PAIN

OVERVIEW

- NOCICEPTORS
  - DETECTION & PERCEPTION NOXIOUS
  - NOC SENSN
  - Aα FNE SUN VISC
  - FAST Aδ III
  - SLOW C IV
  - FIBERS
  - ACTIVATION
    - MBDp TEMP
    - MEC
    - CHEM
    - 30 KPa
  - SENSITIZATION
    - PERIPHERAL
    - ↓ACTIVATION THRESHOLD
    - iFM
    - ↓ALGESIA ALLODYNIA
    - NS
    - "SILENT" NOCICEPTORS
    - NT
    - WDR ns
    - WIND-UP
  - Gu SP CGRP
  - TRPV1 R CAPSAICIN
  - MELOR OPIOID
  - MENTHOL TRPM8 R
  - TRP

PROCESSING IN SPINAL CORD
- PROTEIN F
- SYNAPTIC TARGETS
  - WIND-UP
  - SUB P & CGRP
  - ↑EXCITAN
  - SENSITIZATION

ASCENDING NOCICEPTIVE PATHWAYS
- THALAMUS
  - SPINO-T Tr
  - ALS
  - TEMP. PAIN. LIGHT TOUCH
- LATERAL SENSORY-DISCRIMINATIVE
  - MED S T Tr
  - Aδ
  - "1st" PAIN
  - C
  - SOMATO SENS CORTEX
  - SOMATO SENS 1 & 2
  - DEMANDS PAIN LOC
- MEDIAL AFFECTIVE-MOTIVATIONAL
  - RF
  - VLID B
  - HT
  - LIMBIC
  - "2nd" PAIN
  - PALEO SPINO-T Tr
  - SPINO RET Tr
  - SPINO MES Tr
  - PAG
  - SC
  - NUC T
  - NA⁺ Ec cen
  - 5HT Tc NAChe
  - OPIOID R
  - NORMAL α MMAD
  - INMAT CAM
  - SM
  - SOMATO SENS CEN
  - NEURONS
  - VISC
  - OTHER

MODULATION
- ENDOGENOUS OPIOID
  - DESC INFLUENCES
  - ING INFLUENCES FROM BS
  - GN INPUT
  - R
  - PAG
  - LC
  - RF
  - CAPH
  - NOC
  - MATRIX M
  - ↓BS
  - H
  - alternatve ... abnormality
- GATE CTRL THEORY
  - INHIBN
  - FACILITAN
  - DESCING
  - INHIBITORY
  - LOC CIRC INTERN
- **CORTICAL PAIN MATRIX**
  - SALIENCY
  - WITH DISTRAX REF
  - SALIENT SENSORY INPUT
  - MEDIAL
  - LATERAL
  - Amy G
  - INSULA
  - ACC
  - HT
  - 10 & 20 SOMATO SENS CEN

CHRONIC
- ALGODYNIA
  - HYPERALGESIA
  - NEUROPATHIC
  - MALADAPTIVE PAIN
  - SENSITIZATION
  - DISINHN ↓ALL
  - ALLOD
  - CENTRAL
  - HP PNN
  - ENK CIRC
  - PAG
  - α M MAD
  - NO
  - DEC INH n
  - ME
- NOCICEPTIVE SIGNALING
  - ASTROGLIA
  - MICROGLIA
  - GLIAL SIGNALING

REFERRED PAIN

NOCICEPTOR (4)

