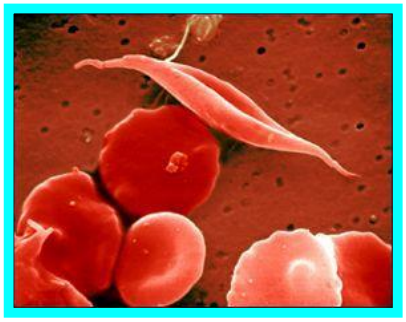

Neuropathic Pain and treatment in SCD

(Is SCD really a neurological disorder that involves red blood cells ?)

September 6, 2019

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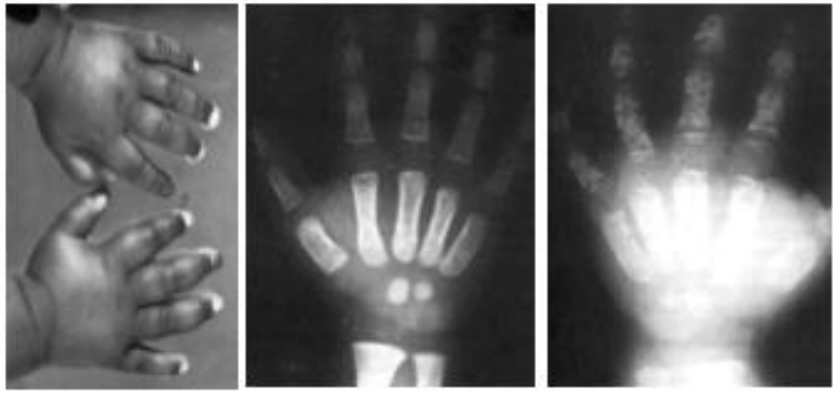
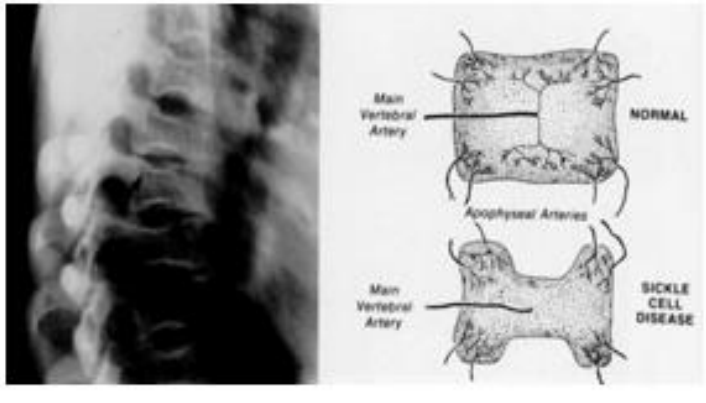
Disclosures

