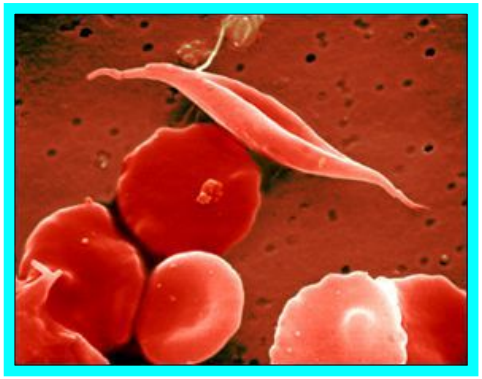
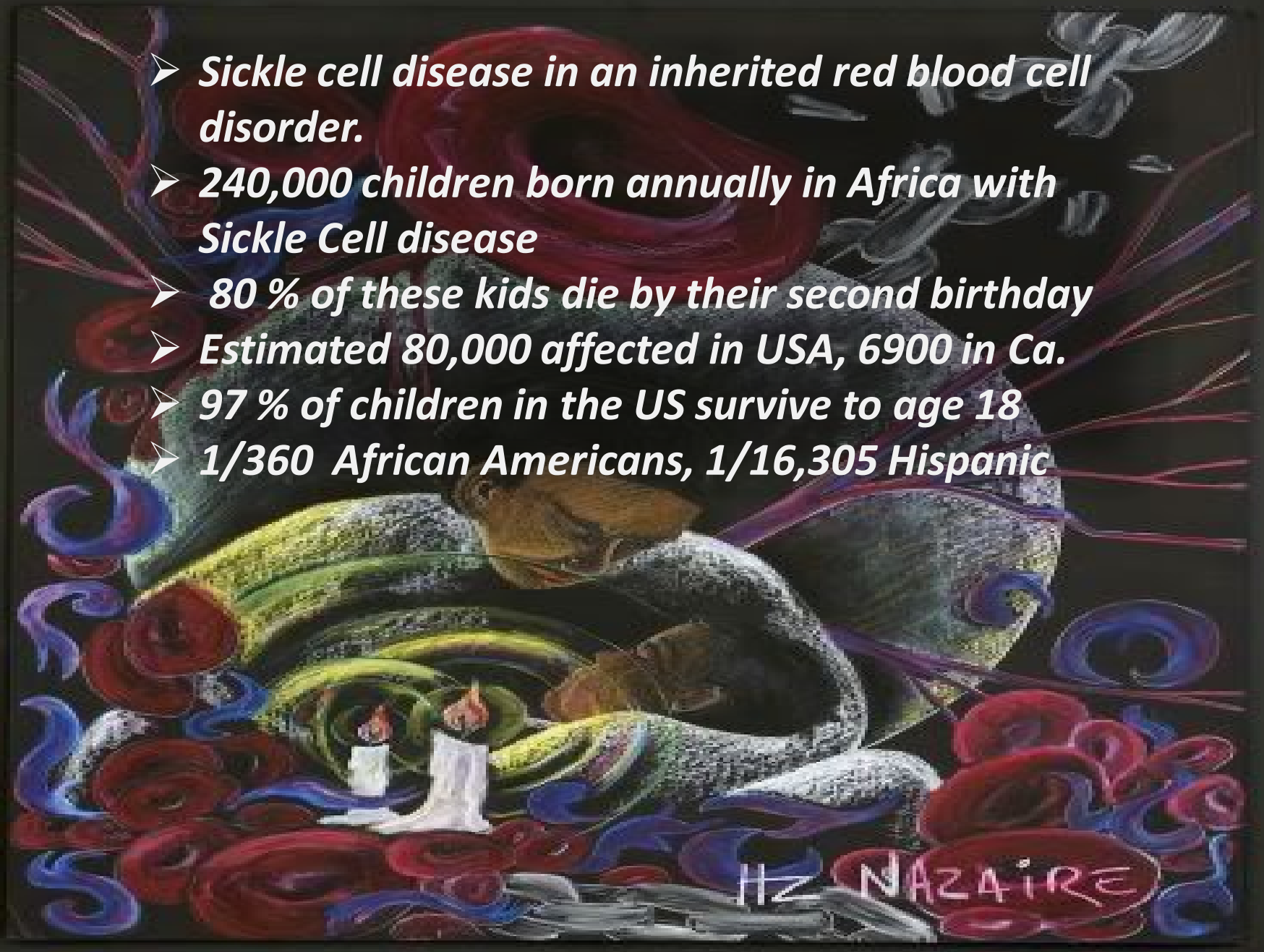


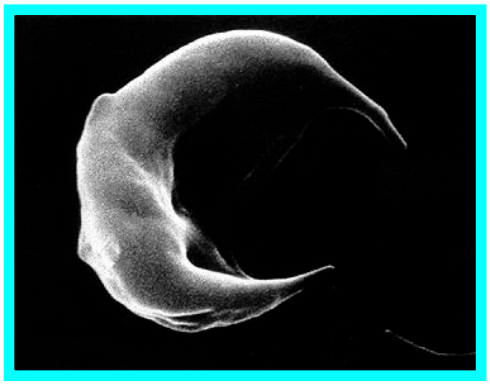
"Neuropathic pain: Can stress and pain itself cause a sickle crisis?

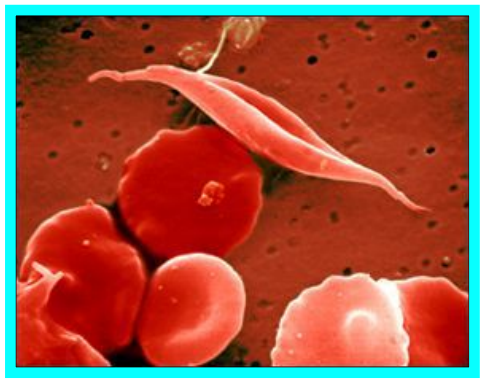
Thomas D Coates, MD
Section Head of Hematology
Childrens Center for Cancer and Blood Disease
Childrens Hospital Los Angeles
Professor of Pediatrics and Pathology
University of Southern California Keck School of Medicine

- *Sickle cell disease in an inherited red blood cell disorder.*
- *240,000 children born annually in Africa with Sickle Cell disease*
- *80 % of these kids die by their second birthday*
- *Estimated 80,000 affected in USA, 6900 in Ca.*
- *97 % of children in the US survive to age 18*
- *1/360 African Americans, 1/16,305 Hispanic*



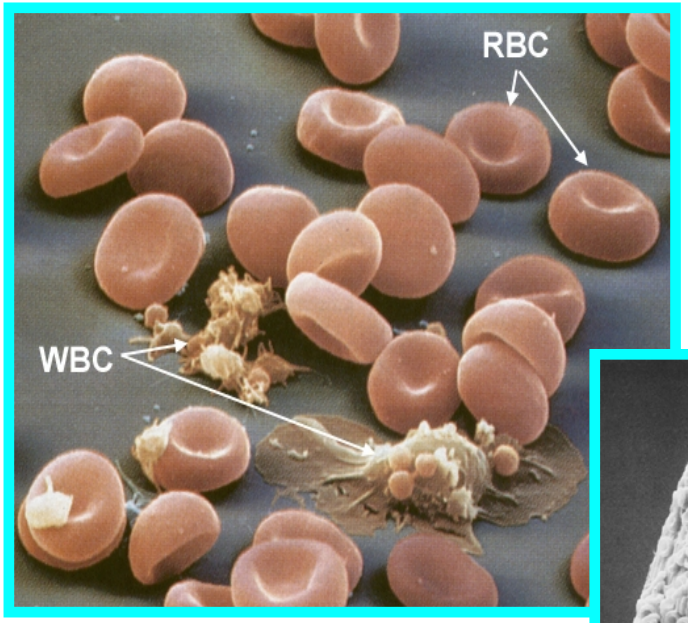
What is Sickle Cell Disease

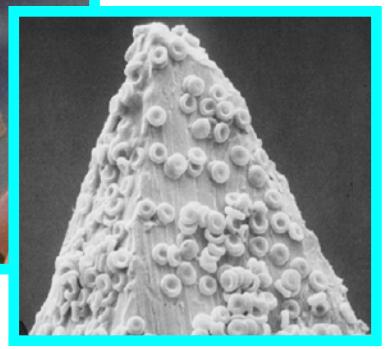




Sickle cell anemia

- Inherited problem with red blood cells that makes them become very rigid when they release oxygen to tissue.
- Affects 1/400 people of African descent
- Rigid red cells block blood flow
- Constant damage to organs.
- Sudden episodes of terrible pain
- Results in poor quality of life and premature death





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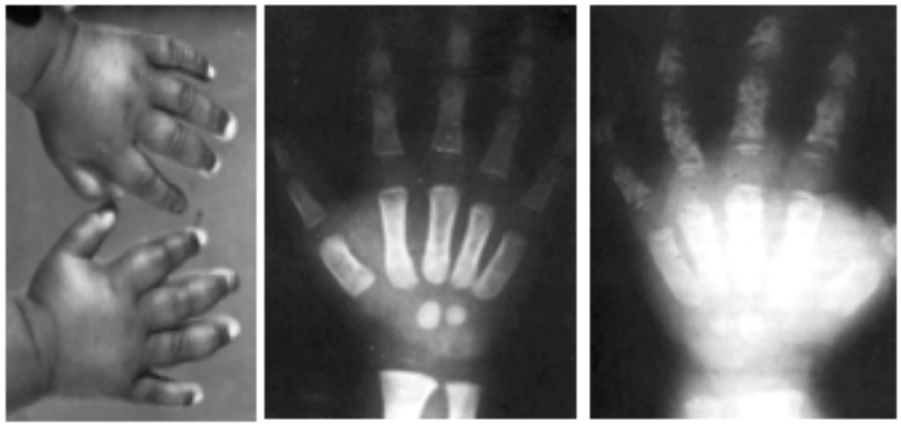
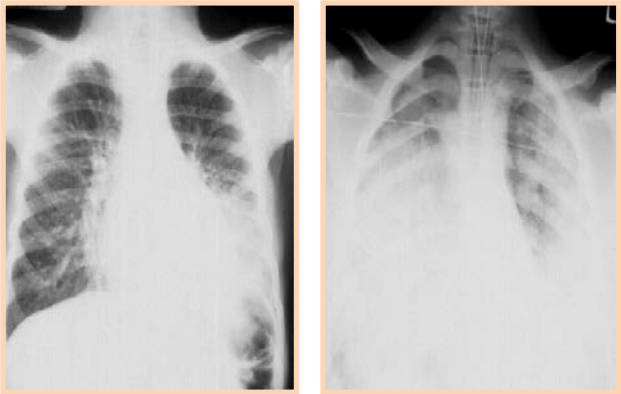
SCD: Clinical manifestations