PRINCIPLES OF PAIN

ALLODYNIA
HYPERALGESIA
ACTIVATION THRESHOLD
SILENT NOCICEPTOR
NEW IT VEHICLE EXPAND NOCICEPTIVE FIELD

PERIPHERAL R
SENSITIZATION
BODY CONTINUITY

PG
BDK
NT
STIMULATES NOCIC
SUP DURING INJURY & IFM
EX MEMBRANE STIMULA NOCIC & CAN

NOXIOUS
ACTIVATION
iFM   LMFM
INTENSE MEC SS
MB DP
Ca+ OPENING
"SILENT" NOCICEPTION

TEMP
THERMAL
TMP M8   Menthol
TRP
familiar trigeminal
TRP V1R
CAPSAICIN

CONTINUED FIRING CAN
NOCICEPTION
THRESHOLD AS PROGRESSIVELY ↑ CODING INTENSITY
ADAPTAN A *
II * SENSITIZATION

SG
THm G
PAIN DETECTED (LBUOIT)
FnE

Aδ MYELINATED
C UNMYELINATED

SHARP WELL LOCALIZED
1st PAIN
DULL POORLY
2nd PAIN
THROBBING BURNING SENSATION
LOCO

Glu
SP
CGRP

IT THRON SC
CROSS MIDLINE   ALS

SG   NUG
in dRGoniS

GM   in dRGoniS

SP   CORP

NT   NOCir

2nd oRDeR
SC
CY   BS

PY AT SITE INJ ★ → REDNESS
SWELLING
TENDERNESS

ALSO → TO NOCIC → REDNESS
THEIR @ THRESHOLD = SENSITZ'N

ADDN

(↓) "SILENT'INOCIC" ⇒ EXPAND RFIELDS OF PAINFULS

THRESHOLD 43°C • SOME
• SOME SUBTYP
BODY
A δ & C
R FOR CAPSAICIN

Q BODIES IN SG

MALIGN
POTENTIAL

TRPV1

HEAT
TEMP ①

COLD TRPM8
< 25°C

A5 or C

SHARP
"1ST"
localiZed

NOCI AND VG
K+ CHAN
POLYMODAL

MEC
PINCHING

A δ & C
LIGHT TOUCH
HIGH THRESHOLD
∼ DAM

BERMAN

MENTHOL

SC

Ⓗ

DIFFUSE
"2 NOII"

POORLY
LOCED   Ⓒ

FINE C
POTENTIAL
OR ITS DAMAGE

CHEM

EITHER BY NOCIcEPTOY
OR THROUGH iFM

Ⓑ NOC Ⓒ

TRP CHAN
PHYSIO PROPTIES
∼ VOLT GATED
CHAN

NOT VGE

NOT

Sensitizan PR

THEY ONLY SIGNAL IN RES TO NOCIC

SENSED BY OTH ⊙ NOCIC) NOT (2.0 BY ANY NOX ↗ PER SE

**

Silent NOCIC

TEMP SUMMAN SPAT

AMPLIFY

TJM

NT IGM MOUR
- ALSO
RECRUIT
RECRNZ) JUECHINE TENDONNES)

: ALL THESE PROTECTIVE

⊙ THRESHOLD NOCIC

=> WZ BE GRAVARD BY FS THAT WOULD NORMALLY NOT BE PERCEIVED AS PAINFUL
SUNBURN

↗ ACTIVITY SKIN NOCIC
& ↓ SPECIFICITY

↗ SENSITIVITY
AXON)
CAN CAUX SPONT DISHANGES

NOW PAINFUL
↓ PANFUL
HYPERALGESIA
ALLODYNIA

PROCESSING IN SPINAL CORD

SYNAPTIC TARGETS — PROJECT → INTO SC
- NS
- WDR
- NT
- WDR NS — "WIWOUP"

SENSITIZAN

↑ EXUTAN

CORD SP & CGRP
- CGRP
- SP

WIND-UP → IN SC
- "CENTRAL SENSITIZAN"

MAINGNDS @ NMETHYLD-ALANINE (ONE OK THE) +CDR
PROCET)

HAS # # of DOWN SMANY THAT LOWER ≥ @ THRESHOLD OF POSITION

⇐ GNTINUED @ TIHMS

PROJECTION OF FIBERS INTO SC

(A) SYN TARGETS

EXCITATORY SYNAPSE IN TH
(1) NTs ⊕

A β c
A δ c
A β c
A δ

enCOdE ONLY for painful S>

POLYN ON 2 LAYERS

DISC TOUCH
PROPRIOC
VIBRAN

NON NOXIOUS STIMULI

ATB
Aδ
C

SG

NOXIOUS STIMULI

INTRICTHERMAL MEC CHEC

PAIN PROCESSING IN SPINAL TRIGEMINAL NUCLEUS

POLYN y

Posterior HORN

POSTERIOR HORN NON NOXIOUS

PAINFUL

② WDR

FIRING PATTERN (NOCN DEPEND) ON ↑ INTENSITY WHICH IS ENCODED BY FREQ C F SIGNALING

CAN AMPLIFY ← THIS SIGNAL THROUGH MECHANISM "WIND UP"