- No relevant disclosures

SCD: Clinical manifestations

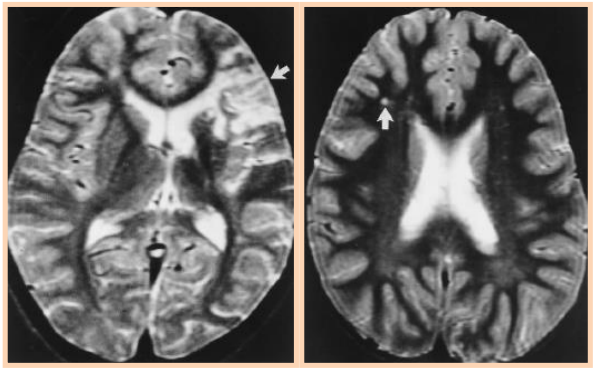


Severe painful damage to bones

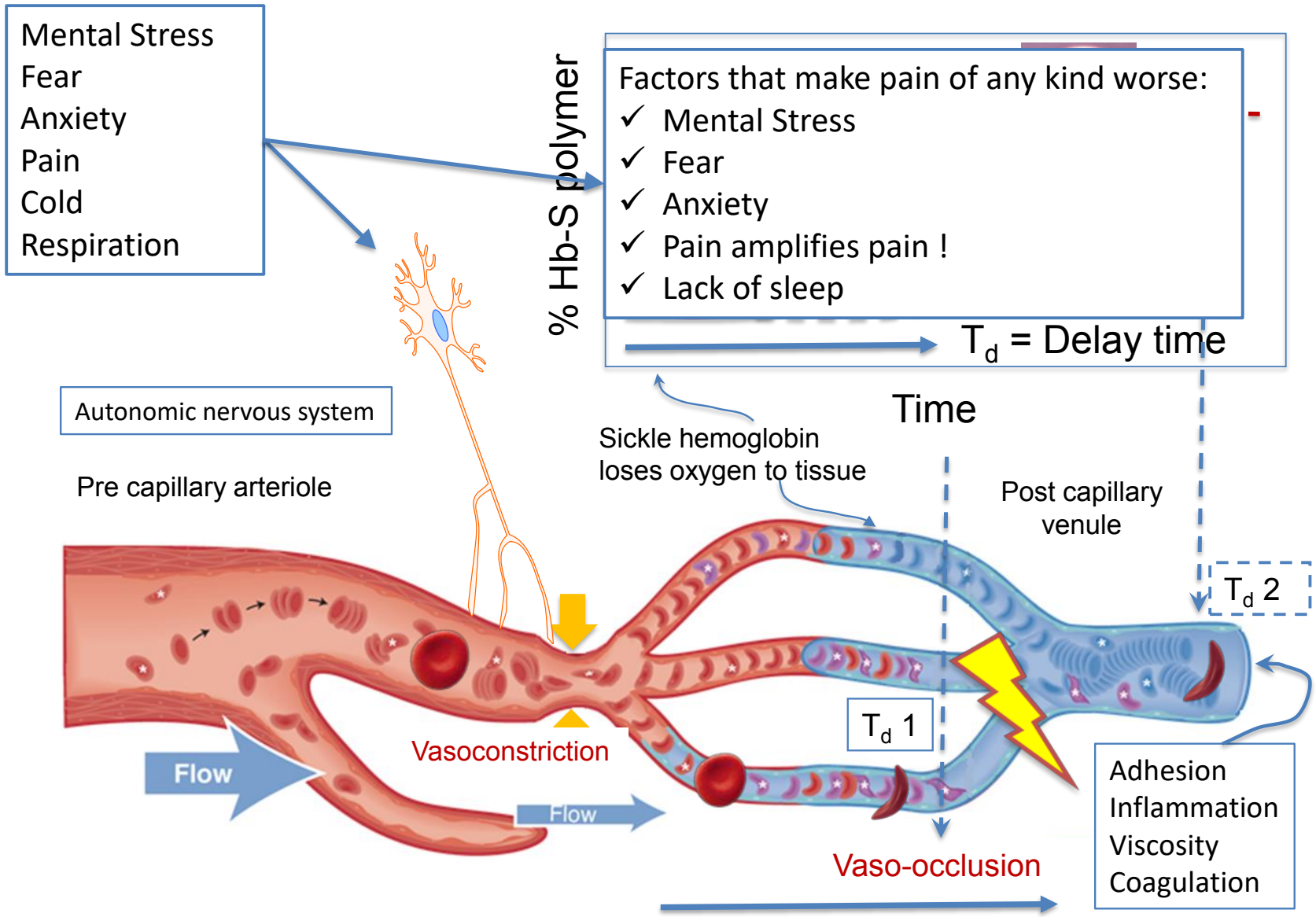


SCD individuals are set up for neuropathic pain

- ✓ **38% have a small strokes by age 8**
- ✓ **50% have blood vessel disease in their brain by age 14**
- ✓ **Crisis pain is like pain from bone fracture**
- ✓ **Adults have pain 50% of days**
- ✓ **30% of adults have pain 95% of days**



Big and small strokes start in childhood and cause brain damage

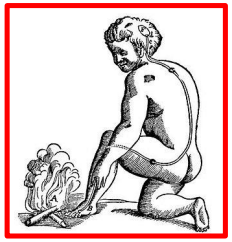

Mental Stress
Fear
Anxiety
Pain
Cold
Respiration
% Hb-S polymer
Factors that make pain of any kind worse:
✓ Mental Stress
✓ Fear
✓ Anxiety
✓ Pain amplifies pain !
✓ Lack of sleep
T_d = Delay time
Time
Autonomic nervous system
Pre capillary arteriole
Sickle hemoglobin loses oxygen to tissue
Post capillary venule
T_d 2
T_d 1
Vasoconstriction
Flow
Flow
Vaso-occlusion
Adhesion
Inflammation
Viscosity
Coagulation

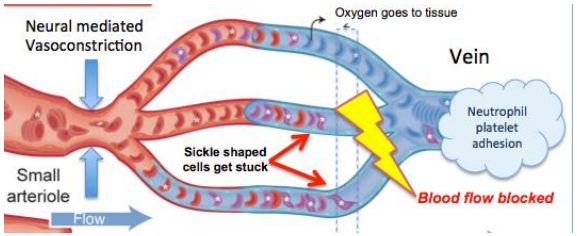
Pain is the hallmark of sickle vasoocclusive crisis

Sickling happens continually. What causes the exacerbations or “crises” ?

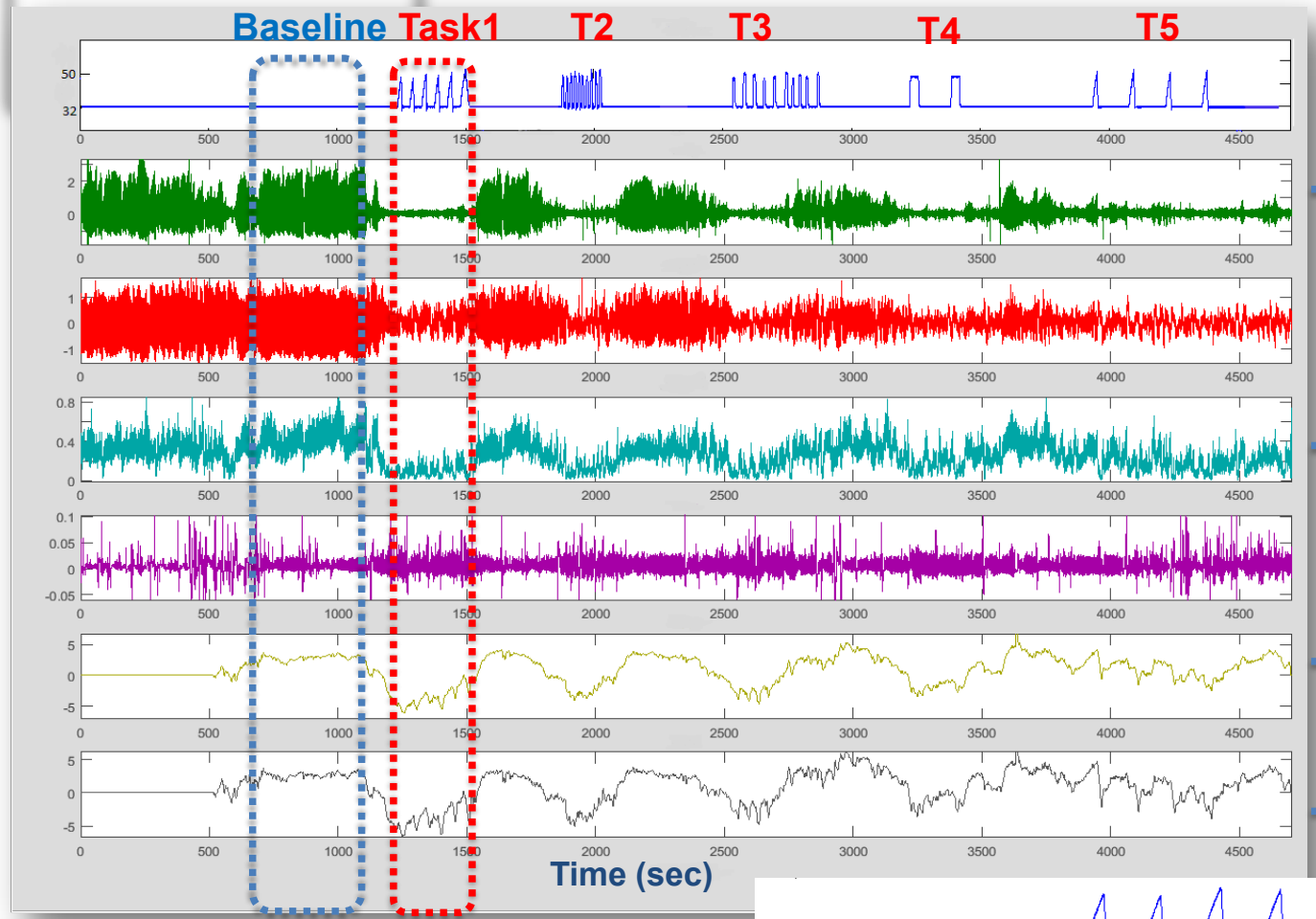
We know sickle-RBCs block blood flow, but we actually do not know exactly why this becomes painful.