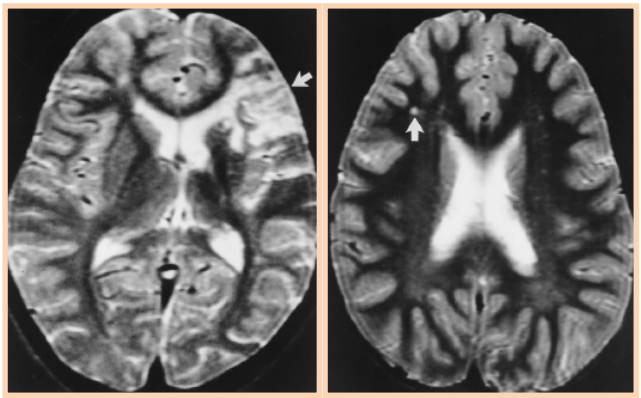
Severe painful damage to bones

Old data we hope are changing

- ✓ 38% have a small strokes by age 8
- ✓ 50% have blood vessel disease in their brain by age 14
- ✓ Strokes reduce IQ by 30%
- ✓ **Half of SS patient pass by age 42-60**
- ✓ Crisis pain is like pain from bone fracture
- ✓ Adults have pain 50% of days
- ✓ 30% of adults have pain 95% of days
- ✓ 50% of adults have chronic lung failure
- ✓ 30% of adults have chronic kidney failure



Small pneumonia can turn into fatal lung failure in hours



Big and small strokes start in childhood and cause brain damage

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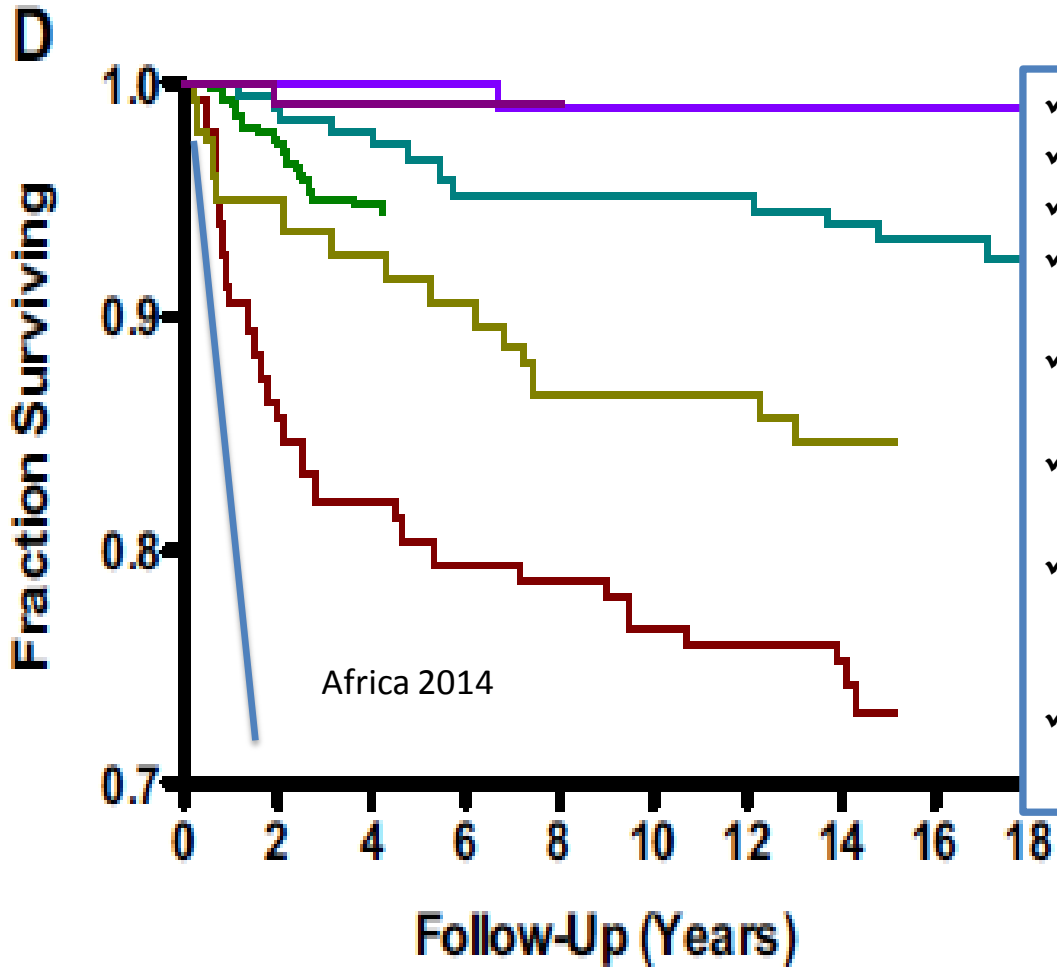
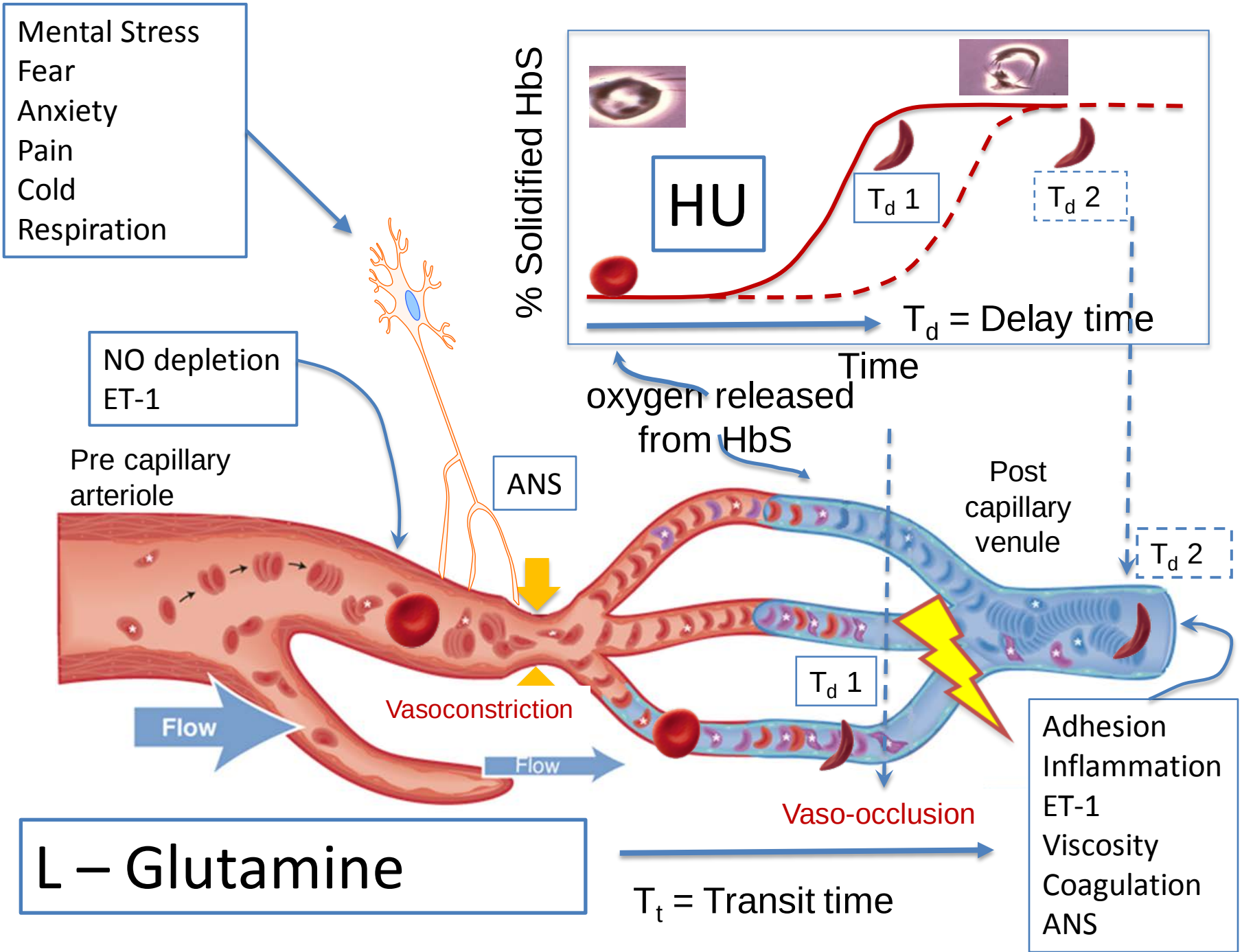
SCD Survival in Children (Survival ≠ Normal)



- ✓ Newborn screening / Early diagnosis
- ✓ Comprehensive SCD center care
- ✓ Penicillin prophylaxis ASAP
- ✓ Immunization for encapsulated organisms
- ✓ Aggressive treatment of fever / infection
- ✓ Hydroxyurea at maximal tolerated dose for all SS/Sβ^0 patients > 9 mo
- ✓ TCD screening and prophylaxis for stroke if indicated
- ✓ Consider bone marrow transplant for all SS/Sβ^0 patients

Quinn et al, 2010 Blood 115(17) 3447


Mental Stress
Fear
Anxiety
Pain
Cold
Respiration
% Solidified HbS
HU
T_d 1
T_d 2
T_d = Delay time
Time
NO depletion
ET-1
oxygen released
from HbS
Pre capillary
arteriole
ANS
Post
capillary
venule
T_d 2
T_d 1
Vasoconstriction
Flow
Flow
Vaso-occlusion
Adhesion
Inflammation
ET-1
Viscosity
Coagulation
ANS
L – Glutamine
T_t = Transit time

Bench to Bedside: Management of SCD

Increase delay time to polymer formation: Use Hydroxyurea

- ✓ Reduces hospitalizations by 50%
- ✓ Reduces hospital duration by 50%
- ✓ Reduces mortality in adults by 40%
- ✓ Reduces TCD velocity
- ✓ Push to max tolerated dose (around 35 mg/kg)
- ✓ Start HU at 9 months of age (NIH recommendation)

Blood Transfusion

- ✓ Dilutes out HbS RBC
- ✓ Improves viscosity, or at least changes it

Maintain good perfusion to improve microvascular flow

- ✓ Gently hydrate
- ✓ Keep patient warm
- ✓ Treat inflammation
- ✓ L-Glutamine
- ✓ **Treat pain**
- ✓ **Airy-Fairy psycho treatments to calm the nerves**

We do this and believe it helps but in fact, it has never really been studied

The important stuff:

Pain is the hallmark of sickle vasoocclusive crisis

Sickling happens continually. We really don't know exactly what causes the sudden exacerbations or "crises" ?