NOC Aδ F C TERMINAL

CGRP

Glu

SP

R TH M

(@ THR R || ⊕ NO ↓ DP & GEN AP)

NMDAR Mg(2+)

AMPA-R

NK1 neurokinin

(N OCICEPTIVE SPECIFIC)
(WDR) Ms

α-AMINO-3-HYDROXY-5-METHYL-4-ISOXAZOLE PROPIONIC ACID

N-METHYL-D-ASPARTIC ACID

Scanné avec CamScanner

Top left (green):
PRIORITY SALIENCE ∴ ON ITS WAY TO G CORTEX

SHORT TERM → (CHRONIC → SPINAL) = OTH TRAUMA = MIGRAINE COMPONENT

SHORT TERM ↑ LT POTENTIATION

YAN WIT

(E) SENSITIZAN

REPETITIVE ACTIVITY

WIND UP WITHIN SERIES

(D) ↗ EXCITAN TO G CORTEX → ⊕ SIGNAL IN SC

(①) INHIBITE PAIN SIGNAL

REPETITIVE EXC ↗
↓
WDR MS THROUGH

NOC ↑ K G TERMINAL

CERBM

(C)

Center:
CGRP

GLU

SP

Right side (blue/black):
⊕ IDENTITY AMPLIFICAN WITHIN SC TO RES TO CUMULATIVE NOC INPUT FROM C

(B) PRINC

★ C SENSITIZAN = "WIND UP"

THM

CGRP R

DOWNSTREAM ENHANCEMENT NMDAR ACTIVITY

(②) SUSTAINED DPN

NMDAR

MAINLY

AMPAN ↑ THEN

mGLU-R

Ca 2+

RELEASE OF Mg²⁺ BLOCK ⟹ NMDA ©

ELECTRO PHYSIO STUMANE PROPERTIES OF WDR

(③) ↗ IC Ca²⁺ ⟹ ↘ C ⊕ (CHAN KINETIC)