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





Pain causes global decrease in peripheral blood flow

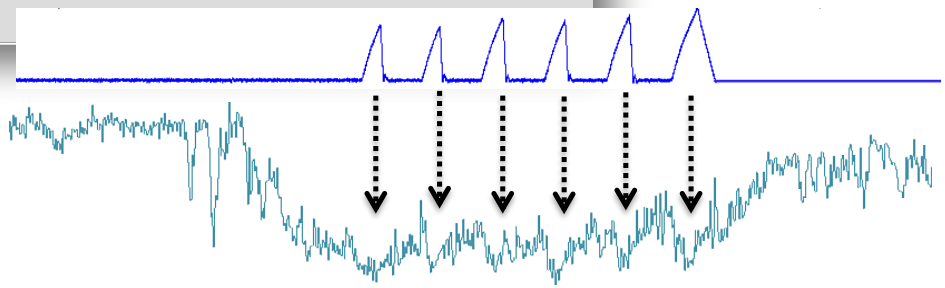


Pain Signal

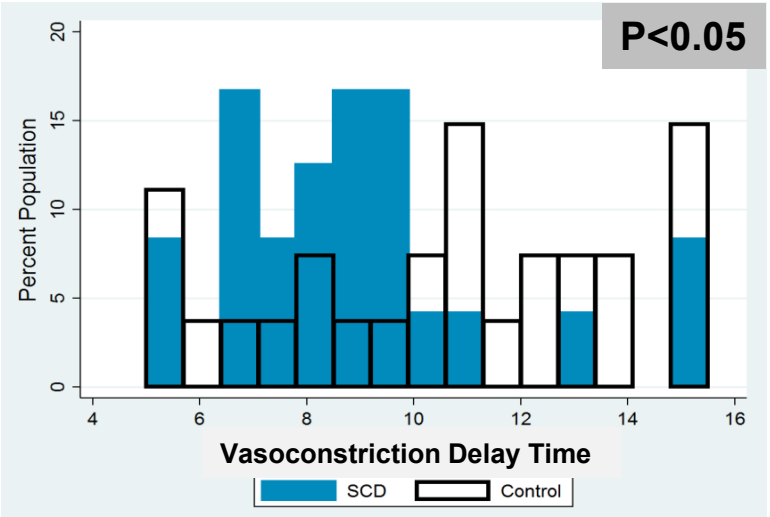
Peripheral Blood Flow (Contralateral hand)

Respiration

Prefrontal cortex oxygen content and forehead blood flow



SCD patients have faster and greater response to pain than non-SCD subjects



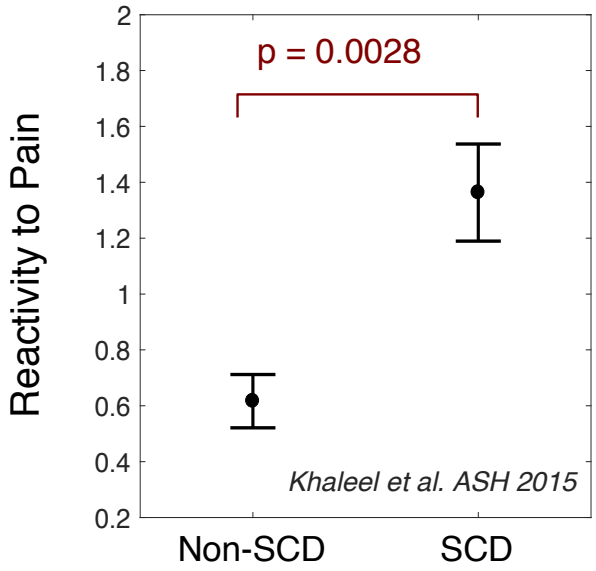
SCD subjects vaso constricted faster in response to pain.