Patients tell us cold, stress, anxiety and pain itself can trigger crisis.

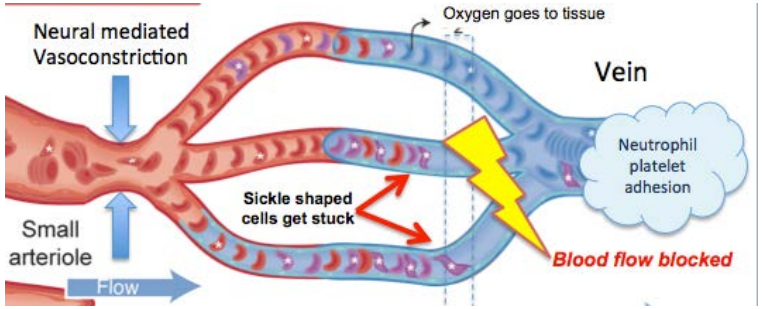
It is very important to get control of severe "crisis" pain with adequate doses of medications quickly (***but***)

Narcotics make you more likely to get neuropathic pain and make neuropathic pain worse.

SCD patients can have both kinds of pain at the same time

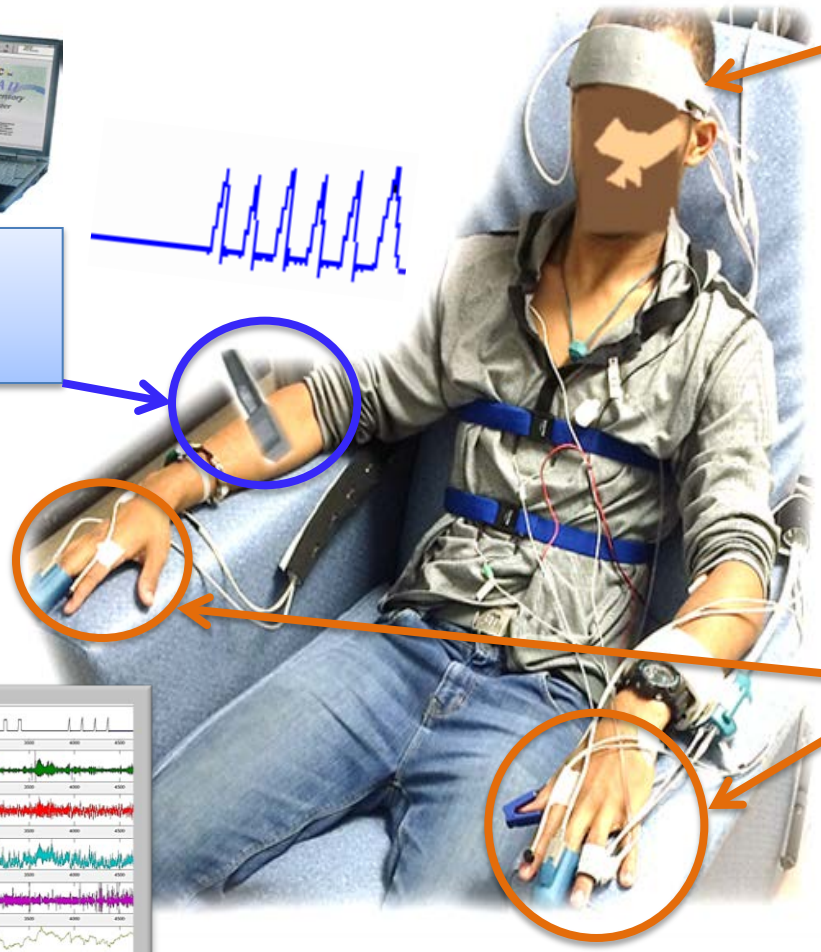
Patients and medical providers need to know the difference between these two kinds of pain.

Anxiety, stress, lack of sleep make any kind of pain much worse.



Measurement of blood flow in response to pain caused by heat

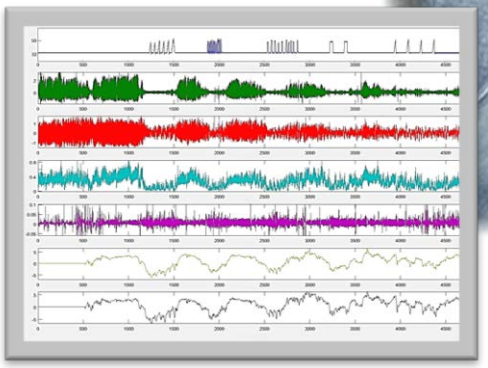
Medoc Thermal Neurosensory Analyzer (TSAII)



Prefrontal cortex Oxygenation changes (fNIR)

Autonomic Parameters (HR variability and Baroreceptor reflexes)

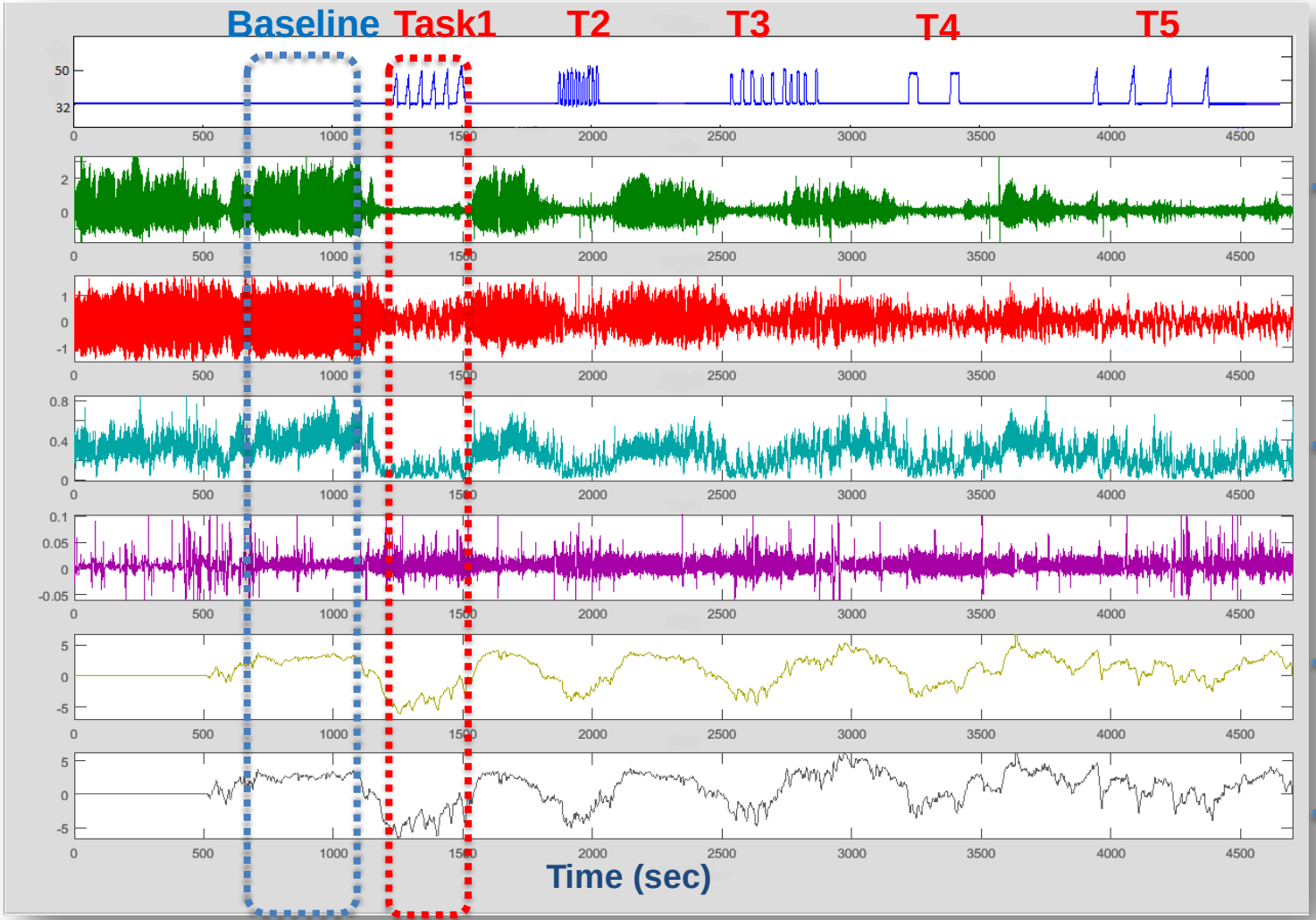
Peripheral Blood Flow:
Laser Doppler
Peripheral Arterial tonometry (PAT)
Pulse Oximetry



M Khaleel

M Puliyel

Could Pain Cause Changes in Regional Blood Flow ?