MORE Na⊕ CHAN & BLOCKADE K⊕ CHAN

↑ t°SUM LONGING LASTING DPN

NK1

Na⊕

K⊕

(④)
|||||
WIND UP
⟹
AMPLIFICAN ✱ OF PAIN

Bottom center:
COMBIN ↗↗ ↑ TH ACTIVITY & AMT INVOLVED IN PAIN PROCESSING

Bottom right (green):
↘ THRESHOLD ↘ C ⊕ CHAN KINETIC) & IN SENSION

AMPLIFICAN OF PAIN SIGNAL

MORE R ⟹ ↗ SENSITIVITY

REFERRED PAIN

LIMBIC

IN FLUENCE NEUROENDOC & VISC RES → SOMATIC, H CONTROL & E & LO VISCNS

HT

DIR & Ncc T

IN FLUENCE MODULATION/WDIR

ROSTRAL QM MODULATION OPIOID R

S-RET T₂

S-MES T₂

STEM

PMED S-T T₂

V SPINAL UCAM
V SPINAL UCAM

④

NEURONAXL
VISCERAL

S-T Tr
ALS

T

CONCEPTUAL OVERVIEW

VPL & VPM

A J

& WC

NEOS-T Tr

SOMATOSENSORY CORTEX GYRIES

"1ST" PAIN

1° & 2°

5HT NAPHE

NA LC

SC

PAG

MEDIAL

AFFECTIVE-MOTIVATIONAL

"2ND" PAIN

LIMBIC

HT

RF

MIDB

T

ASCENDING NOCICEPTIVE PATHWAYS

LATERAL

SENSORY - DISCRIMINATIVE

- LOCALIZATION OF PAIN
- INTENSITY
- QUALITY

SHARP RAPID

2 COMPONENTS

CORTEX AS MOS LIMBIC

ACA
AMYC
& ASSOC A

CAN ALSO IN FLUENCE
WHEN ACTIVATES THROUGH PROJECTION FROM AMYG

HW ACTIVATED THROUGH PROJECTION FROM AMYG

BY LO NA MS

WHERE IT MODULATES AFFECTIVE-MOTIVATIONAL & EMOT RES TO PAIN

ALL OTHER TRACTS OF ALS

PAG

BS WHERE IT IN FLUENCES DESCENDING MODULATION OF PAIN

STM &

LIMBIC HT & ASSOC MEM CORTEX

Scanné avec CamScanner

LIMBIC ASSOC COs

1° SOM-SENS CO

SOMATOTOP

LATERAL Ⓐ

Ⓑ MEDIAL

VMODULAN PAIN

EMOT & VISC → PAIN INFLUENCE

"2nd" DULL THROBBING POOR LOC to EMOT

HT

DM INTRALAM   VPL
VPL Thal

T

NEO S-T Tr

INFLUENCE EYE-MVTS & DIRECT ATTN TO SIDE INJ

Ⓐ

③ PALEO

S-T Tr
DIR BACK

PAG & SC   VIP MOBY COLLICULI   MIDB

⟶ S-MES Tr

LIMBIC
CO   HT

VLDL   TH
NS MODULAN

① S-MES Tr EQUAT BS & BSC ᵉˢ

RF

② S-RET Tr

DESCENDING MODULATION

INTEGRATE @ Ⓒ THROUGH MODULATORY PAIN WAYS

SC

MAIN INPUT

Aδ or C ¢ BODY iN SG

Ⓐ NS & WDR

PAGⓒ

NONDISCRIM → PAIN ↓ DIVERT ↓ IN AFFECTIVE MODELING Ⓑ

↑↑ NOC = ALS NOC PAIN & TEMP

αδ   αC

MODULATE

INFLUENCE MOT ¢

NA LC
5HT RAPH
ROSTRAL αM MEDULLA

μ OPIOID R

DESCENDING   ASCENDING

① CORTICAL INPUT — T—GATES — BG i

PROJECT~ FROM G & LIMB

PROJ FROM HT

PAIN MATRIX

BS ② DEP ↑NOC INPUT BUT ALSO ↓G

● PAG

OPIOID ⊕ FACILITN PAIN TRANSM

⊖ MOSTLY INHY PAIN

↑F ● LC (NA)
● RAPH (5HT)

T ⊕ EXCITON IN TH
⊖ EXCITON IN TH

VARIOUS RF NUCLEI

VITK

NSAIDS   LIDOCAINE
BY Nu ⊖ CHAN
EV CAPSAICIN
TRPVI
AGO ↑↑SP
DEPLETO
SP
NS& VOR TRANSM THANM

⊖ NOCIC

SG

LONABOTULINUM A (BNX) TO RIA (BNX) MIGRAINE PAIN
BY TEMP
BOT TOX ↓ SPASTICITY

MS THEN EPLEM CVD

MOVNN MM VANCITY ↓ GMENTS POTWAN ↑

CONVERGENCE OF PAIN AK & ↓ MODULAN IN TTH

CGRP SNK PC

NOVEL ANTAGOS ↑F ⊖ CGRP OVER ⊕ MIGRAINE

TTH SC

OVERVIEW PAIN MODULATION PATHWAYS

CORTEX ⊕ CBT-REHAB THEN
MIND BODY THER
RELAXN COPING STRAT
ψ PROVOKING PAIN

BS ⊕ NOES TR
ANTIDEP ↑ 5HT NE LT SYN

OPIOID BY FACILITN TR TRANSM BY ⊖

AB → ALLODYNIA OPIOIDS

S-RET TR

BY PREESYN CO ⊕ CHAN BY ⊕ OPEN POTSSN K ⊕ CHAN
OPIOIDS GABAPENTIN α2δ JV ⊕ SYNAPTDN
METHADONE BY NMDAR NEUROP PAIN
OPIOID
KETAMINE WIND UP LOW DOSE
HIGH ANEST

