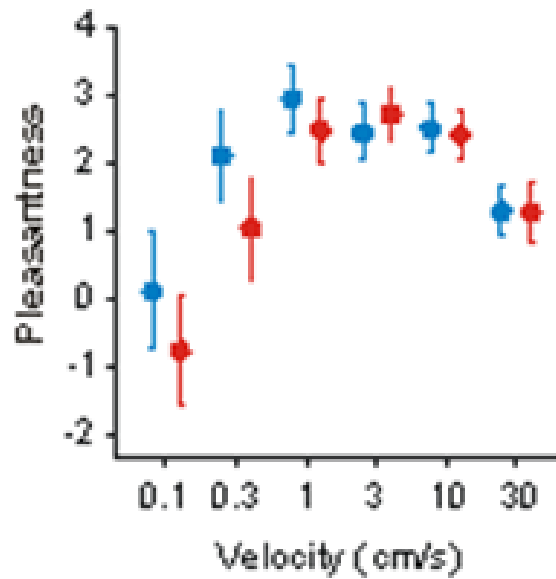
Mothers touch and prenatal stress

- Stress in pregnancy can have an effect on an infant in later life by reducing the activity of genes that play a role in stress response.
- The impact of prenatal stress on infant's development can be either positive or negative depending on the type of environment a child encounters. Some children may experience the effects through being more prone to high levels of fear or anger.
- Mothers who stroke their baby's body in the first few weeks after birth may change the effects that stress during pregnancy can have on an infant's early-life development, researchers have found.

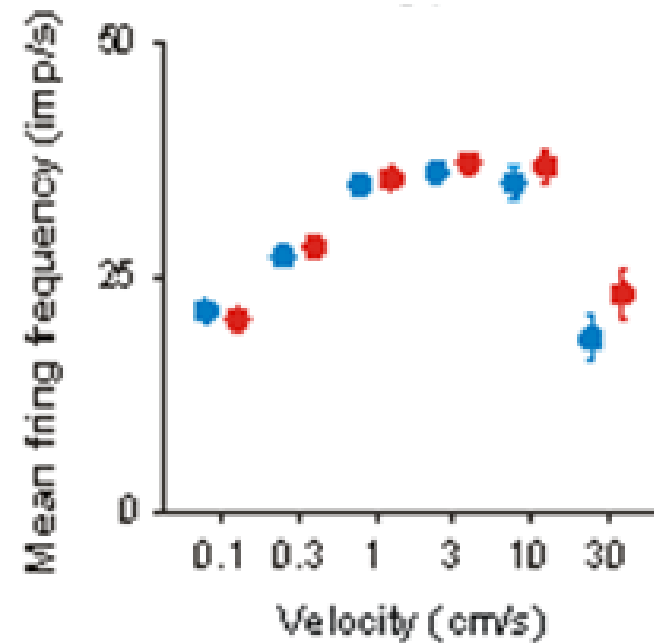


The Inverted 'U'