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

Maha Khaleel

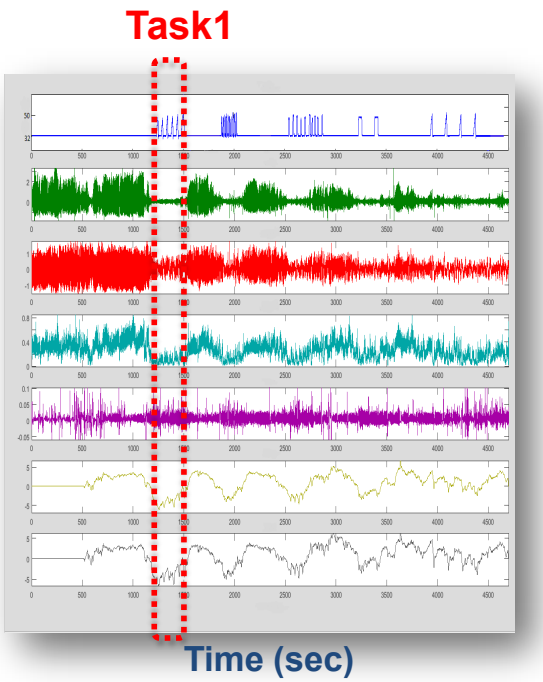
Payal Shah

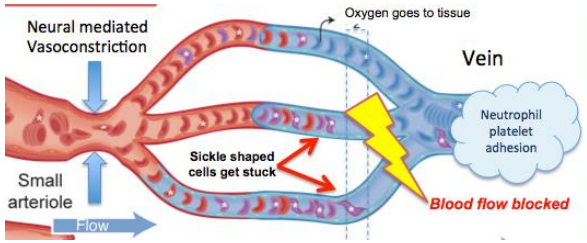
M Puliyel

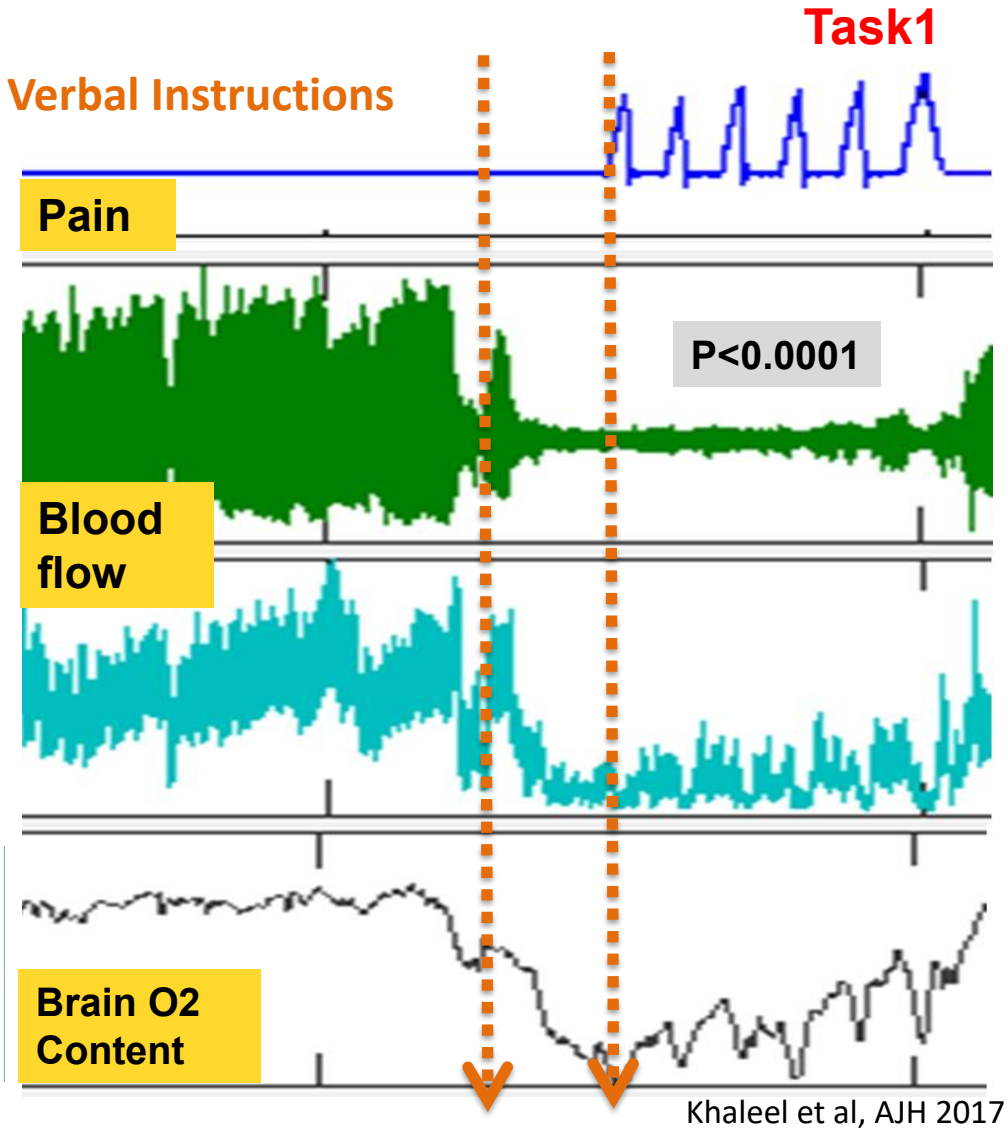


Khaleel et al, AJH 2017

Pain Anticipation causes Vasoconstriction





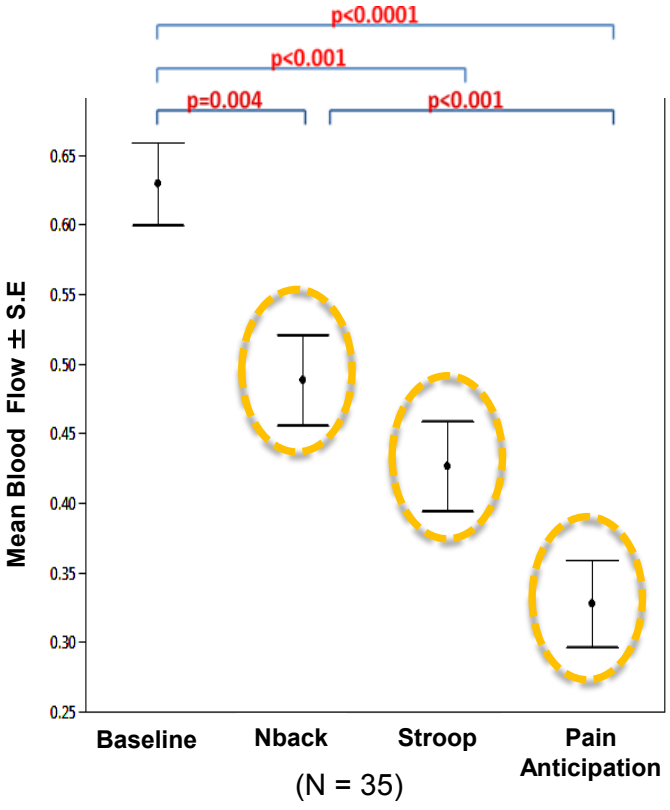


Khaleel et al, AJH 2017

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

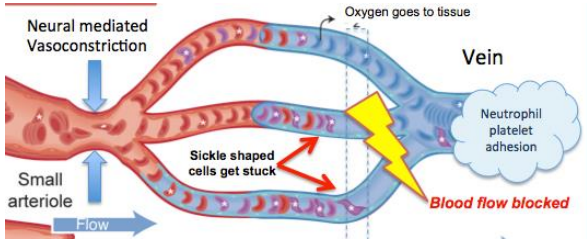
Mental Stress and Pain Anticipation cause Significant Vasoconstriction Response

Significant decrease in blood flow during each mental task



(N = 35)

Maha Khaleel Payal Shah Saranya Veluswamy



Shah et al, Haematologica 2019

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

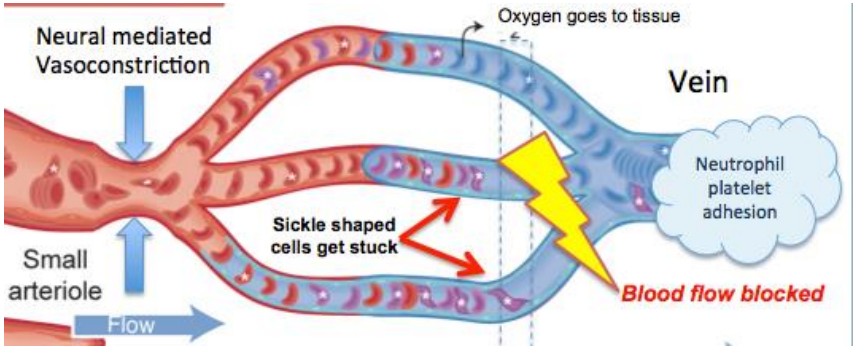
Hypnosis increases peripheral blood flow responsivity in SCD patients

