Gemelli

ITHACA

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Associazione Nazionale
SINDROME DI NOONAN
RASopatie

AngeliNoonan
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ASSOCIAZIONE ITALIANA SINDROME DI NOONAN

Pain in RASopathies

Dipartimento Salute della Donna e del Bambino e Sanità Pubblica
UOS Malattie Rare e Difetti Congeniti

Chiara Leoni, Giuseppe Zampino

Background: definition

- Pain is a **psychosomatic experience** resulting in physical, psychical, and emotional sufferance

International Association for the Study of Pain (IASP) 1979

- Pain is defined as "an **unpleasant sensory and emotional experience** associated with actual or potential tissue damage, or described in terms of such damage"

- Sensory, emotional, cognitive, and behavioral components that are interrelated with environmental, developmental, socio-cultural, and contextual factors

Houlihan et al., 2004; Tonial et al., 2014; Blake et al., 2016

Background: definition

- The **inability to communicate** verbally does not negate the possibility that an individual is experiencing pain and is in need of appropriate pain-relieving treatment

- **Persistent pain** causes suffering, distress, deterioration of quality of life, **negatively influences everyday life and activities**, alters behavioral profiles, impairs sleeping patterns and leads to anatomic changes of sensory perception

Background: prevalence in general pediatric population

- **Prevalence** of pain in general pediatric population: 5-25%

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Review

Neuropathic pain in children: Steps towards improved recognition and management

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PAIN

Pain 87 (2000) 51–58

www.elsevier.nl/locate/pain

Pain in children and adolescents: a common experience

Christel W. Perquin[a,*], Alice A.J.M. Hazebroek-Kampschreur[b], Joke A.M. Hunfeld[c], Arthur M. Bohnen[a], Lisette W.A. van Suijlekom-Smit[d], Jan Passchier[c], Johannes C. van der Wouden[a]

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Received 18 February 1999; received in revised form 21 February 2000; accepted 24 February 2000

Pain type	Prevalence range	Median quality criteria met	Age differences	Sex differences	Psychosocial/demographic factors associated with increased prevalence
Headache	8–82.9%	9	Older > younger	Girls > boys	Presence of anxiety and depression; low self-esteem (girls only); positive family history of headache; low SES (conflicting findings)
Abdominal pain	3.8–53.4%	8	Younger > older	Girls > boys	SES (conflicting findings); emotional symptoms; school stress
Back pain	13.5–24%	7	Older > younger	Girls > boys	Emotional symptoms (conflicting findings); relation between back pain and sociodemographic/psychosocial factors is unclear
Musculoskeletal/ limb pain	3.9–40%	7	Older > younger	Girls > boys	Feeling sad (girls only)
Multiple pains	3.6–48.8%	8	Unclear	Girls > boys	Chronic health problems; frequent change of residence; frequent television watching; poor school performance; fewer interactions with peers
Other/general pain	5–88%	8	Unclear – possible age × sex interaction	Girls > boys	Poor self-rated health; feeling low or irritable; bad temper; feeling nervous

SES, socioeconomic status.

King S. et al. Pain. 2011; Goodman JE, Pain, 1991; Stanford EA et al., Pain, 2008; Friedrichsdor SJ et al., Children, 2016

Background: Pain in RASopathies

- **Pain in RASopathies** is a neglected topic but it is often complained by affected individuals and consistently documented intergroup variability

PERSONAL EXPERIENCE

- **Noonan syndrome**: muscle-skeletal pain mostly affecting joints and legs

- **Costello syndrome**: back pain, muscle cramps, and generalized fatigue, oral hypersensitivity in infancy

- **Cardio-facio-cutaneous syndrome**: discomfort or pain related to tactile stimulation of mucocutaneous areas (oral cavity, palms and soles)

Background: Pain in RASopathies

Received: 1 March 2020 | Revised: 7 May 2020 | Accepted: 22 May 2020
DOI: 10.1002/ajmg.a.61733

RESEARCH LETTER

American Journal of Medical Genetics Part A | WILEY

Beneficial effect of gabapentin in two children with Noonan syndrome and early-onset neuropathic pain

Luisa Cortellazzo Wiel[1] | Laura De Nardi[1] | Andrea Magnolato[2] | Fabio Sirchia[2] | Irene Bruno[2] | Egidio Barbi[1,2]

DOI 10.1186/s12883-015-0310-8

BMC Neurology

CASE REPORT Open Access

PTPN11 mutation manifesting as LEOPARD syndrome associated with hypertrophic plexi and neuropathic pain

Marianna Spatola, Christian Wider, Thierry Kuntzer and Alexandre Croquelois*

RESEARCH ARTICLE

American Journal of Medical Genetics Part A

Chronic Pain in Noonan Syndrome: A Previously Unreported but Common Symptom

Sravanthi Vegunta,[1]* Richard Cotugno,[2] Amber Williamson,[2] and Theresa A. Grebe[3]

RESEARCH ARTICLE

American Journal of Medical Genetics Part A

Medical Complications, Clinical Findings, and Educational Outcomes in Adults With Noonan Syndrome

Patroula Smpokou,[1,2] Erica Tworog-Dube,[3] Raju S. Kucherlapati,[1,3] and Amy E. Roberts[1,2,4]*

CLINICAL REPORT

Publication Info [i]

American Journal of Medical Genetics Part A

Hypertrophic Neuropathy in Noonan Syndrome with Multiple Lentigines

Claire Maridet,[1]* Guilhem Sole,[2] Fanny Morice-Picard,[1] and Alain Taieb[1]

Received: 12 November 2021 | Revised: 23 January 2022 | Accepted: 18 February 2022
DOI: 10.1002/ajmg.a.62714

ORIGINAL ARTICLE

American Journal of Medical Genetics Part A | WILEY

Neurological features of Noonan syndrome and related RASopathies: Pain and nerve enlargement characterized by nerve ultrasound

Willem De Ridder[1] | Baziel van Engelen[2] | Nens van Alfen[3]

A Patient with Noonan Syndrome with a *KRAS* Mutation Who Presented Severe Nerve Root Hypertrophy

Yoshihito Ando[a, b, c] Mikio Sawada[b, c] Tadataka Kawakami[b, d]
Mitsuya Morita[b, e] Yoko Aoki[f]

Genotype-phenotype correlations
Short report

Paraspinal neurofibromas and hypertrophic neuropathy in Noonan syndrome with multiple lentigines