Psychophysics

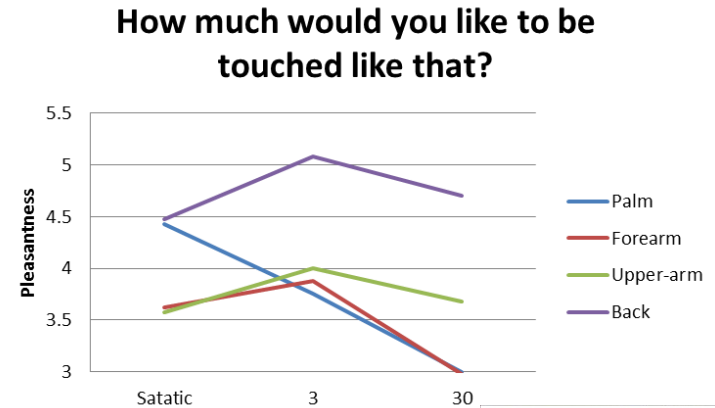


Microneurography



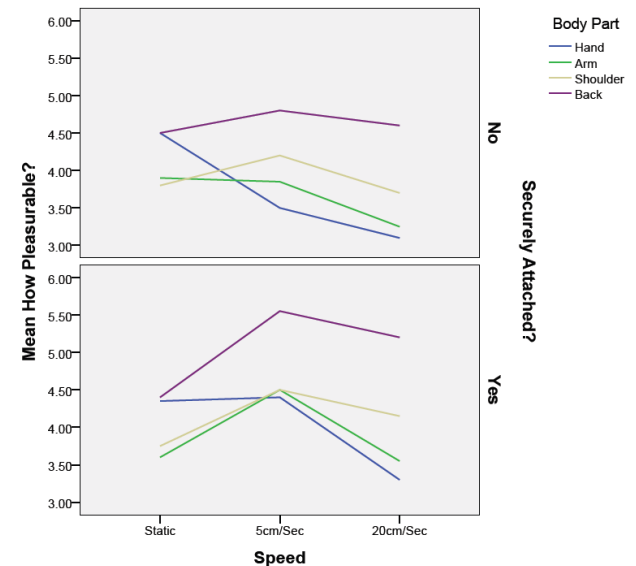
Examples of the inverted U.....

- The 'hedonic homunculus



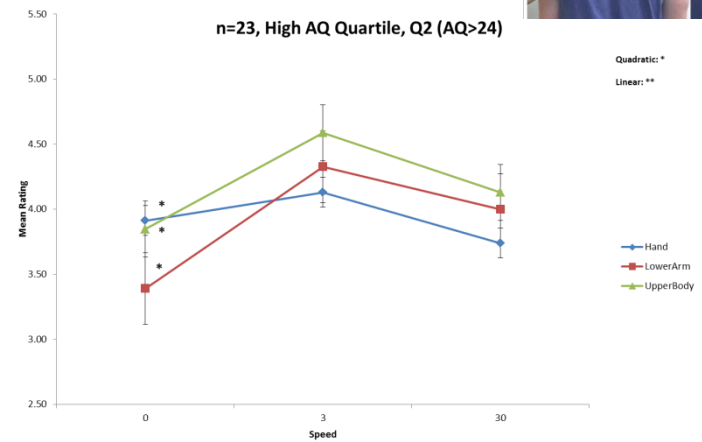
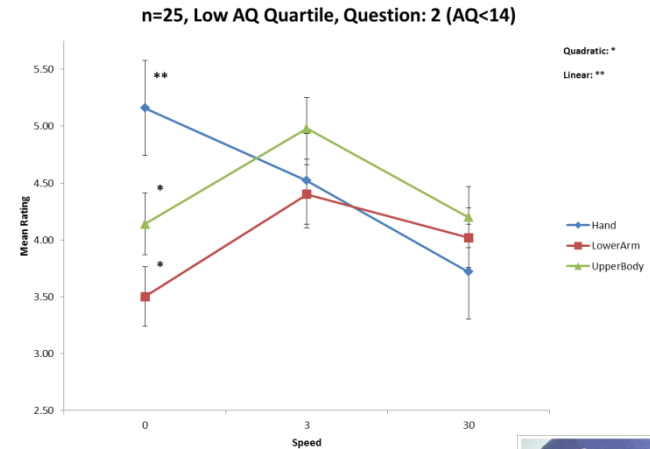
- Attachment and U.....

- Participants who consider themselves securely attached show the quadratic fit.
- Those who fall into the other three attachment categories show linear fit.
- Securely attached show > preference for 3cm/sec over other speeds