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

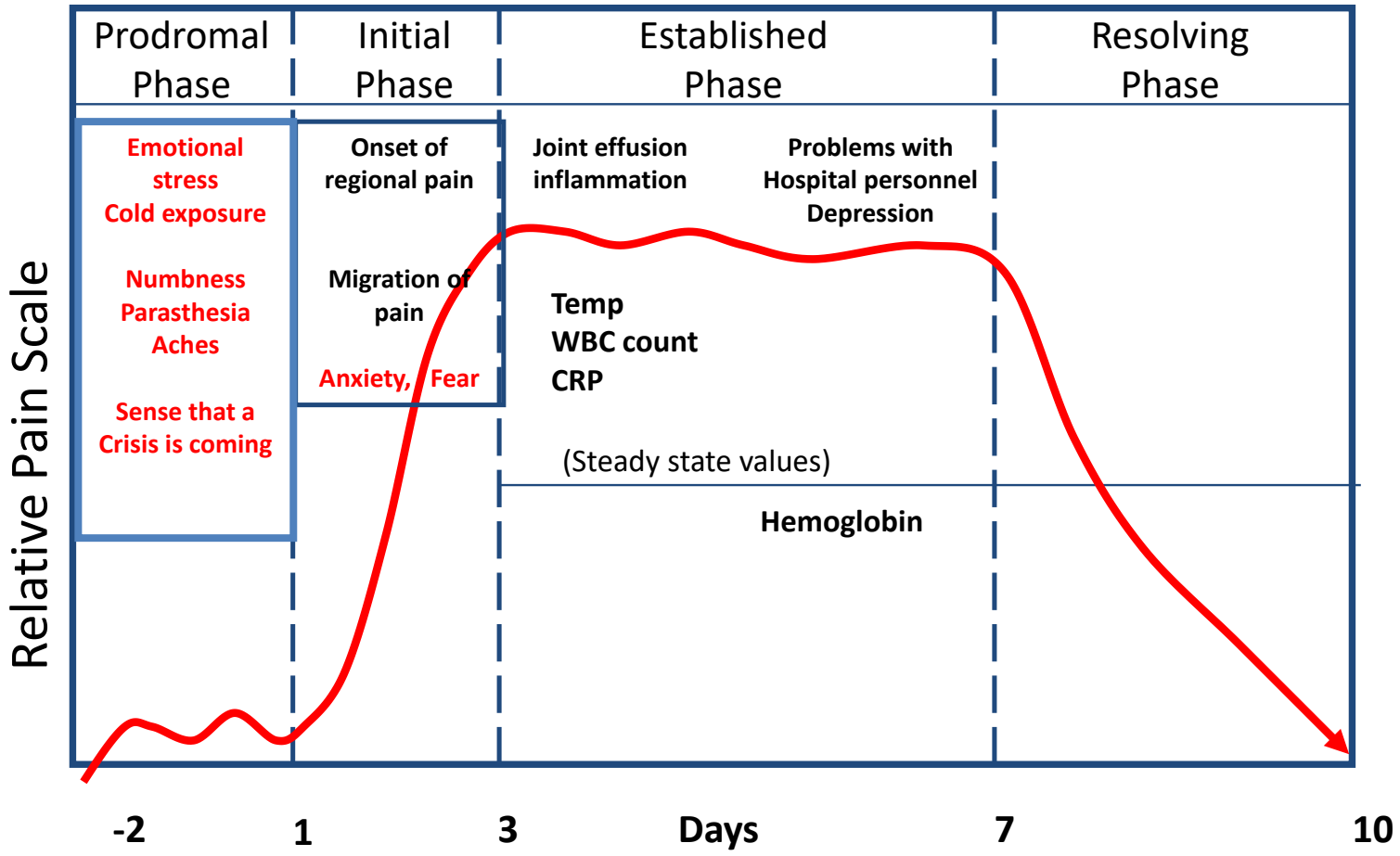
SCD patients have significantly increased nervous system reactivity compared to non-SCD individuals

Anxiety, emotions, and pain are biochemical and physiological responses that decrease peripheral blood flow and increase perception of pain.