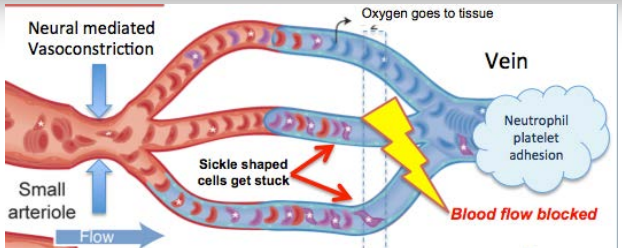


Pain Signal

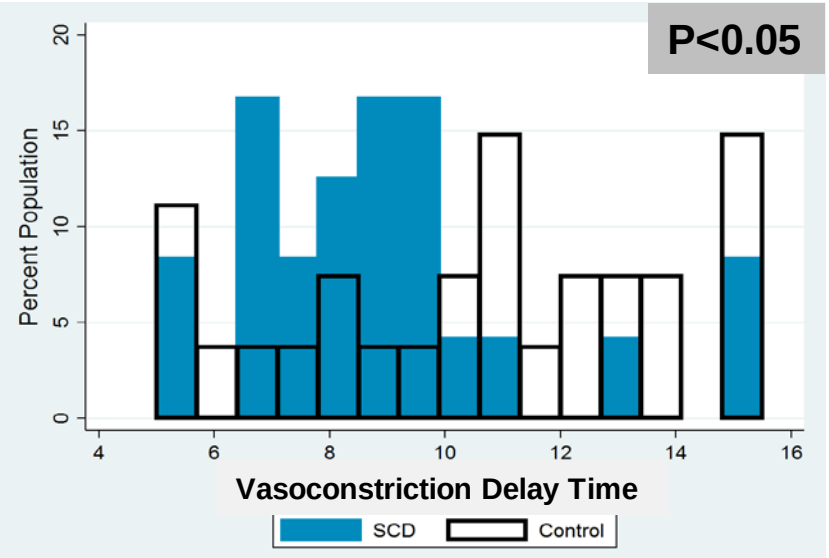
Peripheral Blood Flow (Contralateral hand)

Respiration

Prefrontal cortex oxygen content

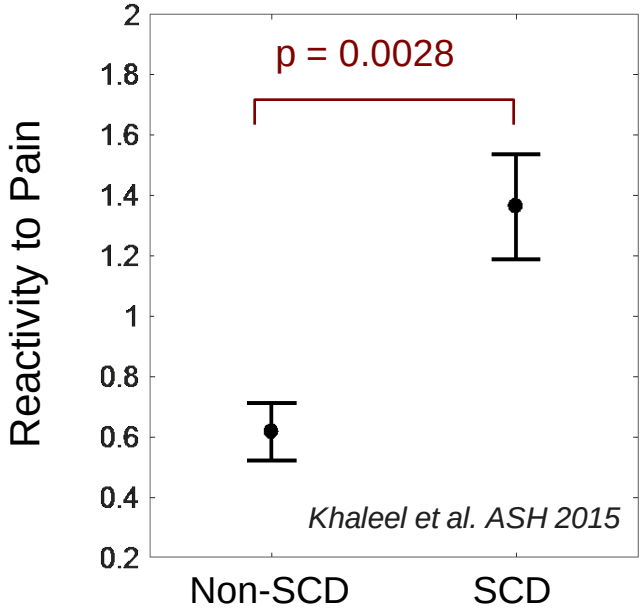


SCD patients have different response than Controls !



SCD subjects vaso constricted faster in response to pain.

SCD subjects had stronger vasoconstriction reactivity to pain than non-SCD



Maha Khaleel

Payal Shah

M Puliyel

Khaleel et al, AJH 2017

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PAIN

Sensitization of nociceptive spinal neurons contributes to pain in a transgenic model of sickle cell disease

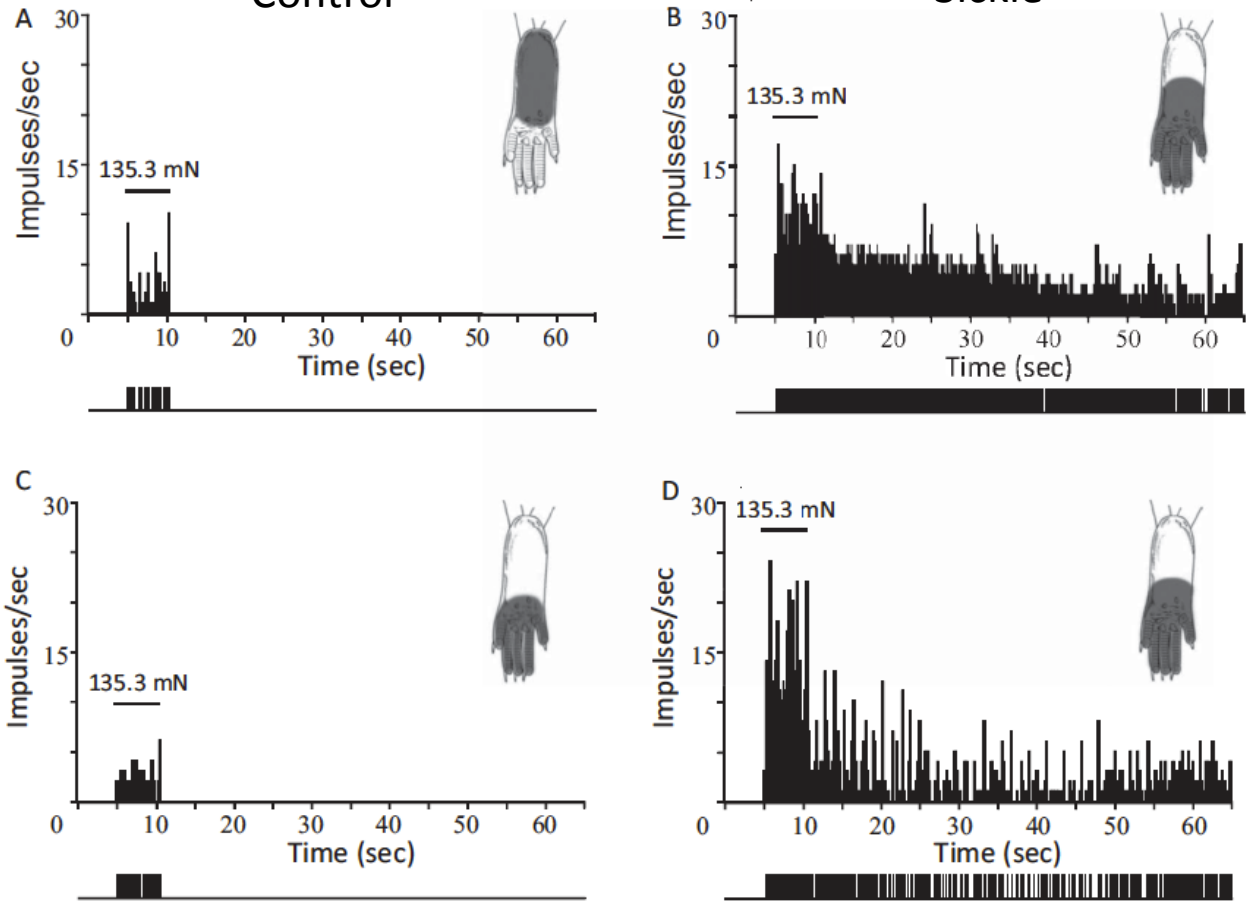
Giuseppe Cataldo[a], Sugandha Rajput[b], Kalpna Gupta[b], Donald A. Simone[a,*]