Erin Conboy [1], Radhika Dhamija [2], Margaret Wang [3], Jing Xie [4], P James Dyck [5], Alina G Bridges [6], Robert J Spinner [7], Amy C Clayton [8], Robert E Watson [9], Ludwine Messiaen [4], Dusica Babovic-Vuksanovic [1, 8]

Pilot study: Pain in RASopathies

AMERICAN JOURNAL OF medical genetics PART A WILEY

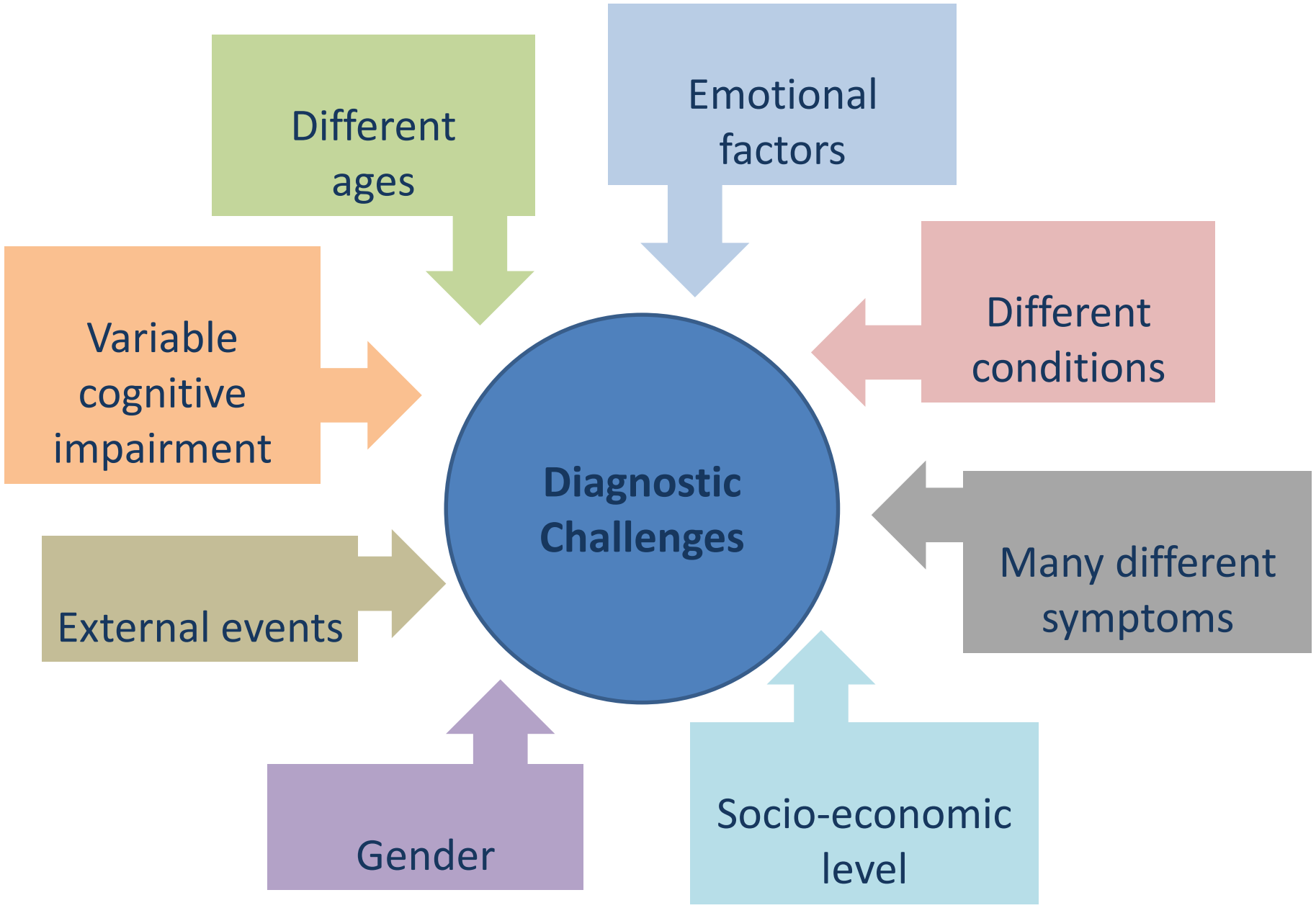
ORIGINAL ARTICLE

Pain in individuals with RASopathies: Prevalence and clinical characterization in a sample of 80 affected patients

OBJECTIVES

- to assess the prevalence of pain among RASopathies
- to characterize pain: duration, body localization and intensity
- to define the aetiology and factors contributing to pain
- to evaluate possible anomalies in pain perception
- to study the influence of pain on quality of life and sleep

Challenges in diagnosing pain



Background: classification

Clinical

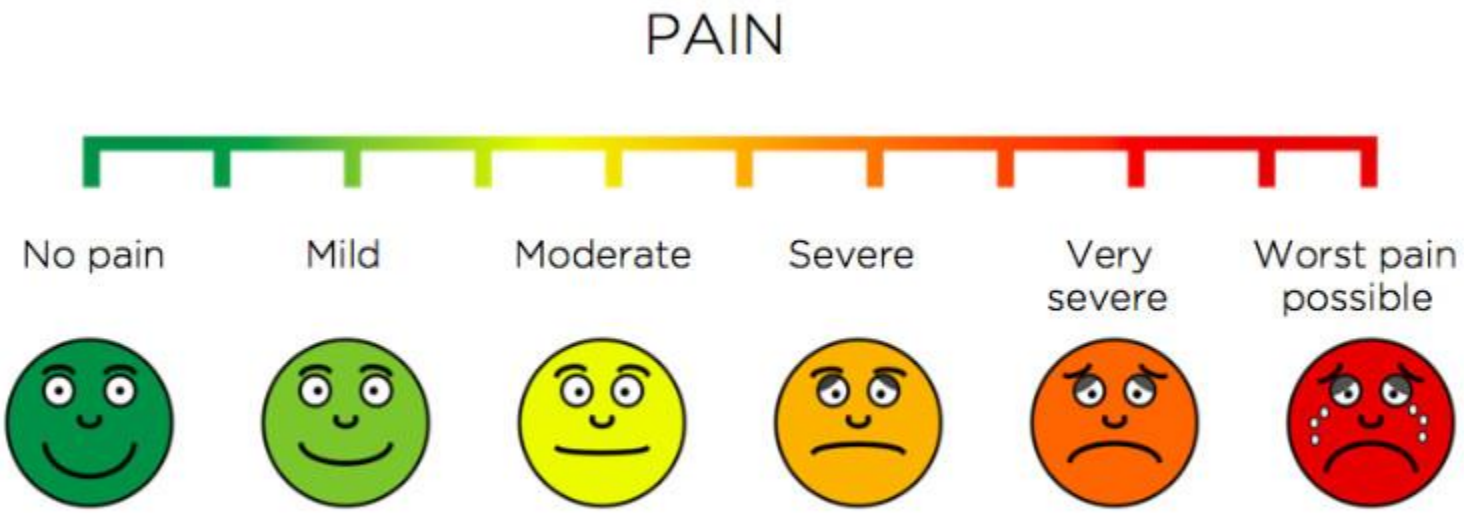
Acute	Chronic
- Recent onset (<3months) - Limited duration - Identifiable temporally and causally related to injury or disease - Alerting signals for potential threats	- Pain that persists after normal time of tissue healing (>3 months) - Perpetuated by non-causal factors - Accompanied by an important emotional component (irritability, isolation, depression)