Pain management is extraordinarily complex in SCD

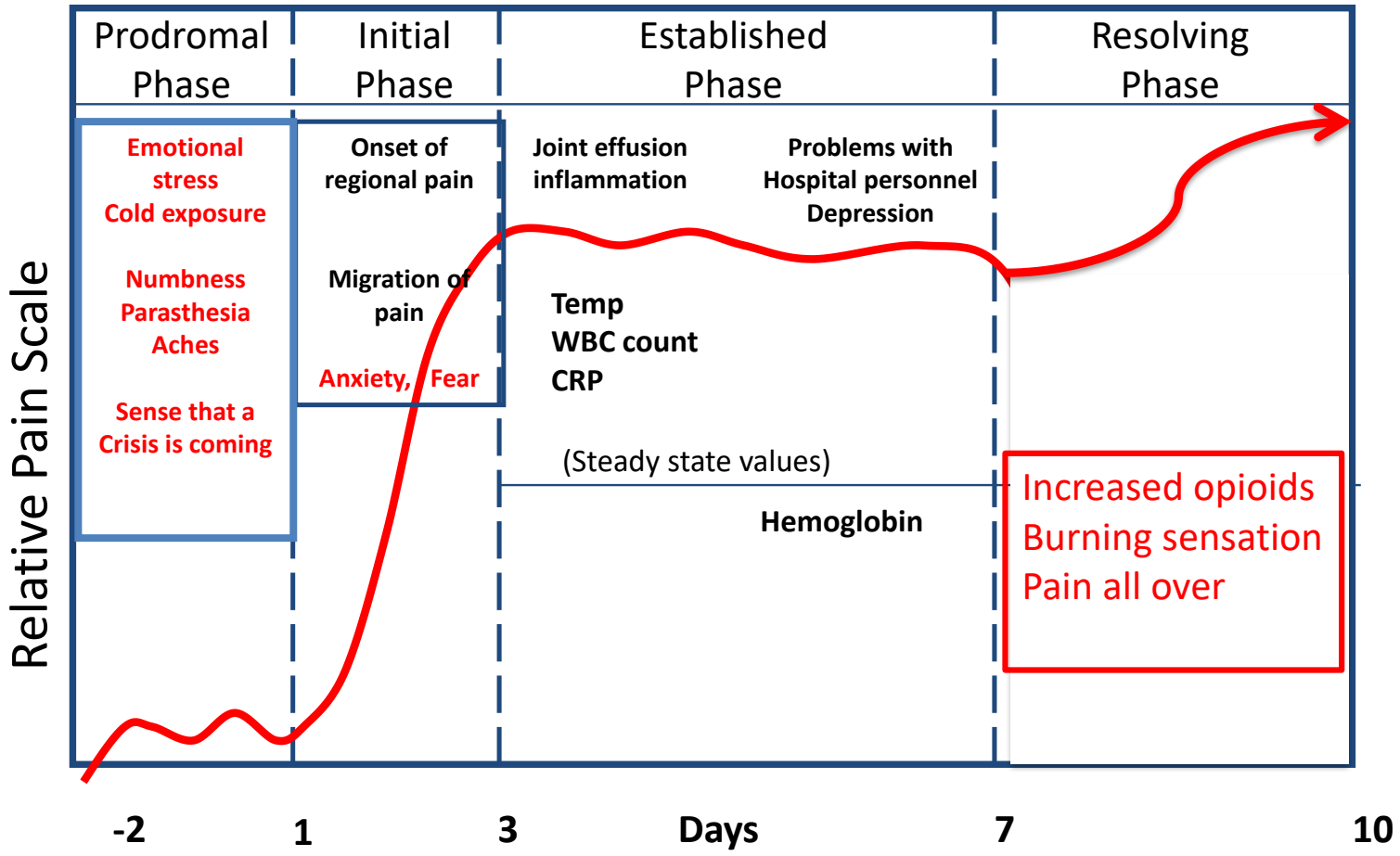


Course of Pain Crisis



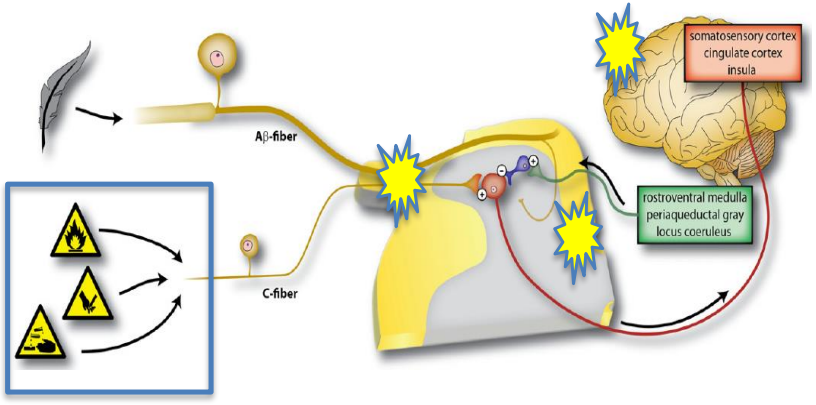
After Ballas 1995

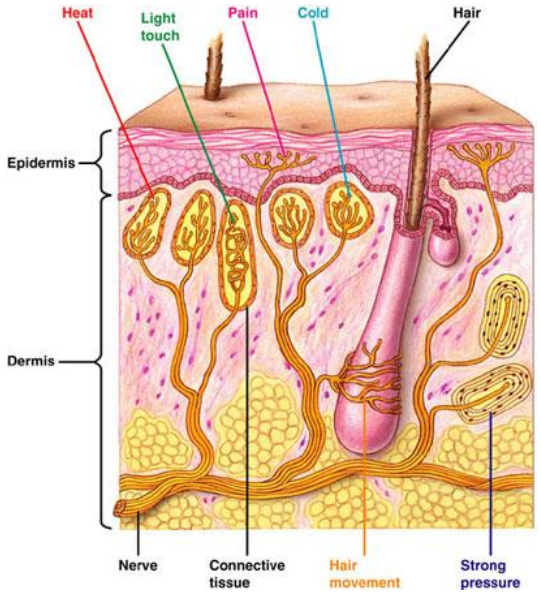
Pain Crisis evolution to neuropathic pain



After Ballas 1995

Pain is complex





Types of pain

- ✓ Nociceptive: normal response to tissue damage
- ✓ Neuropathic: pain signal amplified in cord or brain or nerves fire in absence of noxious stimulus