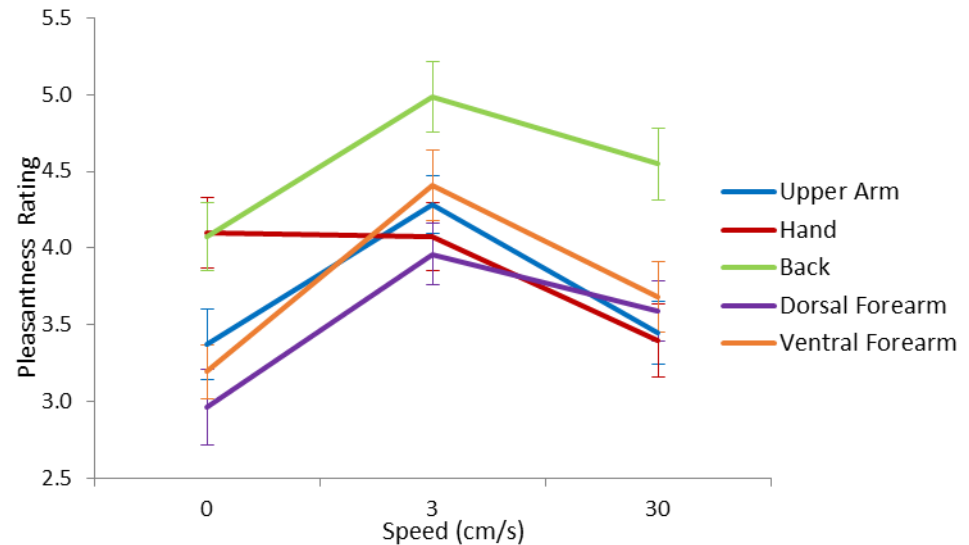
Examples of the inverted U.....

- N=96 males completed AQ and were asked in response to seeing touch videos:
 - You like
 - The other persons likes
- Linear best fit for speed on the hand, quadratic all other sites
- Significant effect of group found:
 - lowest AQ sig > pleasantness than Highest AQ.
 - significant Group x Speed and Group x Location Interaction
 - highest AQ don't show linear for hand



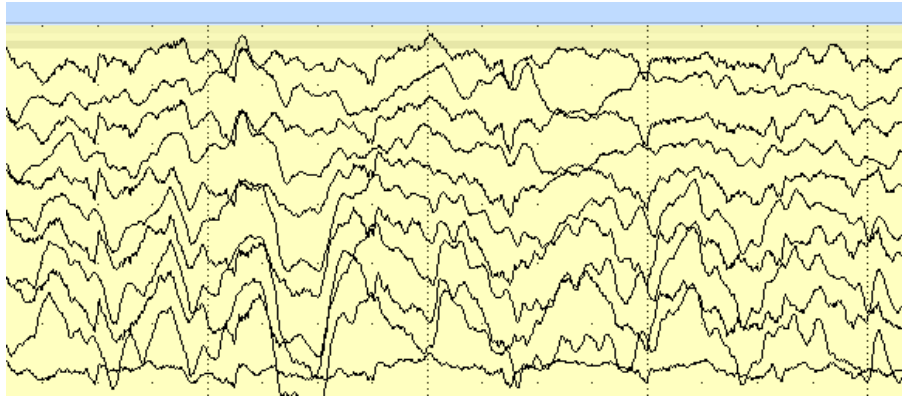
Examples of the inverted U.....

- N=78 females completed EDI-3, reported height & weight for BMI and were asked in response to seeing touch videos:
 - You like?
- Main effect of location, main effect speed, Speed x Location interaction
- 3>30 all locations except the palm. Back preferred.
- Anorexics have low BMI and high Eating Disorder Risk Composite (EDRC)
 - those with low BMI and high EDRC are more sensitive to touch (high U)
- poster