Control

Sickle

WDR

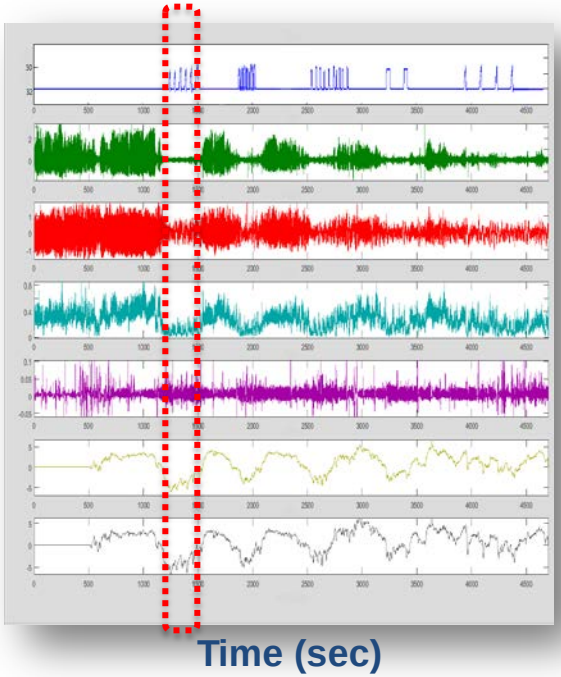
HT

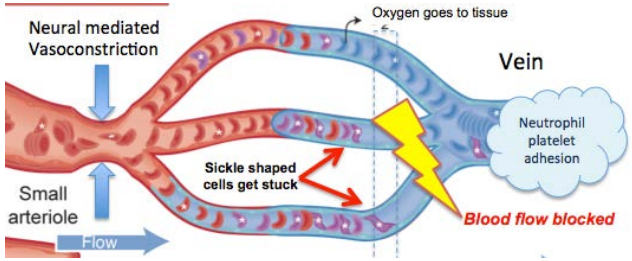


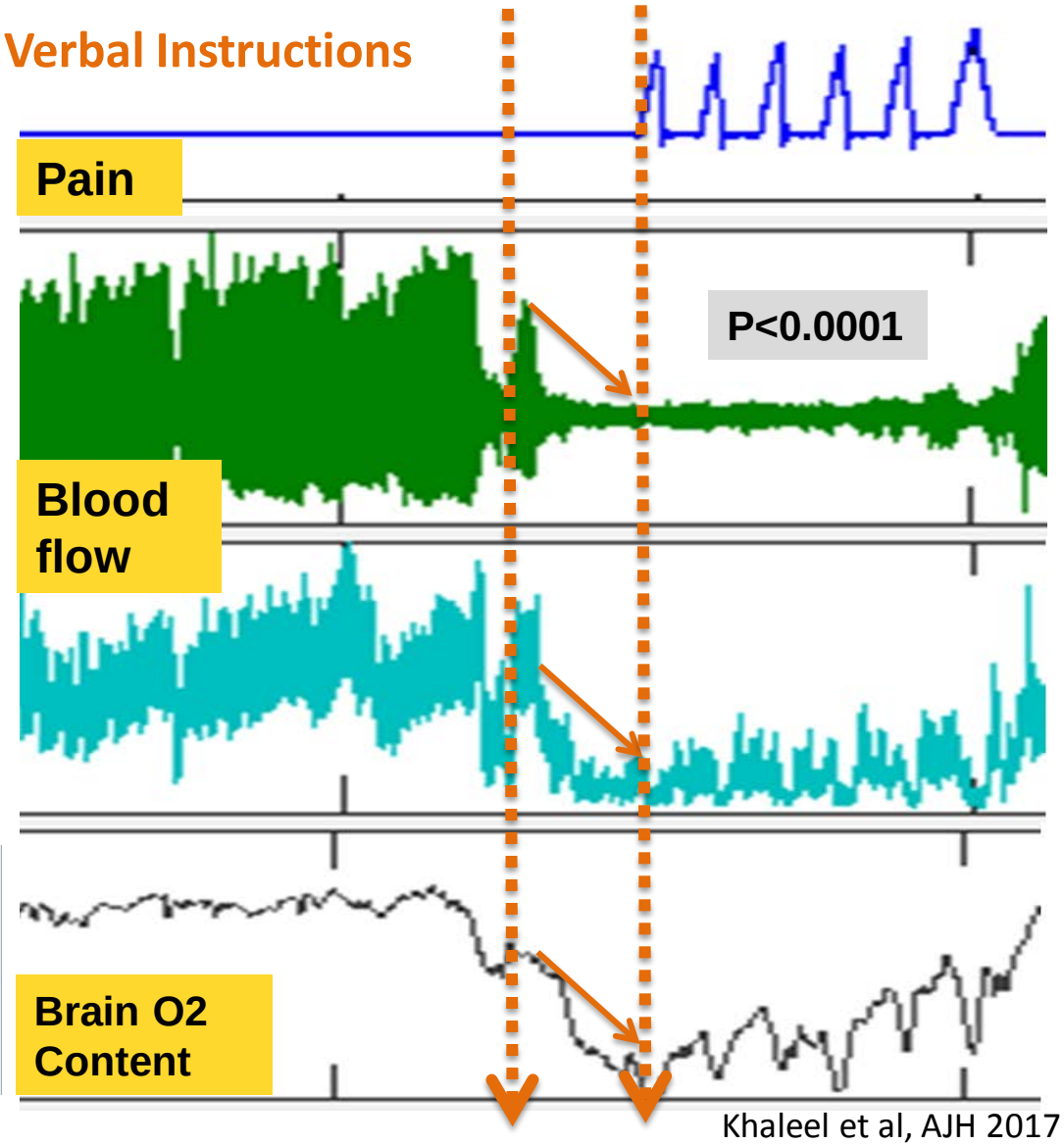
Cataldo et al, Pain 2015 156:722-730

Pain Anticipation causes Vasoconstriction

Task1





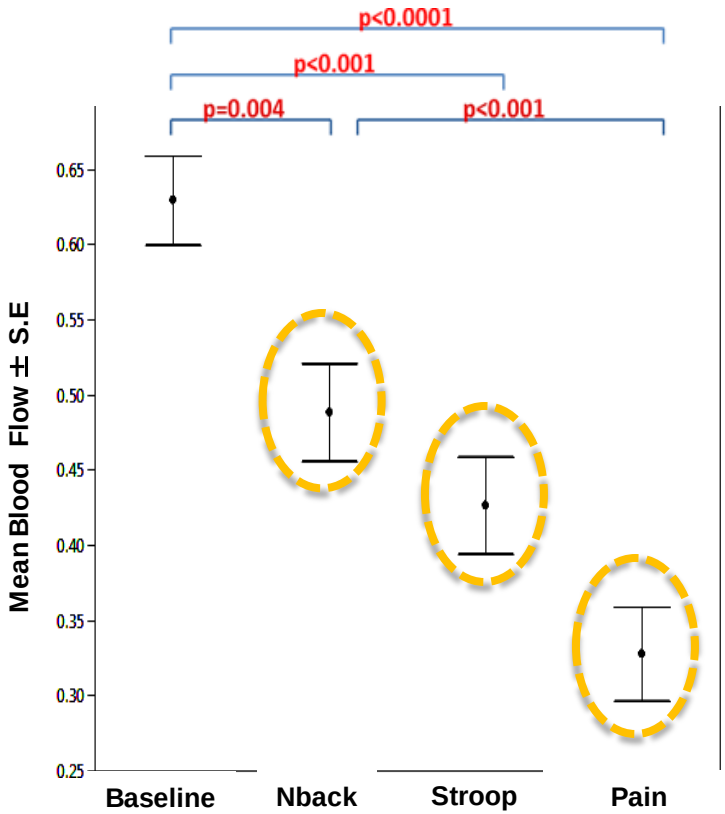


Khaleel et al, AJH 2017

Both fear or anxiety of pain as well as pain itself can cause decreased perfusion

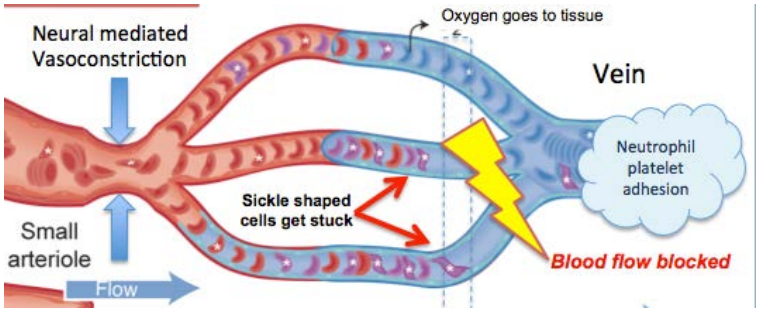
Mental Stress and Pain Anticipation cause Significant Vasoconstriction Response

Significant decrease in blood flow during each mental task



(N = 35)

Maha Khaleel Payal Shah Saranya Veluswamy



Manuscript in preparation

The Effect of Hypnosis on Pain and Peripheral Blood Flow in Sickle Cell Disease: A Pilot Study

Table 2.

Effects Of Hypnosis Flow On Peripheral Blood Flow Responsivity

	Control			SCD		
	t	*p*	*d*	*t*	*p*	*d*
Pre-Hypnosis Anticipation Period	-.207	.84	.06	5.722	.0002	1.73
Pre-Hypnosis Pain Task	-.010	.99	.003	-.587	.57	.18
Post-Hypnosis Anticipation Period	.187	.85	.05	1.294	.23	.39
Post-Hypnosis Pain Task	.255	.80	.07	.719	.49	.22

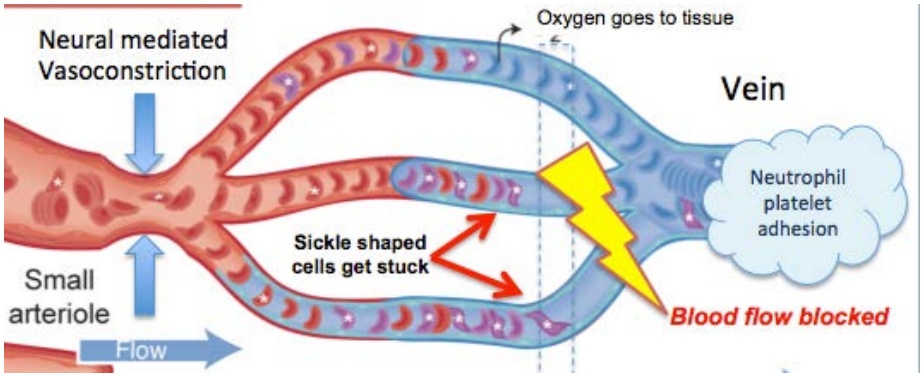
Hypnosis increases peripheral blood flow responsivity in SCD patients

Ravi Bhatt Lonnie Zeltzer Jenny Tsao et al J. Pain Research Jul 14 2017

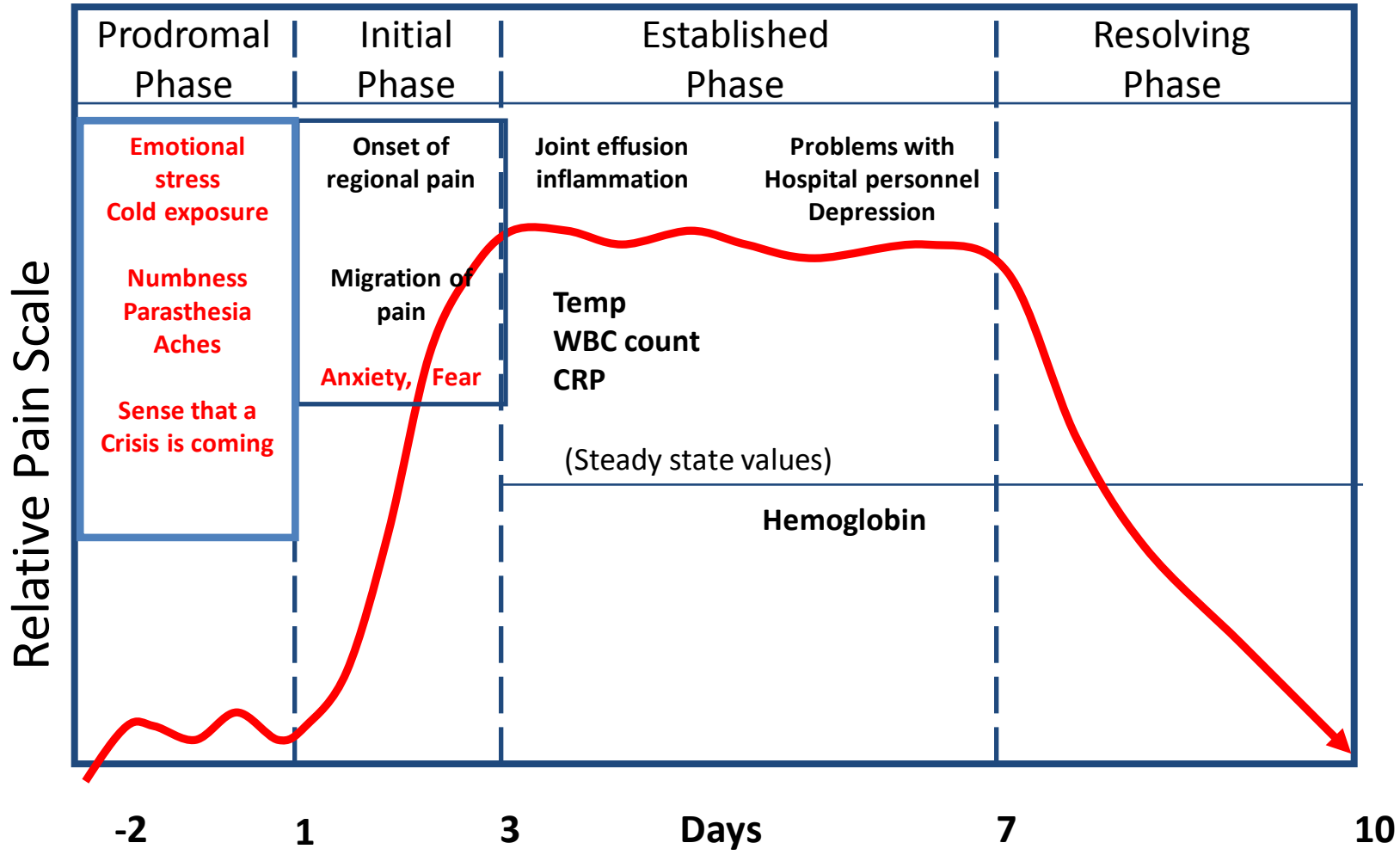
Pain management is extraordinarily complex in SCD

Anxiety, emotions, and pain are biochemical and physiological responses, not psychiatric disorders.