ALS

REFERRED

- C3 C4 C5

- DERMATOMES
  Σ F

L & F

- ALSO
  ONE JOM TO ANOTHER

& GMUS

ΔD & DIAP

SI
OVARIES

APP

COLON

URIN
BLAD
URETER

(IV)

CORTICAL PAIN MATRIX

AMYG MTHC   BS (M)

CBC
BG
② VOL
AMYG → structure

WITHDRAWAL SC ← CO
AVOIDANCE BEHAV
COMMIT
BACKGROUND
SALIENT
SENSORY INPUT
& DYNAMIC
ON PAST
△ S
NOT NEC'Y SPEC TO NOC INPUT
RECENT EVIDENCE
SALIENCY

limb ASSOC
GOAL
LOC N
PROJECTIONS
G

MIRROR NEURON
SNS
NOT NEC'Y
SPEC PAIN
MAYBE (a os)
BY MANY OTHER FS
ANTICIPATION
PAIN
MEM PAIN
VIS NO CUES
SOM SEN)

SOME MS
EMPATHIZE PS TH

MEDIAL
LIMBIC
HT
AMYG
INSULA
ACC

PAIN SYSTEM

ACTIVATED IN RES TO PERCEPTION OF PAIN

LATERAL
1° & 2°
SOM SENS
CONTRA LES

BOTH NECESSARY

Scanné avec CamScanner

LATERAL SYSTEM

SOMATATOP LOCⁿ

1° SOM SENS
S1

4 2°

CONTRA GOTTA

THALAMUS

VPL
VPM

NEO S-T PATHW

DISCRIMINATIVE
LOCALIZAⁿ
PAIN
& INTENSITY

MEDIAL

INSULA

AMYG

HC

RELAY TO LIMB
VISCERMOT PAIN
MODING
LEARNING & MEMORY
ANT PROCESSING

VISC AFF
MODULATES

LD   DM

MOTOR GATI M   PAIN MATRIX

NEURON INGRANULATE
ACC CORTEX

HT

OBS N
SOMEONE?
BEING
SUBJECTED
PAIN

IMAGINED   ACTUAL

DIR
BEHAV

- AFFECTIVE-MOTIVATIONAL
  COMPONENT

- EMOT COMPONENT
  " SUFFERING "