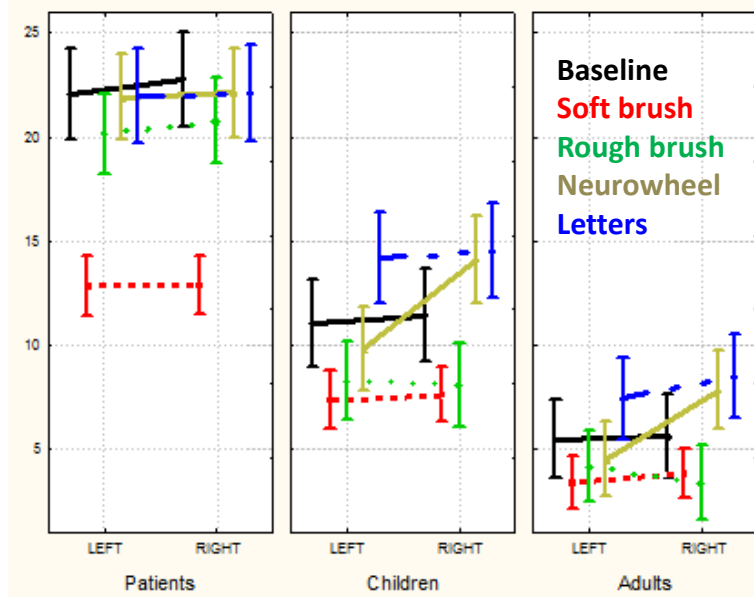
CT stimulation in acute TBI coma: a pilot study

Portnova et al., IHNA RAS, Moscow



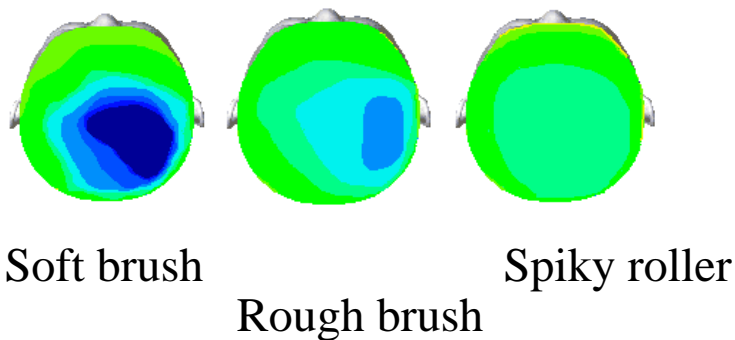
- **Subjects:** 25 healthy adults and 19 severe coma patients, 2-10 days after coma onset (average age was 21.2 years, 9 males).
- EEG was characterized by prevalent theta patterns.
- **Stimuli:** Subjects passively touched by soft, rough, and sharp at their left wrist. Our stimuli were presented with the velocity about 3-5 cm per sec. Healthy adults put eye bandage over their eyes and inserted earplugs to block the noise.

CT stimulation in acute TBI coma: a pilot study



- Prominent delta and theta power decrease compared to background level for coma patients for CT stimulation only (Condition effect $p < 0.0001$)
- Most pronounced over right parietal regions
- Similar but less pronounced effect for both preschool children and healthy adults

Lower theta decrease for coma patients (4-6 Hz)



Autistic traits are associated with diminished neural response to affective touch

- This paper characterizes a network of regions that support the perception of affective touch processed by CT-afferents.
- Regions of the social brain showed a diminished response to CT-touch in individuals with more autistic traits.
- “This work sets the stage for future studies to explore the early development of these neural systems and disruptions associated with disorders with pathognomonic social impairments, such as autism.”

Autistic traits are associated with diminished neural response to affective touch

- Studies in a mouse model have identified a specific subpopulation of unmyelinated, nonpeptidergic sensory nerves, marked by MRGPRB4 that exclusively innervate hairy skin and share many important properties of the CTs including the selective response to massage-like stroking of hairy skin.
Liu et al (2007) Nature Neuroscience; Vrontou, et al (2013), Nature
- These findings, when combined with the recent finding of abnormal brain responses to CT-targeted touch in individuals with ASD, raise a provocative possibility:

The abnormal brain response to CT-targeted touch in ASD might represent a novel neuroimaging biomarker of dysfunction in a particular class of neurons.

What do CTs do?

- The Affective Touch Hypothesis:

The essential role of the CT afferents is to signal affective (pleasant/emotional/social) aspects of light touch based on data from:

- Microneurography
- Psychophysics
- Neuroimaging (PET, fMRI, EEG)
- Behavioural studies
- Studies in denervated subjects
- Studies in ASD and anorexia

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