Narcotics make neuropathic pain worse

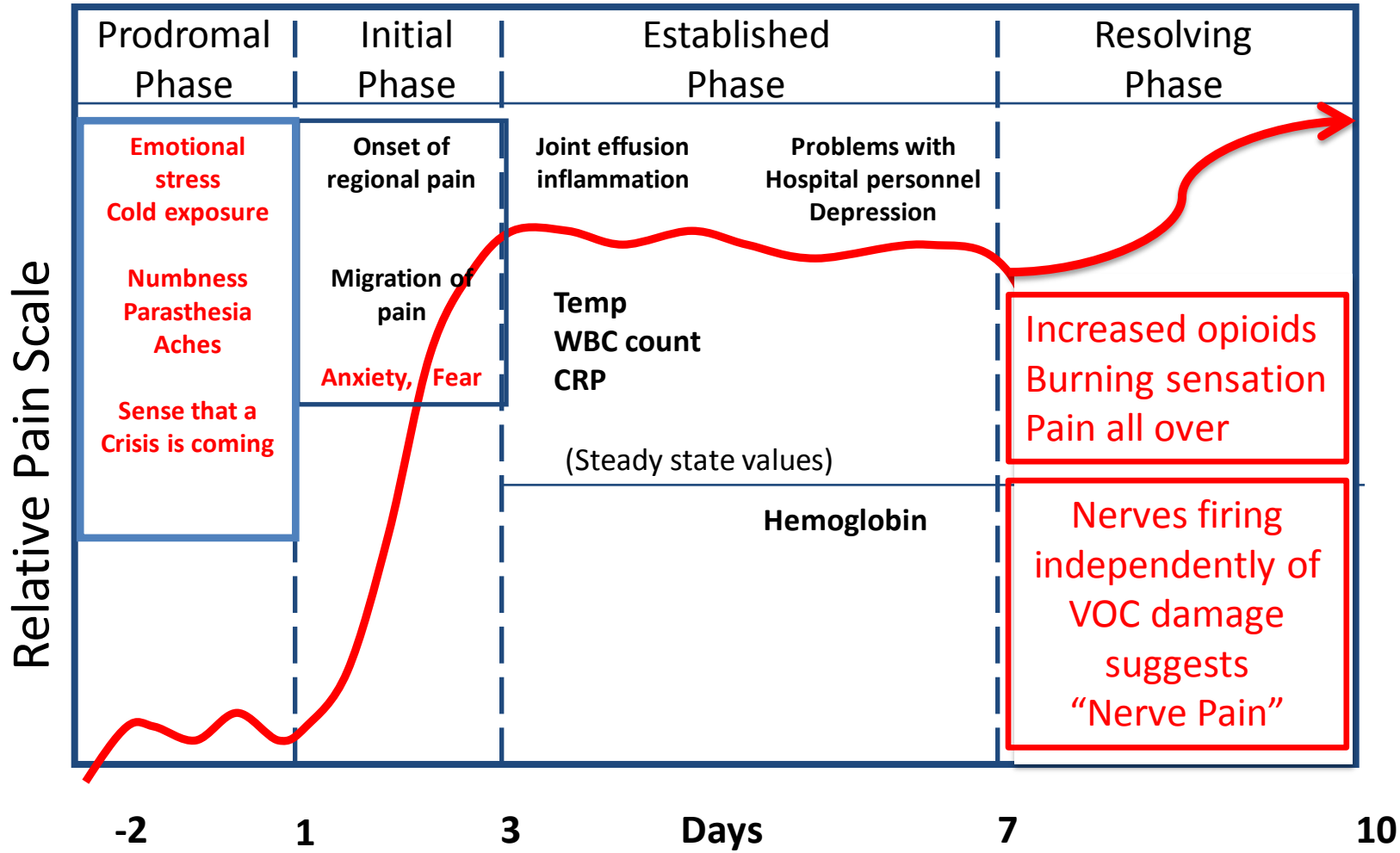


Course of Pain Crisis



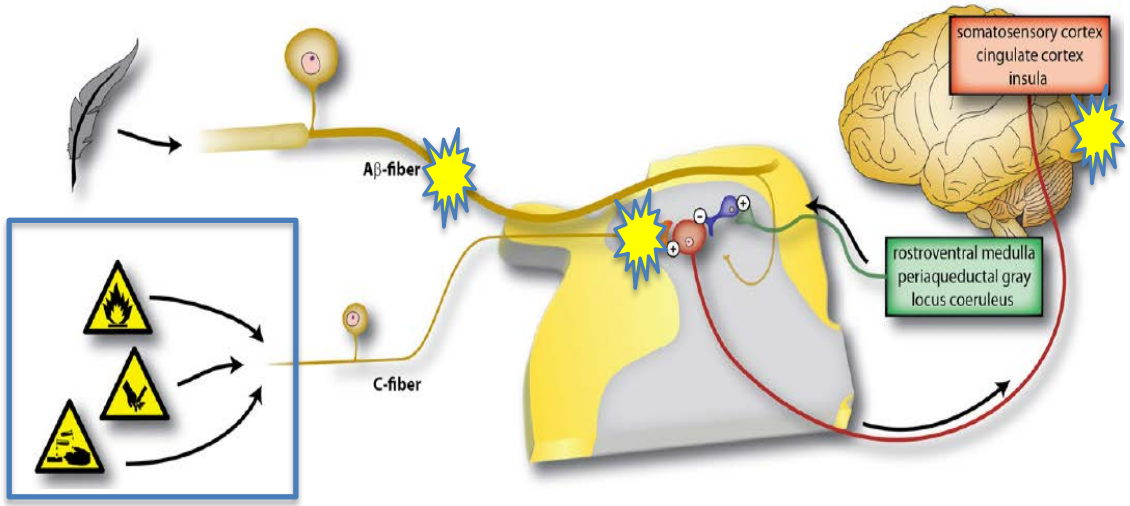
After Ballas 1995

Pain Crisis evolution to neuropathic pain



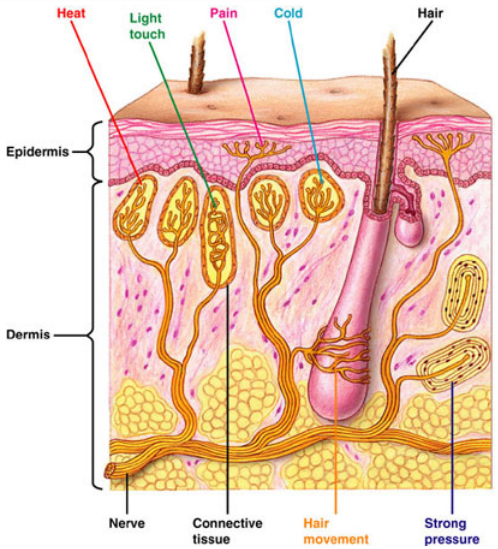
After Ballas 1995

There are several kinds of Pain



Types of pain

- ✓ Nociceptive
- ✓ Inflammatory
- ✓ Neuropathic

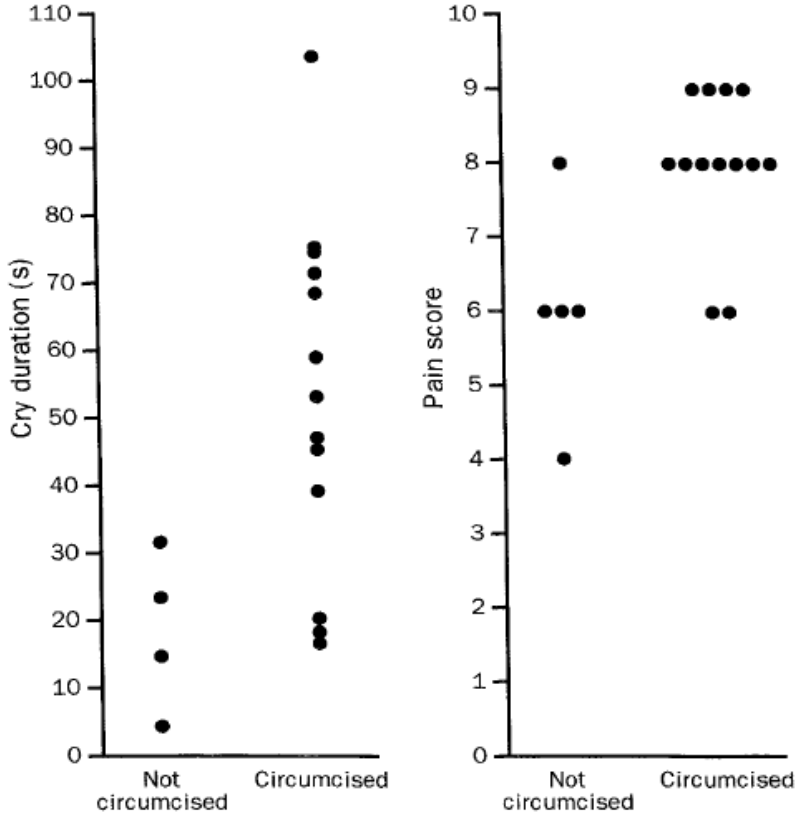


Pain perception is modulated by

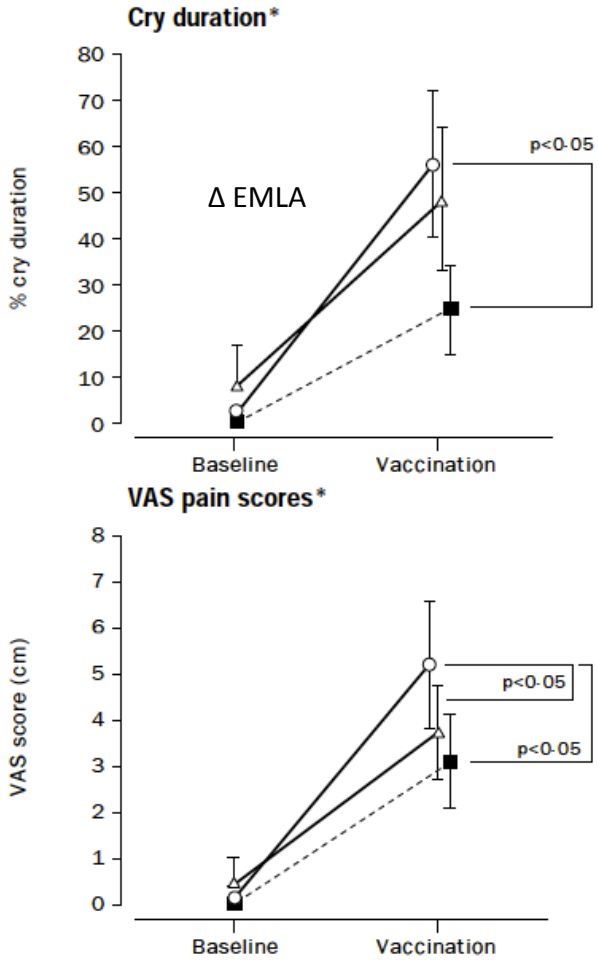
- ✓ Previous experience
- ✓ Anxiety and Stress
- ✓ Gender
- ✓ Many other complex issues