PNN
HP
R

ENK R DESCENDING circ.m
INHIBITION
PAG
ROSTRAL
& M MEDULLA

ANOTHER

ENDOGENOUS
OPIOID SYSTEM

Endogenous Dynorphins
ENKEPHALIN
TTH SC
matrix
VBS

SENSITIZAV
BROADER SYSTEM
COMPETING
SYNERGY
DE-PRIORITIZED

$\ominus - BUSY!$
$\oplus$ ITH

$\oplus \rightleftarrows \ominus$
EMOT
IFM
SOMA

NM
DESCENDING INHIBITION
FACILITATION

SHIFT IN
BALANCE
OF
INPUT

NOC f
TOUCH f
± PAIN
TRANSMN

1st

LEVELS

LEVEL
SC

PAIN
MODULAT
GATE CONTROL THEORY
GRAINED

LOCAL circ in man

INHIBITORY

DESCENDING INFLUENCES
FROM
BS
RF
& PAG

ANALGESIC SYSTEM

NOCICEPTIVE
MODULATION
DESCENDING
CORTICAL INPUT

PAG
RF
LOC COER
RAPHE

SIGNALING
CONTEXT
DEPENDING
ON BEHAV NEEDS
OF SITUATION

$\ominus$ EXTREM
$\oplus$

SENSORY
FILTER

MODULATION
$\oplus$
$\ominus$

GATED

CORTEX

GATE
(A) CONTROL
THEORY

INPUT FROM Aβ
DAMPENS
NOC INPUT < Aβ
            C x
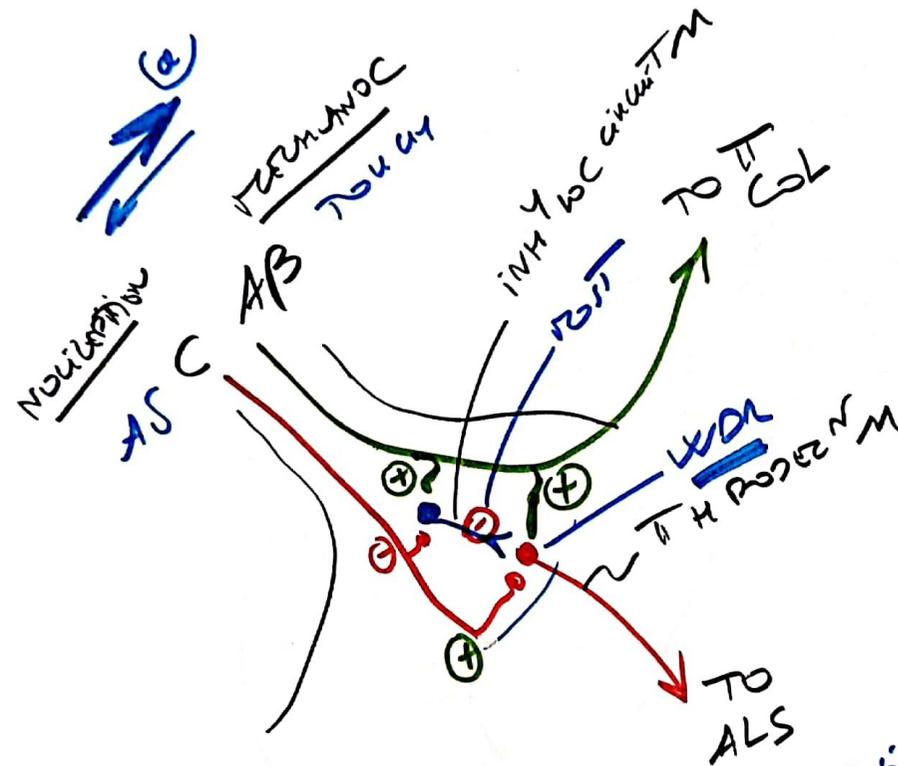
AB > C
C > AB

LESS SIGNALING
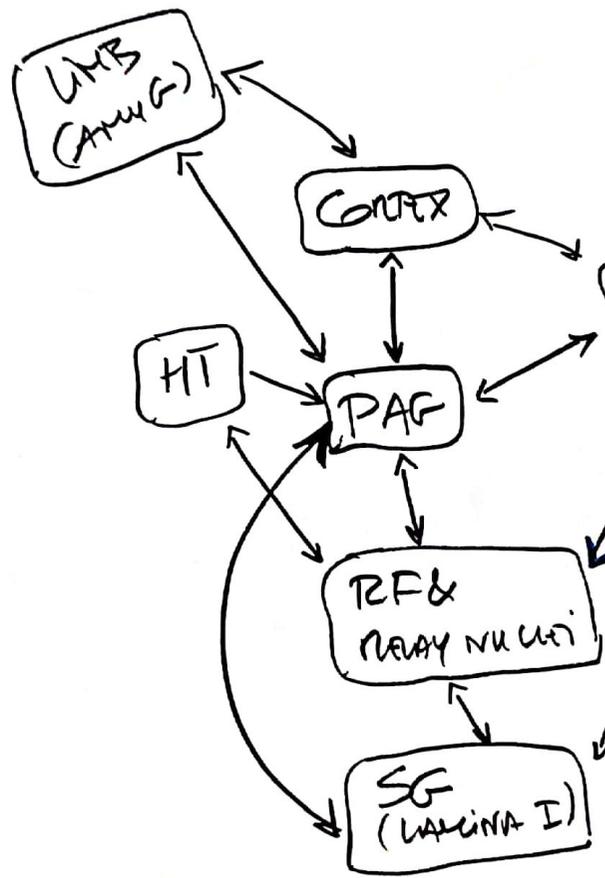
B ↓ INFLUENCES GNL(?)ORONAL
FROM OVERVIEW
BS OF PAIN
MODULATION
NETWORKS

LMB (AMYG?)