Emine OB et al., Pain Med 2021

Rolf-Detlef Treed et al., Pain 2015

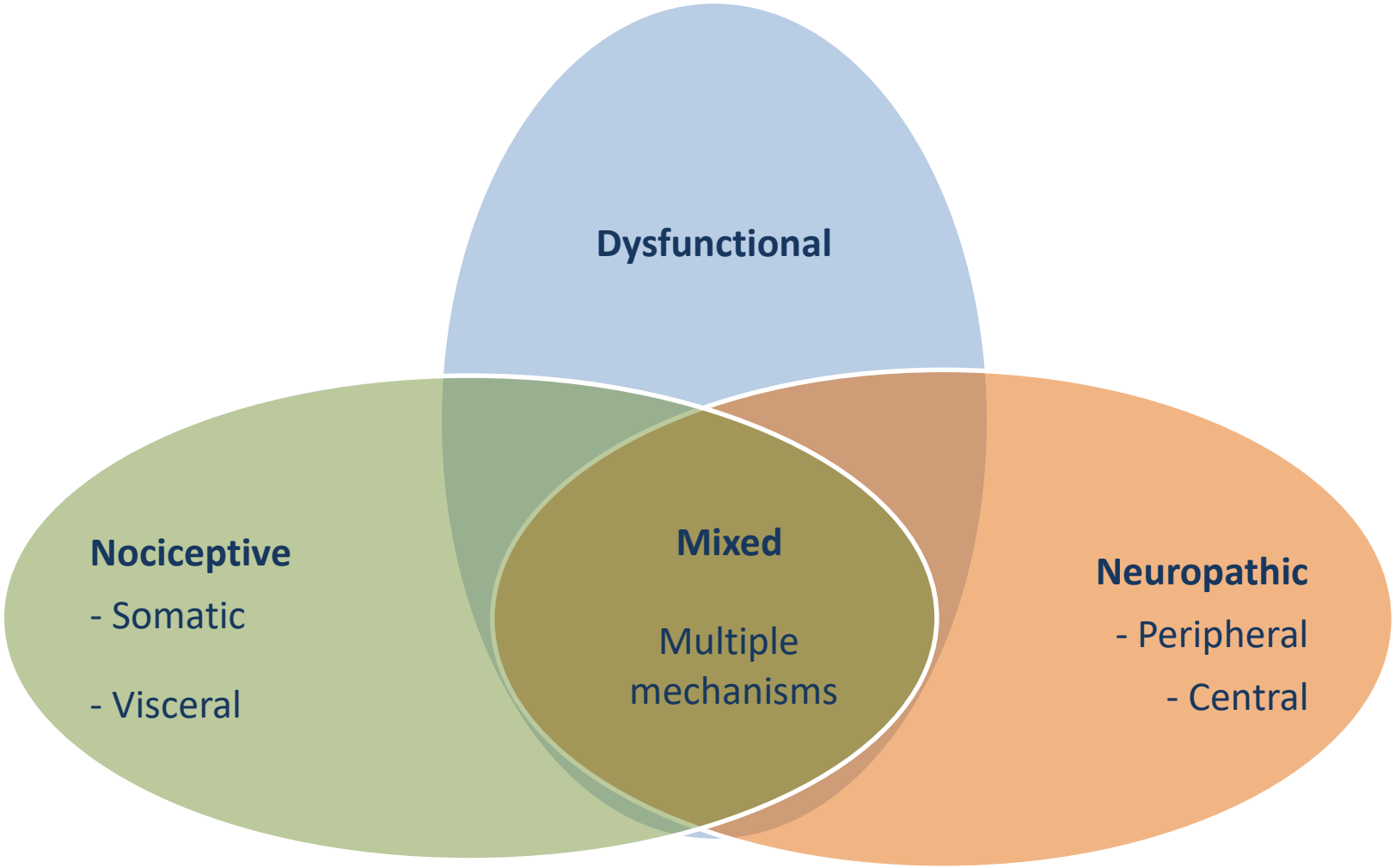
Background: classification

Intensity



Background: classification

Pathophysiological



Pilot study: Pain in RASopathies

AMERICAN JOURNAL OF medical genetics PART A WILEY

ORIGINAL ARTICLE

Pain in individuals with RASopathies: Prevalence and clinical characterization in a sample of 80 affected patients

METHODS

- multisystemic clinical evaluations (orthopedics, gastroenterologist, neurologist)
- standardized questionnaires and rating scales to detect pain (self report and caregiver report) based on patient's age, IQ, and adaptive behavior profile
- neurophysiological tests (Laser Evoked Potentials - LEPs)