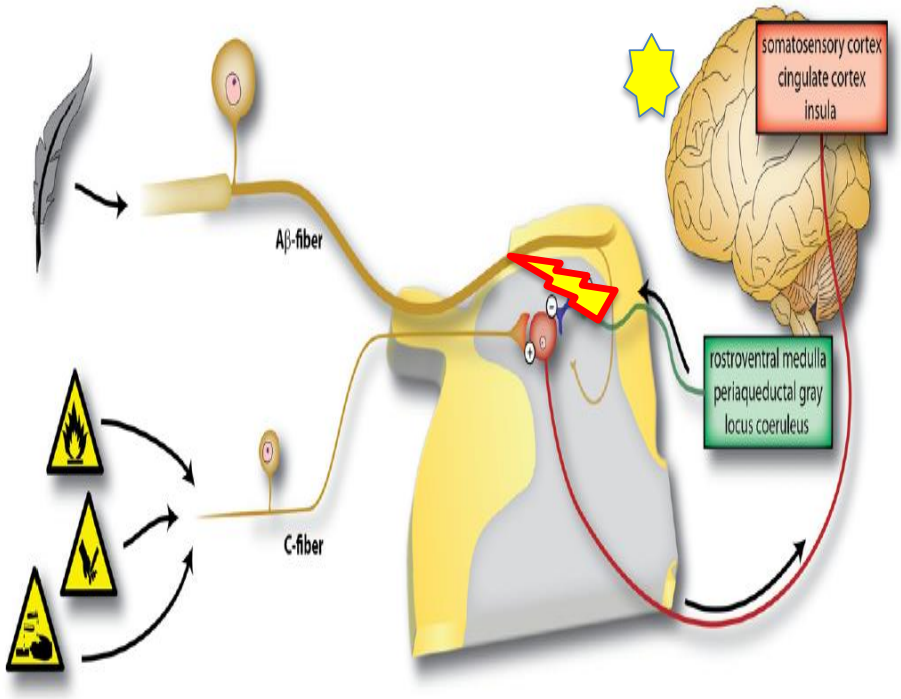
Pain perception is modulated by

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

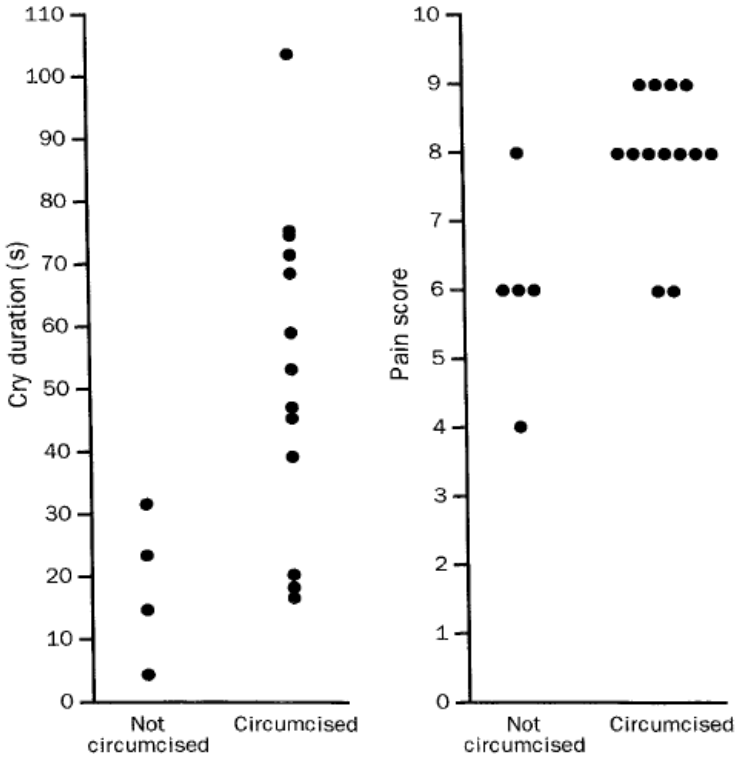
Von Hehn, Neuron 2012 73: Feb 23

Neuropathic pain Syndromes

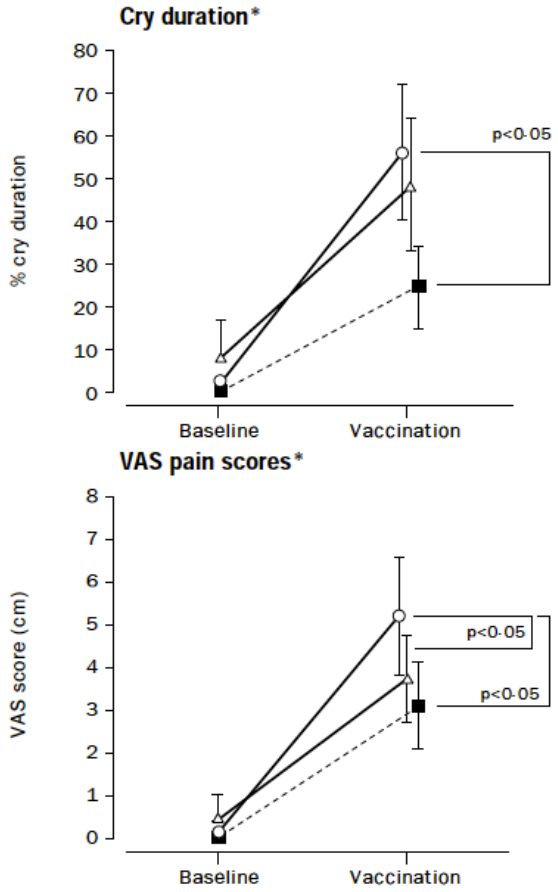
- ✓ Chronic pain damages neurons and they start firing by themselves with no noxious stimulus
- ✓ Low intensity stimuli then cause perception of intense pain (allodynia).
- ✓ Results from hypersensitization to pain.
- ✓ This is an organic, not psychiatric process. This pain is very real and very severe.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



Future effects of pain exposure



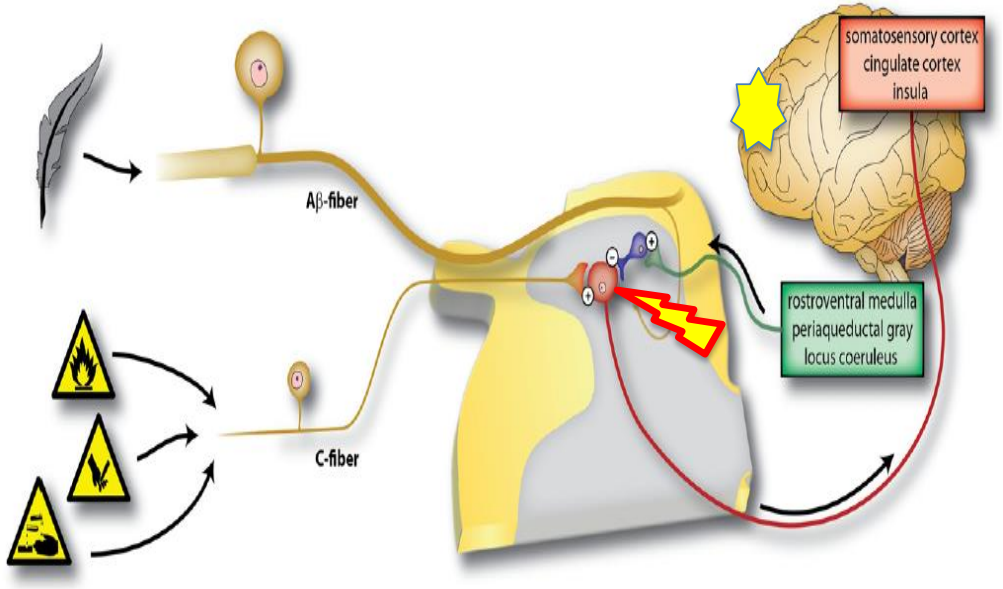
Taddio, A et al, Lancet 1994; 344:291



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

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.