CONTEX

HT

PAG

© ENDOGENOUS OPIOID SYST

RF & RELAY NUCLEI

SG (LAMINA I)

INSULA
CING
MEDIAL
PAIN MATRIX
↑ LEVELS
ANOTHER MODULATORY
↓ BS SYS
TH SPINAL CORD
MODULAT

Scanné avec CamScanner

TGT POT ↑OR ↓OTH

POSTSYN
∝ M MEDULLA
PONS/MIDB
PAG
NUC
V SC MAT INHIB
RAPH MAGNU
LC
HIGH DENSITY

② DESCENDING INHIBITION

OPIOID R *

ENK
DYN
END
ENDOG
PEP
NT OR NEUROMODULATION

OPIOIDS — ANALG — STRONG
MOD
WEAK CODEINE
DIHYDROCO
DESTRO PROPO XYPHENE

MORPHINE
DIAMORP HEROIN
OXYCODONE +
PENTAZOCINE +
METHADONE + *
BUPRENORPHINE *
FENTANYL

ENK IC MS

SC ENK R INCIRCUIT MS
TH
POLARIZE ⊖ 2nd ORDER M

↓ MOD
SUPRASPINAL N PRIMARY ROLE
RELAY NEURONS
DC SYSTEM
PARTICULAR MORPHINE
PAIN ⇒

5HT→
NA

NEURO M

↑↓ AKM

1° AKM
SP GW
J ROOT SC

OPIOID R *
① μ
δ
K

C POLYMOD AS MECANO

* ... PARTIAL AGO
+ MIXED AGO/ANTAGO

PNN UP REGULAT

ENK ENDO R
PRECURSOR μ OR

RAGO
MAY GIVE
iHM Cl

↑ RED iHM

TO RELAY MS MAINLY IN T

- ACTION OPIATES AT SYN
- R ANTAGON

BOTH PRE POST SYN *

PRE

OPIOID R (θ)

SYN VES

Ca (2+) ↓ INFLUX IN RES TO INCOMING ACTION POT

↓ INFLUX IN RES TO INCOMING ACTION POT

TXS ↓ NR

⊕ NT SUCH AS GLU

Glu

POST

Blok

K(+)

K(+) ↑ EFFLUX

OPIOID R (θ)