Pilot study: Pain in RASopathies

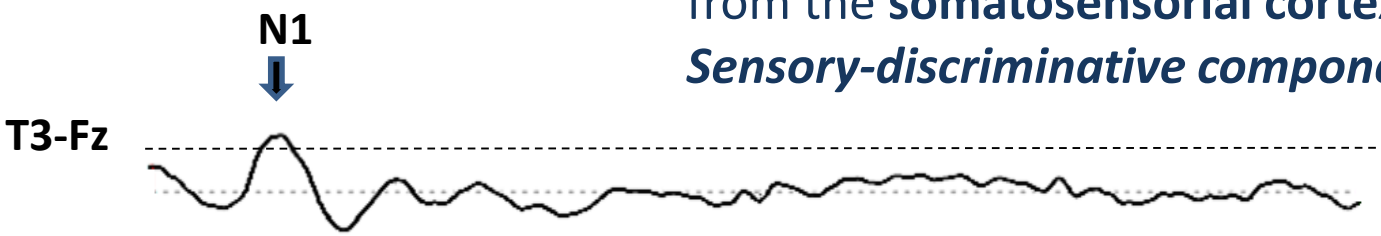
METHODS

Scale	Age	Type of pain	Scoring	Cognitive level
R-FLACC	2 m-7 y	AP / (CP)	0-10	Any
Wang Baker	>3 y	AP	0-10	Normal-mild CI
VAS/NRS	>8 y	AP	0-10	Normal-mild CI
NCCPC-R	>3 y	AP / (CP)	0-90	Severe CI
BPI	>3 y	AP/ (CP)	1-10	Normal-mild CI
NPSI	>3 y	AP / (CP)	1-100	Normal-mild CI
Rome IV	>4 y	AP / (CP)	-	Self/parent
SDCS	Ped Age	/	-	Self/parent
PedsQL	Ped Age	/	-	Self/parent
SF-36	>18	/	-	Self/parent

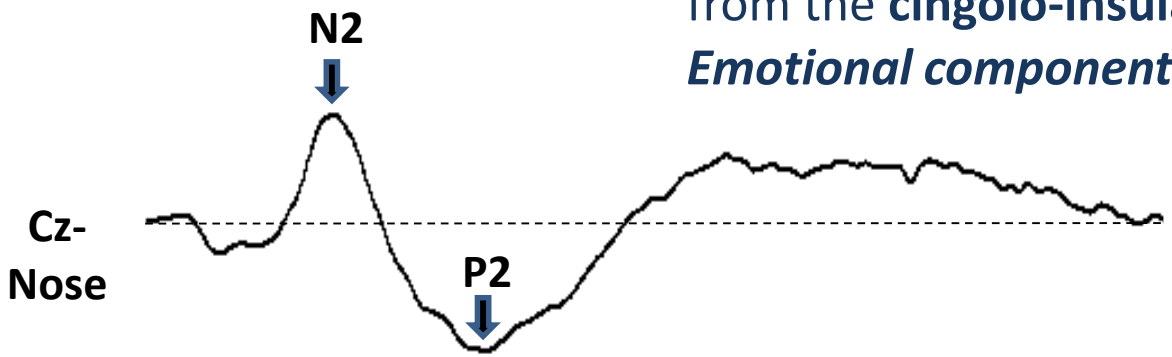
Methods: LEP to study nociception

LEP: N1 potential and N2-P2 complex

N1 potential seems to originate from the **somatosensorial cortex.** ***Sensory-discriminative components of pain***

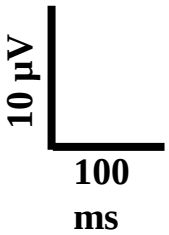


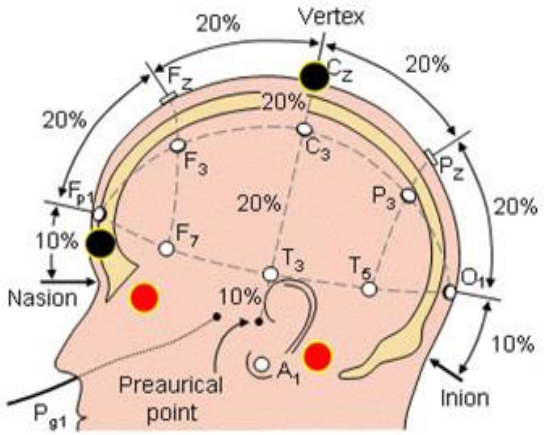
N2-P2 complex seems to originate from the **cingolo-insular region.** ***Emotional components of pain***