Von Hehn, Neuron 2012 73: Feb 23

Previous pain experience affect current pain perception

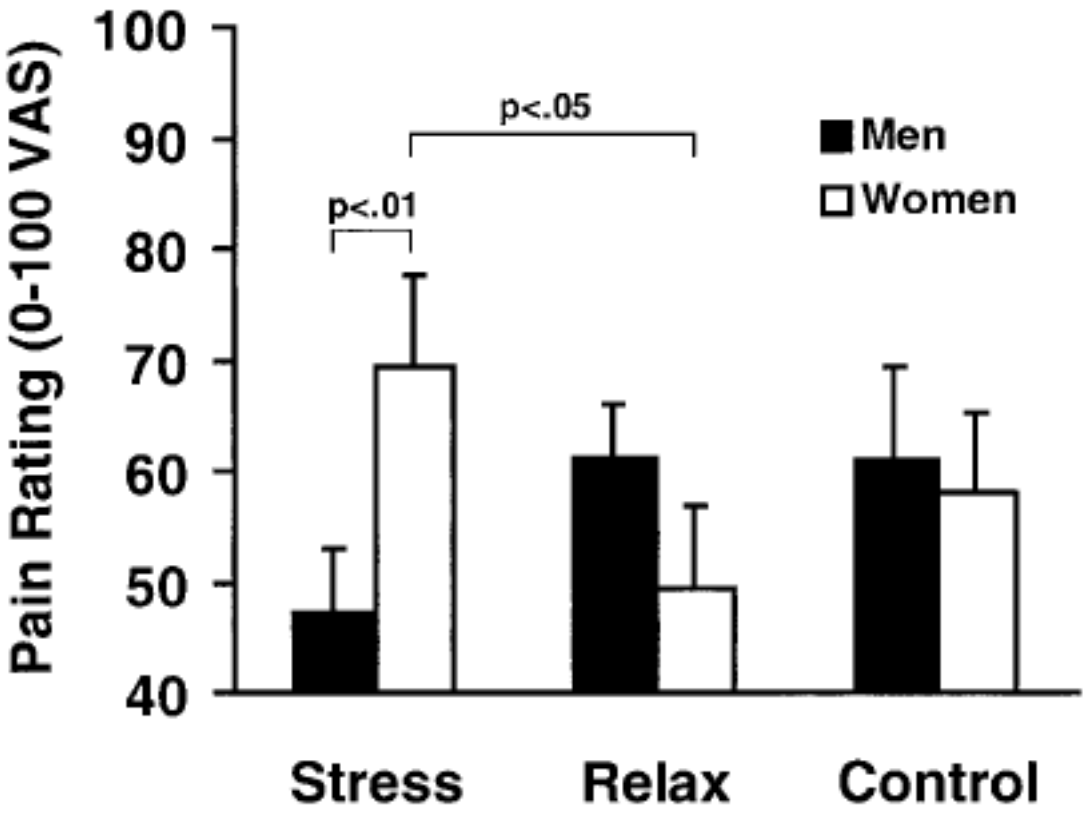


Taddio, A et al, Lancet 1994; 344:291



Taddio, A et al, Lancet 1997; 349:600

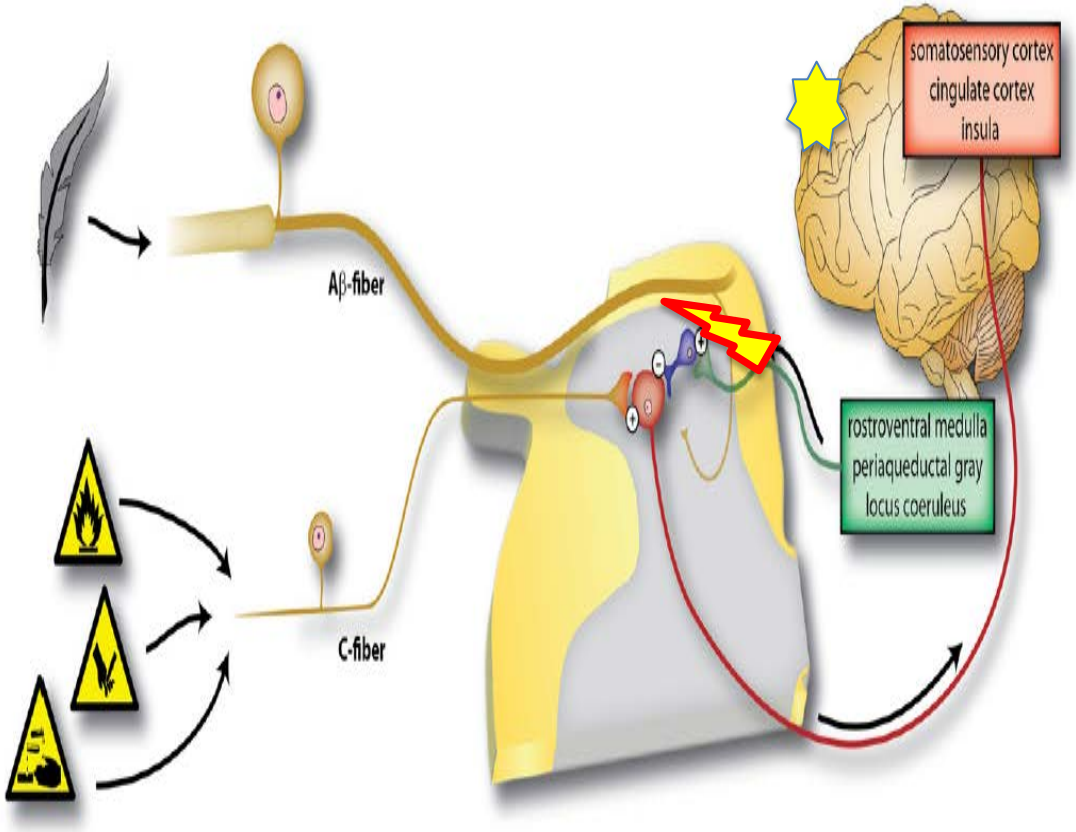
Stress and Gender modify pain perception



Logan H, et al J. Pain 2001 2(3) 160

Neuropathic pain Syndromes

- ✓ Chronic pain damages neurons and they start firing by themselves with no noxious stimulus
- ✓ Low intensity stimuli then cause perception of intense pain.
- ✓ Results from hypersensitization to pain.
- ✓ This is an organic, not psychiatric process. This pain is very real and very severe.
- ✓ **Opioids as well as emotional stressors make this worse.**



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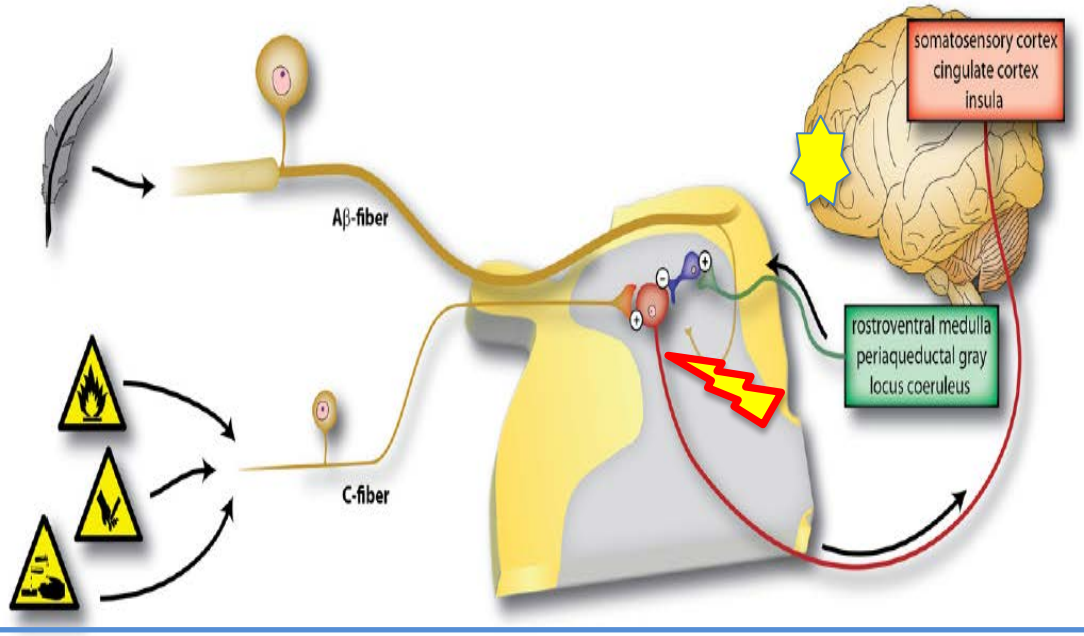
Pain Amplification Syndromes

- ✓ Pain is the mechanism to sense tissue damage
- ✓ Chronic pain damages neurons and they start firing by themselves with no noxious stimulus
- ✓ Low intensity stimuli then cause perception of intense pain.