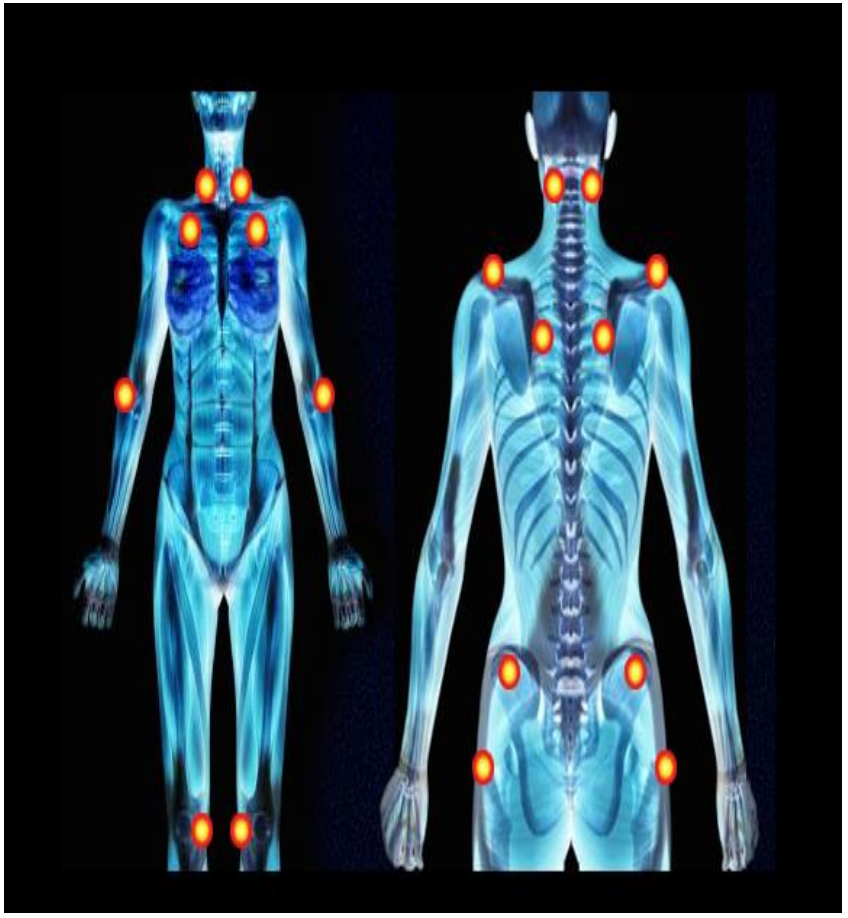
- ✓ Any painful event can start this process
- ✓ Patients describe intense pain, “burning ”, “hurts all over”, “my skin is on fire”
- ✓ Narcotics do not help much. Often doses are escalated with no effect**. High dose narcotics cause emotional lability and can even make pain worse.**
- ✓ Anticonvulsants (Lyrica), antidepressants, muscle relaxants, massage, acupuncture, psychotherapy, physical therapy, time.
- ✓ This is the most difficult kind of pain to treat ....

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 redness of the painful region.
- May have signs of autonomic dysfunction such as “postural orthostatic tachycardiac syndrome (POTS)”
  - Tachycardia on standing
  - Sudden onset of overwhelming feeling of sleepiness, exhaustion

Myofascial pain syndrome

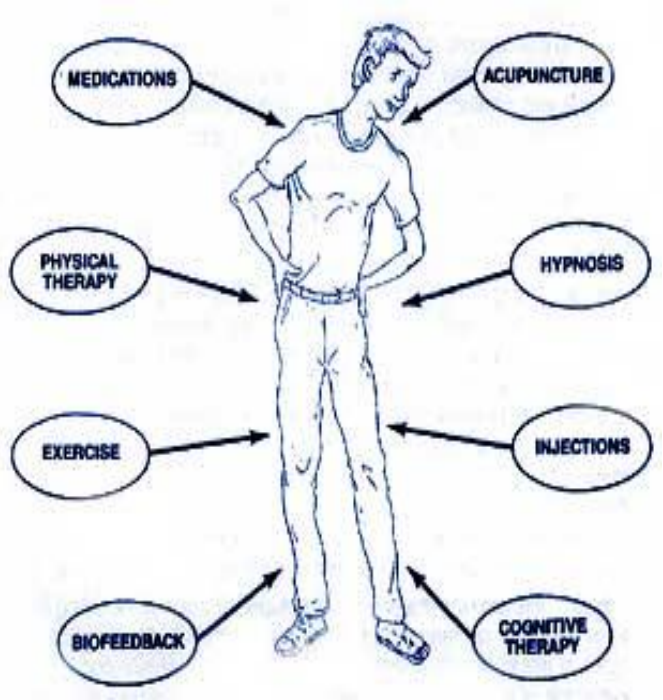
- Type of neuropathic pain
- Inflammatory foci develop in characteristic spots called “tender points”
- These can results in severe pain
- These points are often involved in patients with other neuropathic pain syndromes
- Probably 80% of all people will develops some type of myofascial pain at some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



Treatment of neuropathic pain

- Non-pharmacologic approaches
  - Distraction (Art, Music Rx)
  - Exercise
  - Acupuncture
  - Physical therapy
  - Massage
  - Hypnosis
  - **Stay out of the hospital !!!**
- 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



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.**

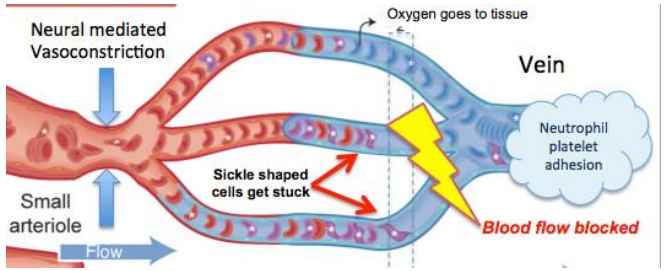
Even in the best of hands with full access to a multidisciplinary pain services, there is only a 40% success rate with getting rid of chronic neuropathic pain. It is a chronic disease that needs long term management.

Pain management in SCD

- It is extremely difficult to tell sickle VOC pain from worsening of chronic neuropathic pain. In fact, they both often happen at the same time. Pain and anxiety cause vasoconstriction which promotes VOC. The hospital is a terrible place to try to treat neuropathic pain.
- Use sufficient pain meds including narcotics at the onset of severe VOC to control pain quickly and hopefully prevent development of neuropathic pain.
- Neuropathic pain responds to drug treatment over days to weeks, not in minutes like pure VOC pain.
- Listen to the patient and earn their trust. If you think the problem is primarily neuropathic pain, part of the treatment is to reduce their narcotics because of neuropathic pain and you wont have a prayer of doing this if the patient doesn't trust you.
- Make a correct pain diagnosis and find the cause of the pain. These are complex patients with many simultaneous pathologies.

In Summary

- Management of pain in SCD is extremely complex and requires a collaboration between the patient and medical professional.
- Fear, anxiety, cold temperature and pain itself cause significant vasoconstriction and promote vasoocclusion. 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. We need to start teaching SCD patients this at a young age.**
- 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.



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