N1: S1 ed S2

N2-P2: cingulate cortex



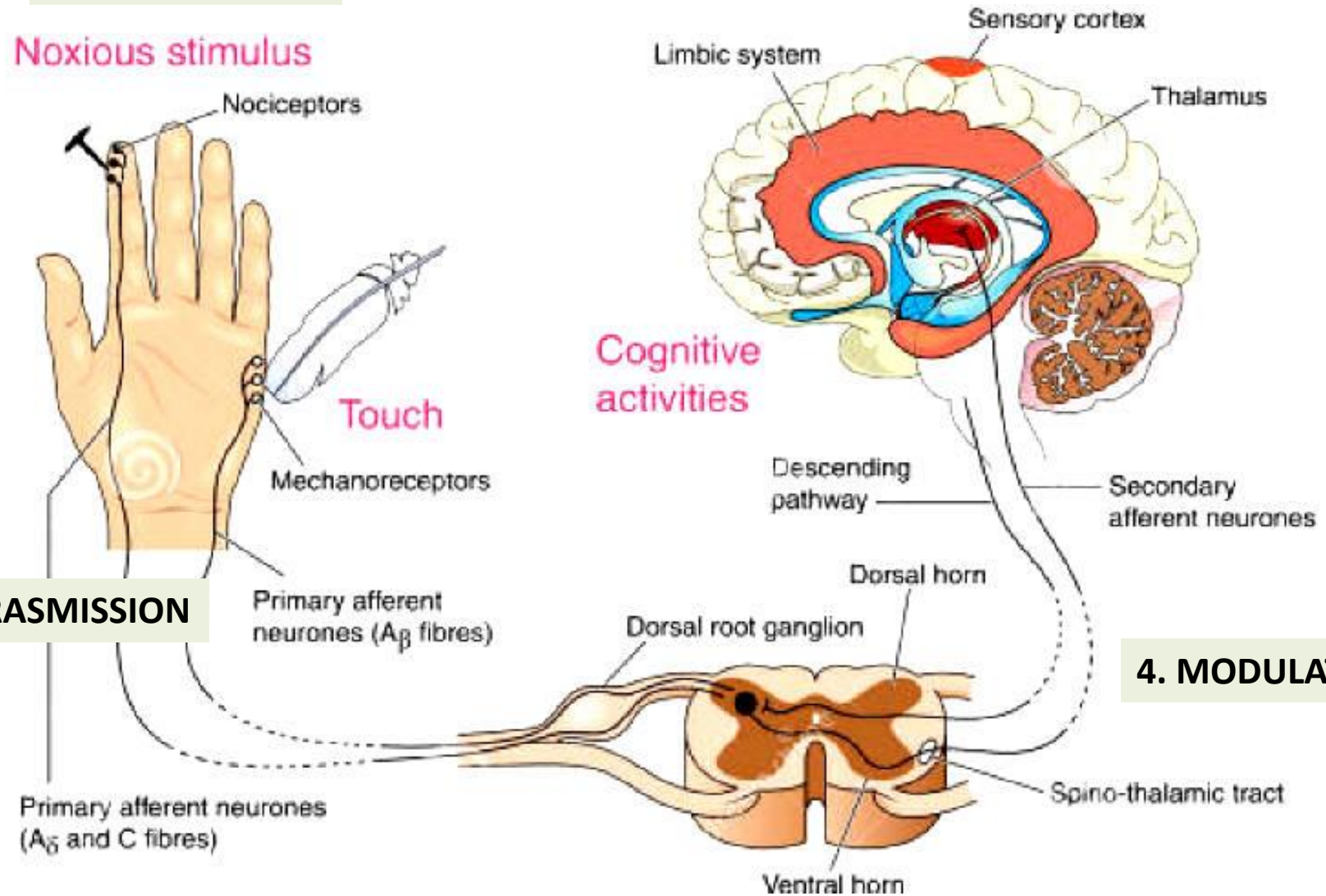


Leoni et al., 2019

Nociception circuit

1. TRASDUCTION

3.PERCEPTION

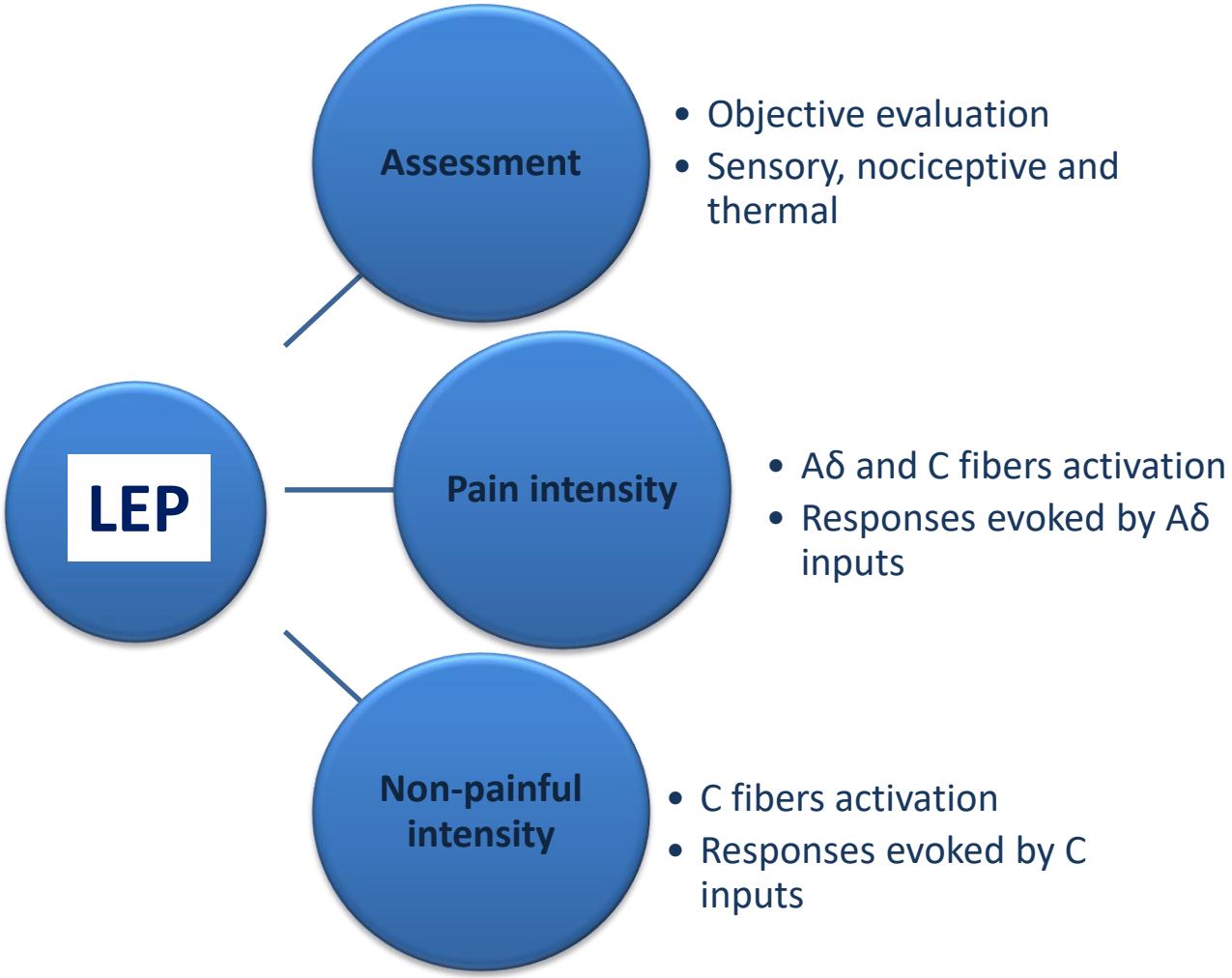


2. TRASMISSION

4. MODULATION

Pilot study: Pain in RASopathies

METHODS



- Objective evaluation
- Sensory, nociceptive and thermal

- Aδ and C fibers activation
- Responses evoked by Aδ inputs

- C fibers activation
- Responses evoked by C inputs

Exclusion criteria

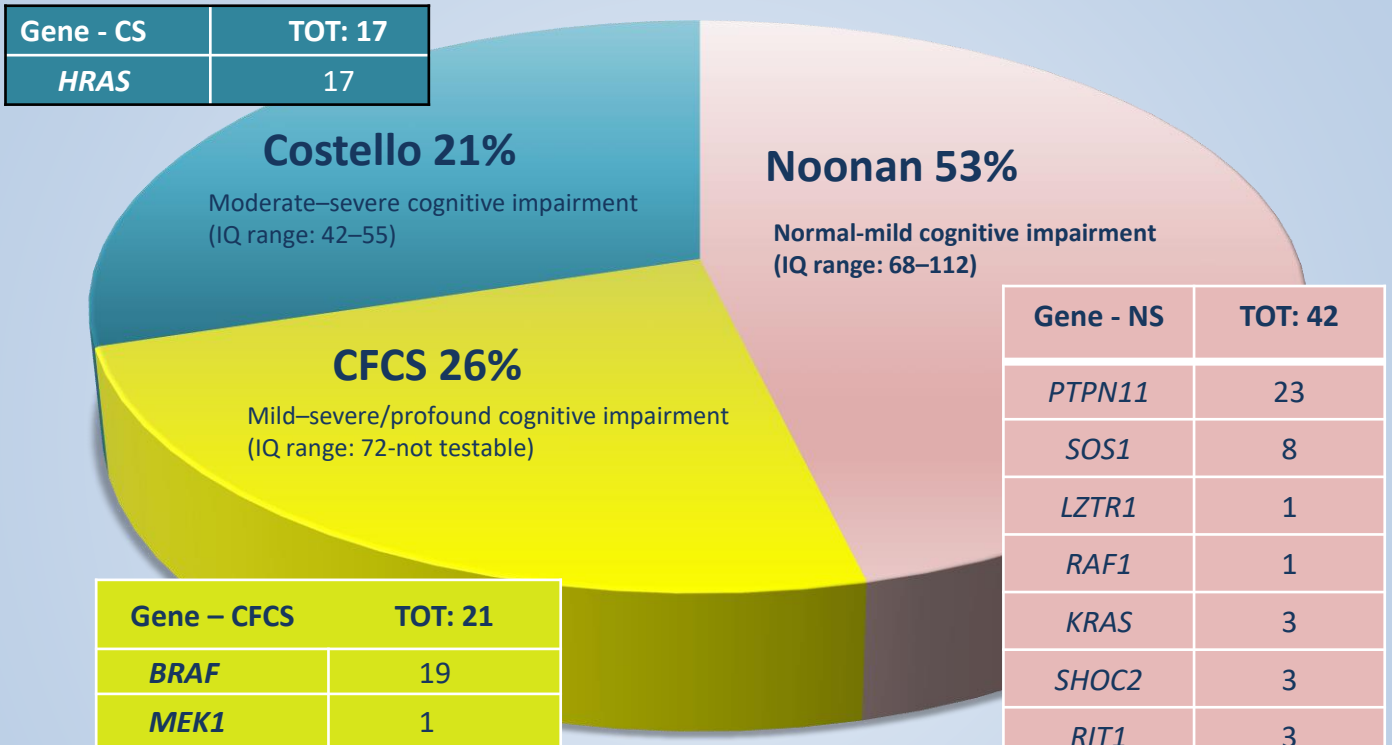