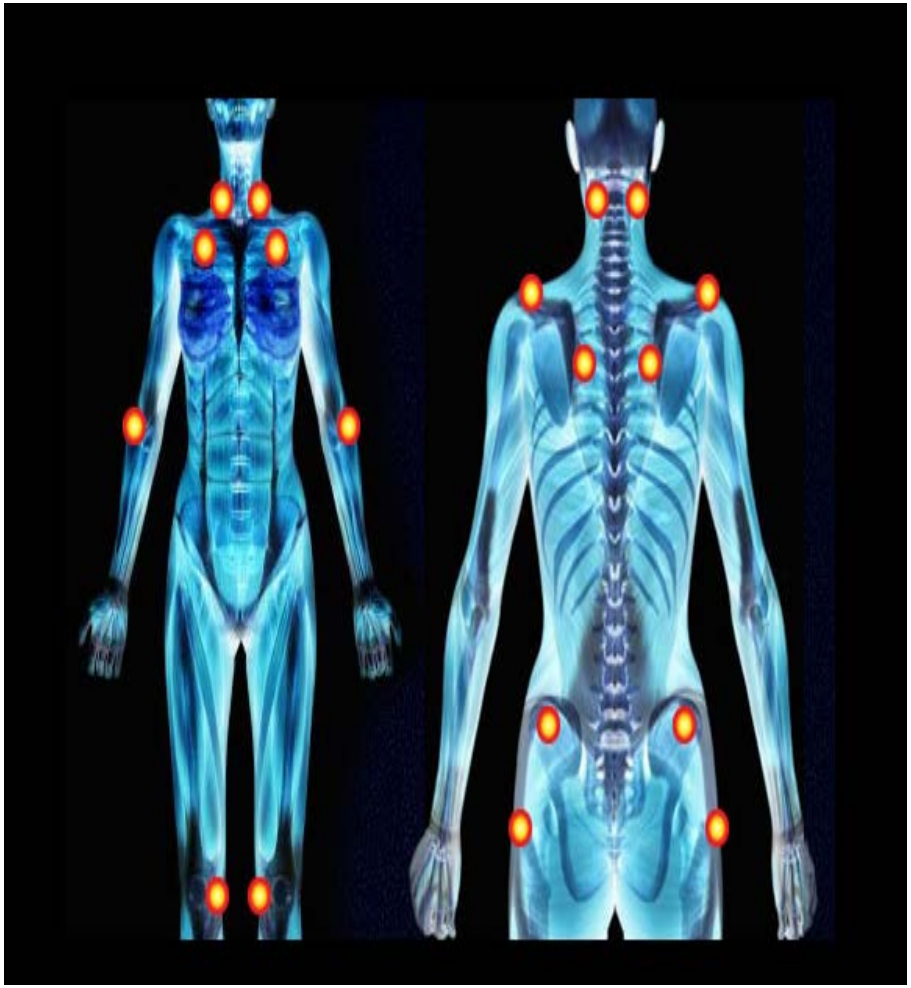
- ✓ Any painful event can start this process
- ✓ Patients describe intense pain, "burning ", "hurts all over", "my skin is on fire"
- ✓ Narcotics do not help much. Often doses are escalated with no effect. **Narcotics hypersensitize to pain can make this pain worse.**
- ✓ Anticonvulsants (Lyrica), antidepressants, muscle relaxants, massage, acupuncture, psychotherapy, physical therapy, time.
- ✓ ***This is the most difficult kind of pain to treat*** ....
- ✓ ***Response to treatment occurs in days to weeks or longer, not minutes to hours as is the case with nociceptive pain.***

Neuropathic pain

- **Typically not very responsive to narcotics**
- May respond to distraction
- Burning
- Shooting pain
- Feels like I am walking on glass
- Hurts all over
- Skin is on fire. Lightest touch is painful (allodynia)
- May be associated with diffuse swelling of a limb or region of the body.
- May be associated with erythema.
- May have signs of autonomic dysfunction such as "postural orthostatic tachycardiac syndrome (POTS)"
  - Dizziness on standing
  - Sudden onset of overwhelming feeling of sleepiness, exhaustion

Myofascial pain syndrome

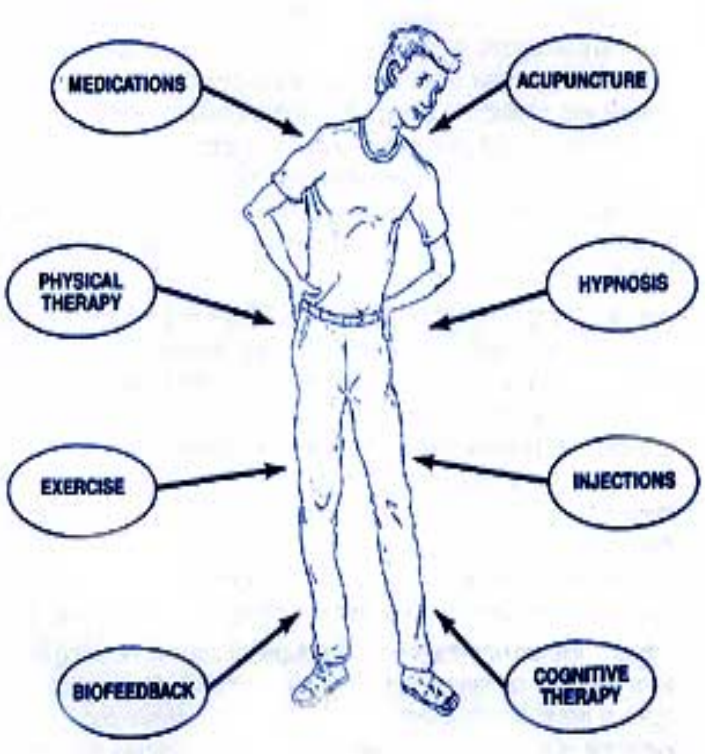
- Type of neuropathic pain
- Inflammatory foci develop in characteristic spots called “tender points”
- These can results in severe pain
- These points are often involved in patients with other neuropathic pain syndromes
- Probably 80% of all people will develops some type of myofascial pain at some point



Treatment of neuropathic pain

- Non-pharmacologic approaches
  - **Distraction** (Art, Music Rx)
  - Exercise
  - Acupuncture
  - Physical therapy
  - Massage
  - Hypnosis
- Counseling / treatment of depression, anxiety and stress
- Vocational rehabilitation
  - Get the patient back to work (school), don't wait for the pain to go first
  - Return to normal activity will make the pain go away
- Good sleep practices

Needs a multidisciplinary approach



The hospital is the worst place to be for treatment of neuropathic pain

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Drug treatment of neuropathic pain

- Anticonvulsants, in particular gabapentin (Neurontin) and pregabalin (Lyrica)
  - Increase dose to maximum over a couple of weeks
  - Should see effect within 6 to 8 weeks
- Tricyclic antidepressants and serotonin-noradrenalin reuptake inhibitors (Amitriptyline, nortriptyline, duloxetine (Cymbalta))
- Topical Lidocaine patches
- Opioids (second line Rx)
  - Methadone
  - Other opioids
  - Remember: **Opioids can induce pain sensitization. The goal should be to avoid them. The pain may improve with stopping these agents.**
- New agents

Even in the best of hands with full access to a multidisciplinary pain services, there is only a 40% success rate with getting rid of chronic neuropathic pain. It is a chronic disease that needs long term management.

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Pain management in SCD

- Patient with SCD and with chronic pain may not show the standard physiological responses to pain (hypertension, tachycardia etc)
- Pain is one of the most difficult things to manage because we have no way to asses the severity except by the patients words.
- Never tell a patient in pain you "can tell he is not in pain". This is about the most stupid mistake you can make. You have absolutely no way to tell for sure and telling a patient this will prove to the patient you don't know what you are doing.
- Listen to the patient and earn their trust.
- Use adequate doses of pain meds to rapidly control VOC pain.
- Make a correct pain diagnosis and find the cause of the pain. These are complex patients with many simultaneous pathologies. Learn to recognize and treat neuropathic pain.
- **Teach your families from an early age that there is a secondary type of pain "nerve pain" that is made worse by narcotics and encourage non-pharmacologic approaches to pain management.**

Recap of the important stuff:

Cold, stress, anxiety and pain itself can trigger crisis.

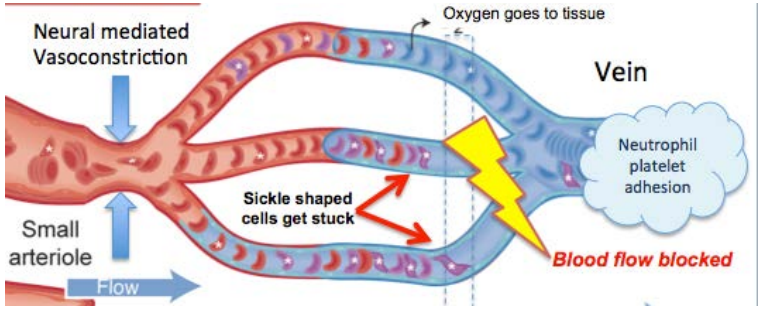
Anxiety, stress, lack of sleep make any kind of pain much worse.

It is very important to get control of severe "crisis" pain with adequate doses of pain medications quickly (***but***)

Narcotics make you more likely to get neuropathic pain and make neuropathic pain worse.

SCD patients can have both kinds of pain at the same time

Patients and medical providers need to know the difference between pain from tissue damage (VOC) and neuropathic pain. They also need to know the differences in management strategy.



Team Effort

- Matthew Borzage*
- Adam Bush*
- Thomas Coates
- Sang Chalacheva*
- So Young Choi*
- Julie Colognier*
- Jon Detterich
- Eamon Doyle*
- Christopher Denton*
- Subhadra Evans
- Mammen Puliyel*
- Henry J. Forman
- Roberta Kato
- Maha Khaleel*
- Michael Khoo
- Honglei Liu
- Brandon Lung
- Herbert Meiselman
- Natali Ornelas
- Anne Nord
- Sharon O'Neil
- Ajay Perumbeti
- Laura Seidman
- Nathan Smith
- Payal Shah
- Richard Sposto
- John Sunwoo*
- Jennie Tsao
- Sarah Martin
- Wanwara Thuptimdang*
- Rosalinda Wenby
- Saranya Veleswamy*
- John Wood
- Ana Ratiu
- Lonnie Zelter

NIH National Heart, Lung, and Blood Institute

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Quaerite Veritatem:

Seek the Truth

(And stay as far away as possible from those who think they have found it …)

Thank you for your attention

Children's Hospital LOS ANGELES
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USC UNIVERSITY OF SOUTHERN CALIFORNIA

Executive Summary

- All SCD pathology is explained by the relation between delay time (give HU to increase delay time) to polymerization and rate of microvascular flow (hydrate, keep warm, anti inflammatory, anti adhesive, anti-stress to increase flow).
- Fear, anxiety, pain cause significant vasoconstriction and probably promote Vaso-occlusion. They also markedly increase perception / severity of any type of pain.
- **Recognition of neuropathic pain is critical. It does not respond well to narcotics. Narcotics hypersensitize patients to pain and make neuropathic pain worse.**
- All patients with SS and S-β^0thal should be on maximal doses of HU starting at 9 mo of age regardless of crisis frequency. L-Glutamine in addition may be helpful.
- All patients with SS and S-β^0thal with HLA matched sibs or >10/10 MUD matches should be encouraged consider BMT