↑ K(+) ↑ EFFLUX & ↓ RES POSTSYN N TO ⊕ NT

⊕ RES

HP

CAN BE AMPLIFIED ← P Os SENSITIZA͂

MALADAPTIVE © STATES P

2 BROAD CATEGORIES
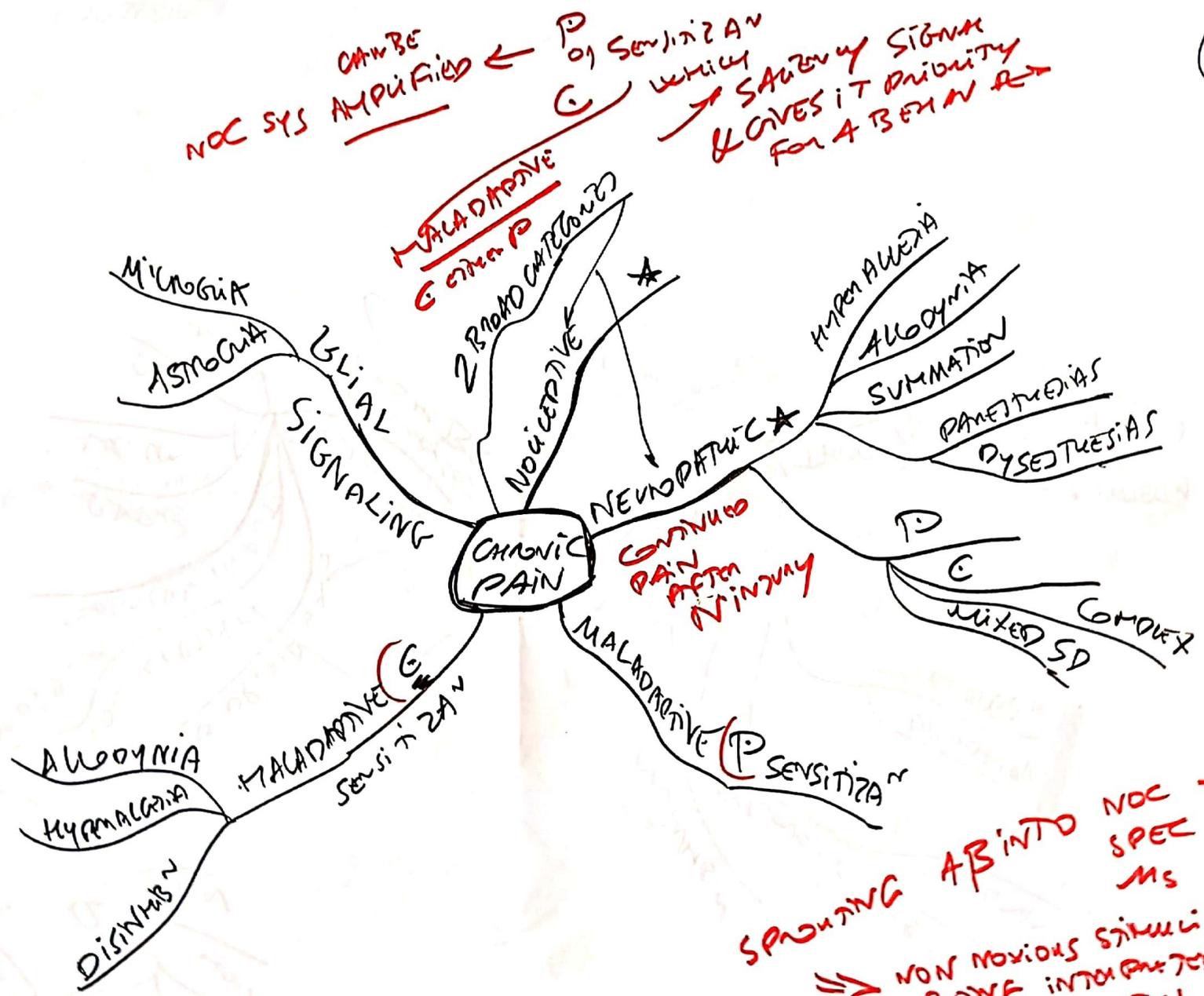
NOC SYS AMPLIFIED

WHICH ↗ SALIENCY SIGNAL & GIVES IT PRIORITY FOR A BEHAV R͂

MICROGLIA
ASTROCIA
GLIAL SIGNALING

NOCICEPTIVE

NEUROPATHIC ★

HYPERALGIA
ALLODYNIA
SUMMATION
PARESTHESIAS
DYSESTHESIAS

CHRONIC PAIN

CONTINUED PAIN AFTER INJURY

P
©
Complex

MIXED SD

MALADAPTIVE © P SENSITIZA͂

ALLODYNIA
HYPERALGIA
MALADAPTIVE © SENSITIZA͂
DISINHB͂

SPROUTING Aβ INTO NOC TH SPEC Ms

⇒ NON NOXIOUS STIMULI BEING INTERPRETED AS PAINFUL

MANY TREYE CHANGES CAN RESULT PERMANENT REWIRING

Scanné avec CamScanner

BS ↓ 5HT & NA RF

↓ NEUROP

ASTROC MICROG) ↑ α iFN
↑ CXN
IFBY M-GLIA SIGNALING →

↑ M EXION

PROINFY ↑ FUNCN
(iFN) ⊕

NOCIREPN

(ASTROC MICROG

PROINFY SIGNALING MOLEC

↓ NOCICEPTION SIGNALING

DUAL SIGNALING IN GP?
GP

MICROGLIA ↓ α

T WUNDE

NOCICEPTION ↑ GP

SYN FORMAN ↑ N
PLASTICITY ON SYN FORMAN & CONNECTIVITY

LASTING ⇒

R2 N
COVER N

GABAic ⊖ SIGNALING IN TH

↑ PAIN SIGNALING

↑ EXCY POST SYN MS

STH ↑ MOVE
PLASMT MS
↑ EXC ADJAC
↑ EXCITATORY NT UN IN CLEFT
ADD N
DOWNREG THEIR CNN NEUROTRANS
GLU ⊕

CAN GUIDE SPROUTING AB
POSSIBLY TO WRONG ◎

Scanné avec CamScanner