- Age ≤7 y
- No compliance
- Neuropathies
- Diabetes
- Headache
- Cyclic vomiting
- Epilepsy

**Bromm e Treede RD. Human Neurobiol 1984*

Pilot study: Pain in RASopathies

COHORT: NS, CS and CFCS with molecular diagnosis (n=80)

(50 F; 30 M; age range 6 months-31 years)



Gene - CS	TOT: 17
HRAS	17

Gene – CFCS	TOT: 21
BRAF	19
MEK1	1
MEK2	1

Gene - NS	TOT: 42
PTPN11	23
SOS1	8
LZTR1	1
RAF1	1
KRAS	3
SHOC2	3
RIT1	3

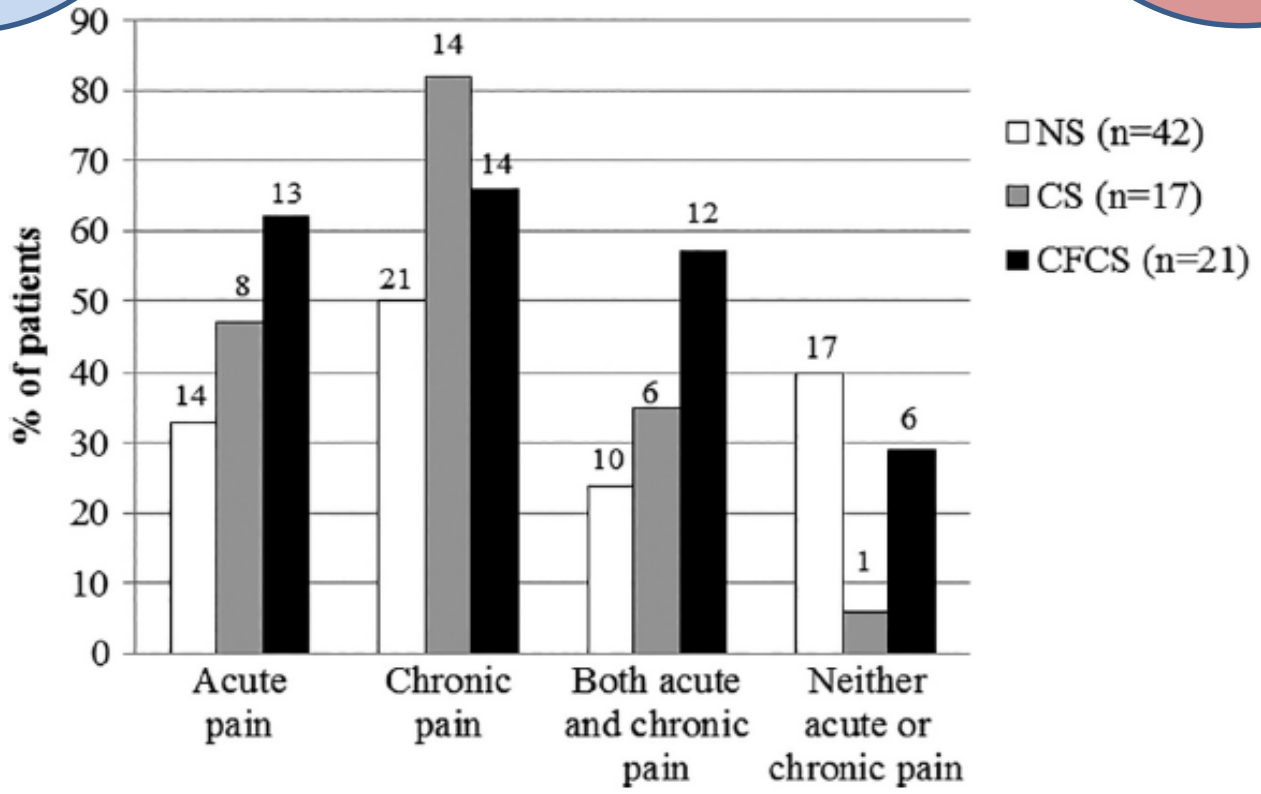
Pain in RASopathies: results (1)

Acute pain
44%
(35/80)

Chronic pain
61%
(49/80)

PREVALENCE

33% NS
47% CS
62% CFCS



50% NS
82% CS
67% CFCS

No statistically significant differences among subgroups

Leoni et al., 2019

Pain in RASopathies: results (2)

BODY LOCALIZATION

Muscle-skeletal and gatrointestinal systems

Body district	AP[a,b]	CP[a,c]
Abdomen	2 NS, 1 CS	12 NS, 8 CS, 1 CFCS
Head	1 NS, 1 CS, 1 CFCS	9 NS, 2 CS
Feet	3 NS, 1 CS	2 NS, 7 CS
Legs	1 NS	2 NS, 1 CS, 1 CFCS
Back	1 NS	5 NS
Neck	1 CS	2 NS, 1 CS
Joints		
Knees	1 NS	3 NS
Hands	1 NS	0
Hip	0	2 NS, 1 CS
Ankle	0	2 NS
Wrists	0	1 NS
Site of surgical procedure[d]	1 NS	0
Undetermined	3 NS, 2 CS, 12 CFCS	3 NS, 2 CS, 12 CFCS

Leoni et al., 2019

Pain in RASopathies: results (3)

Acute pain
52%
(18/35)

BODY LOCALIZATION
Muscle-skeletal anomalies

Chronic pain
67%
(32/49)

Muscle-skeletal anomalies and CP (p=0.04)

TABLE 4 Prevalence of muscle-skeletal abnormalities

	NS (*n* = 42)		CS (*n* = 17)		CFCS (*n* = 21)	
District	AP *n* = 14 (33%)	CP *n* = 21 (50%)	AP *n* = 8 (47%)	CP *n* = 14 (82%)	AP *n* = 13 (62%)	CP *n* = 14 (66%)
Short neck	6 (43%)	10 (48%)	3 (37%)	6 (43%)	4 (31%)	4 (28%)
Webbed neck	7 (50%)	9 (43%)	0	2 (14%)	2 (15%)	2 (14%)
Cubitus valgus	3 (21%)	8 (38%)	6 (75%)	8 (57%)	6 (46%)	7 (50%)
Pectus anomalies	10 (71%)	14 (67%)	8 (100%)	14 (100%)	10 (77%)	11 (78%)
Hip dysplasia/dislocation	0	1 (5%)	1 (12%)	0	1 (8%)	1 (7%)
Pes planus	4 (28%)	8 (38%)	3 (37%)	7 (50%)	8 (61%)	7 (50%)
Joint limitation	2 (14%)	3 (14%)	6 (75%)	10 (71%)	6 (46%)	6 (43%)
Hyperextensibility of small joints	8 (57%)	9 (43%)	2 (25%)	4 (28%)	5 (38%)	5 (36%)
Lumbar hyperlordosis	1 (7%)	1 (5%)	2 (25%)	4 (28%)	0	0
Scoliosis/Kyphoscoliosis	6 (43%)	10 (48%)	7 (87%)	11 (78%)	9 (69%)	9 (64%)
Reduced bone mass (DXA scan)	6 (43%)	7 (33%)	6 (75%)	7 (50%)	6 (46%)	5 (36%)
Other[a]	3 (21%)	5 (24%)	3 (37%)	5 (36%)	2 (15%)	2 (14%)

[a]Dysmetry of the lower limbs; genu valgum, hallux valgum, protrusion of cervical vertebrae.

Leoni et al., 2019

Pain in RASopathies: results (4)

Overall prevalence of GI pain (BPI) 44% (35/80)

NS (36%)
(20% AP, 80% CP, 7% AP+CP)

CS (59%)
(65% AP, 47% CP, 12% AP+CP)

CFCS (48%)
(40% AP, 60% CP, 40% AP+CP)

BODY LOCALIZATION

Gastrointestinal findings: abdominal pain

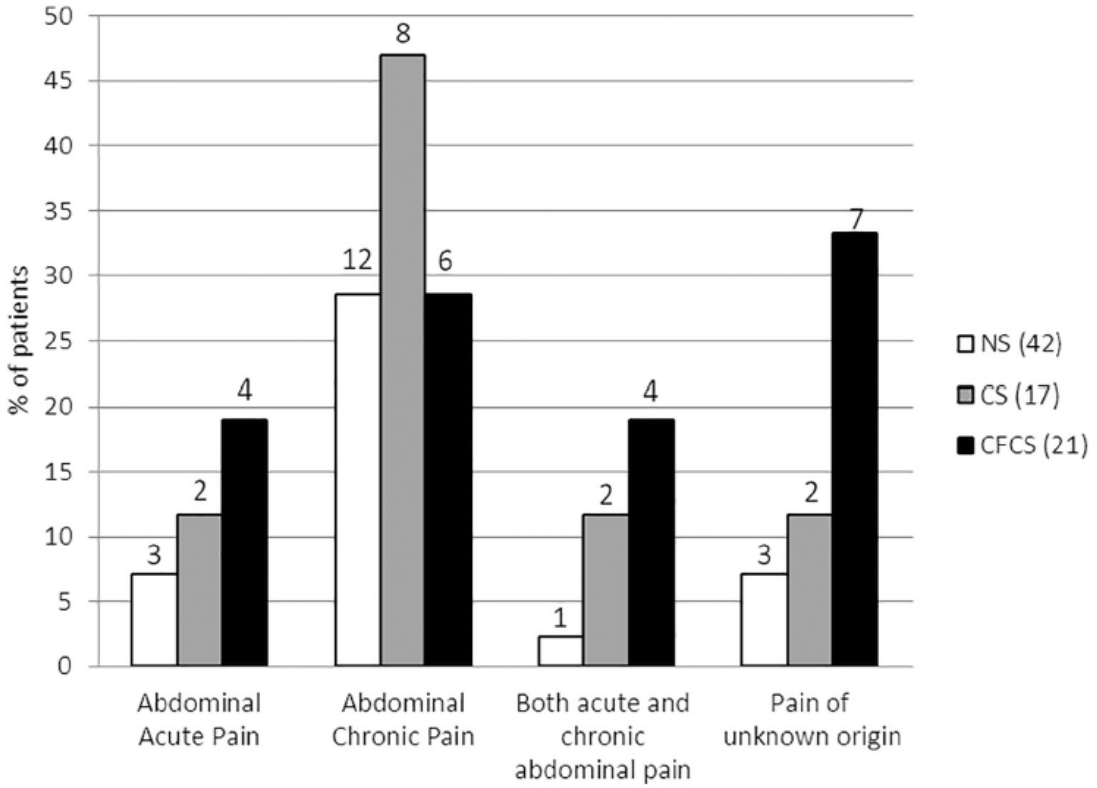


FIGURE 1 Prevalence of abdominal pain in the study sample

Leoni et al., 2022

Pain in RASopathies: results (5)

Rome IV 65/80 (81%): prevalence of functional GI disorders 78%

BODY LOCALIZATION

Functional gastrointestinal disorders

NS (35%)

CS (28%)

CFCS (37%)

TABLE 4 Rome IV questionnaire results

	NS N = 30 (%)	CS N = 15 (%)	CFCS N = 20 (%)	Total sample N = 65 (%)
Gender	F = 19/M = 11	F = 9/M = 6	F = 13/M = 7	F = 41/M24
Functional constipation	14 (47)	13 (87)	17 (85)	44 (68)
Functional abdominal pain	16 (53)	13 (87)	11 (55)	40 (61)
Aerophagia	2 (7)	3 (20)	15 (75)	20 (31)
Irritable bowel syndrome	2 (7)	3 (20)	3 (15)	8 (12)
Functional dyspepsia	0	0	1 (5)	1 (2)
Abdominal migraine	2 (7)	0	1 (5)	3 (5)
Non retentive fecal incontinence	0	0	2 (10)	2 (3)
Cyclic vomiting	0	1 (6)	0	1 (2)

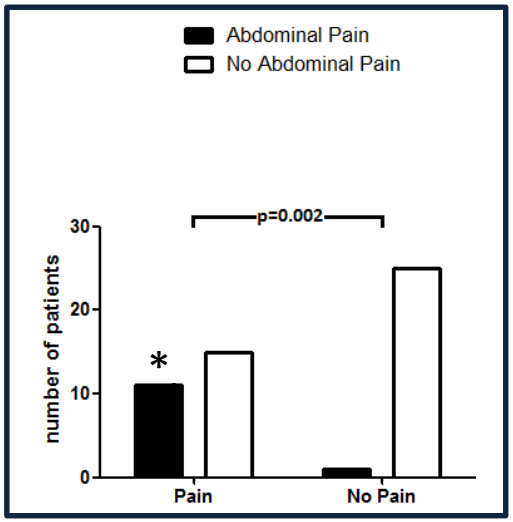
Leoni et al., 2022

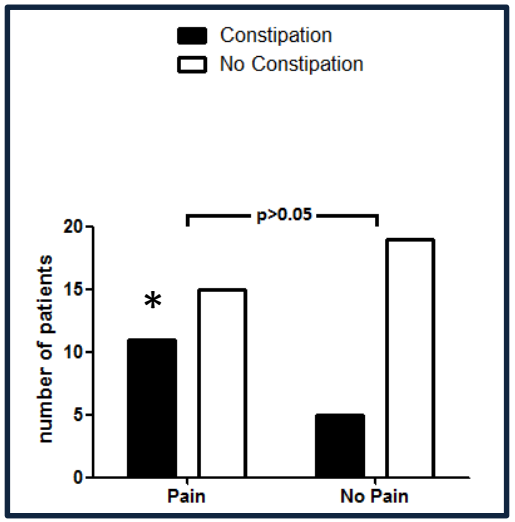
Pain in RASopathies: results (5)

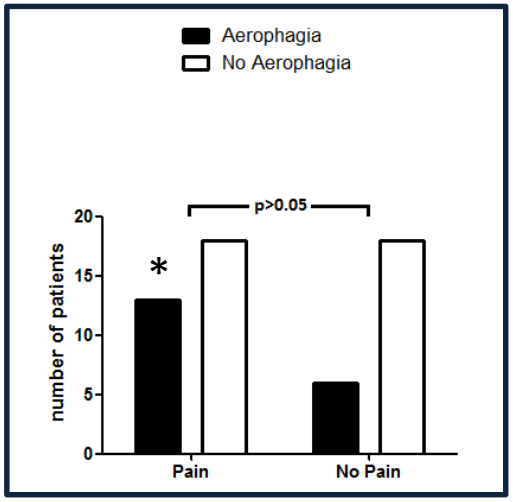
Rome IV 65/80 (81%): prevalence of functional GI disorders 78%

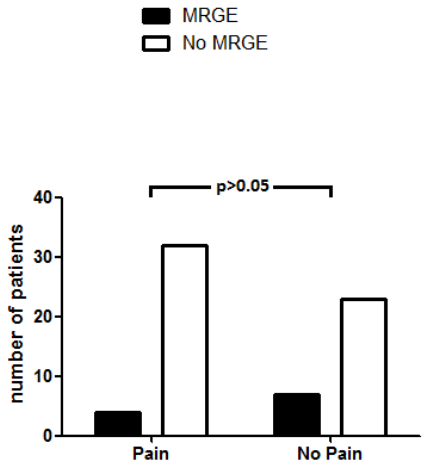
BODY LOCALIZATION

Functional gastrointestinal disorders









Leoni et al., 2022

Pain in RASopathies: results (6)

Hypotonia and AP (p=0.04)

BODY LOCALIZATION

Neurological findings

General muscular hypotrophy and AP (p=0.001) and CP (p=0.007)

TABLE 5 Prevalence of neurological findings

	NS (*n* = 42)		CS (*n* = 17)		CFCS (*n* = 21)	
Neurological feature	**AP *n* = 14 (33%)**	**CP *n* = 21 (50%)**	**AP *n* = 8 (47%)**	**CP *n* = 14 (82%)**	**AP *n* = 13 (62%)**	**CP *n* = 14 (66%)**
Hypertonia	2 (14%)	2 (9%)	6 (75%)	9 (64%)	5 (38%)	5 (36%)
Hypotonia	3 (21%)	4 (19%)	1 (12%)	2 (14%)	12 (92%)	11 (78%)
General muscle hypotrophy	6 (43%)	9 (43%)	8 (100%)	12 (86%)	11 (85%)	10 (71%)
Epilepsy	2 (14%)	3 (14%)	1 (12%)	2 (14%)	5 (38%)	4 (28%)
Autonomous deambulation[a]	12 (85%)	19 (90%)	8 (100%)	14 (100%)	7 (54%)	8 (57%)

[a]Five patients with NS and 1 with CFCS were not evaluated for "autonomous deambulation" skill, since they were younger than 18 months of age.

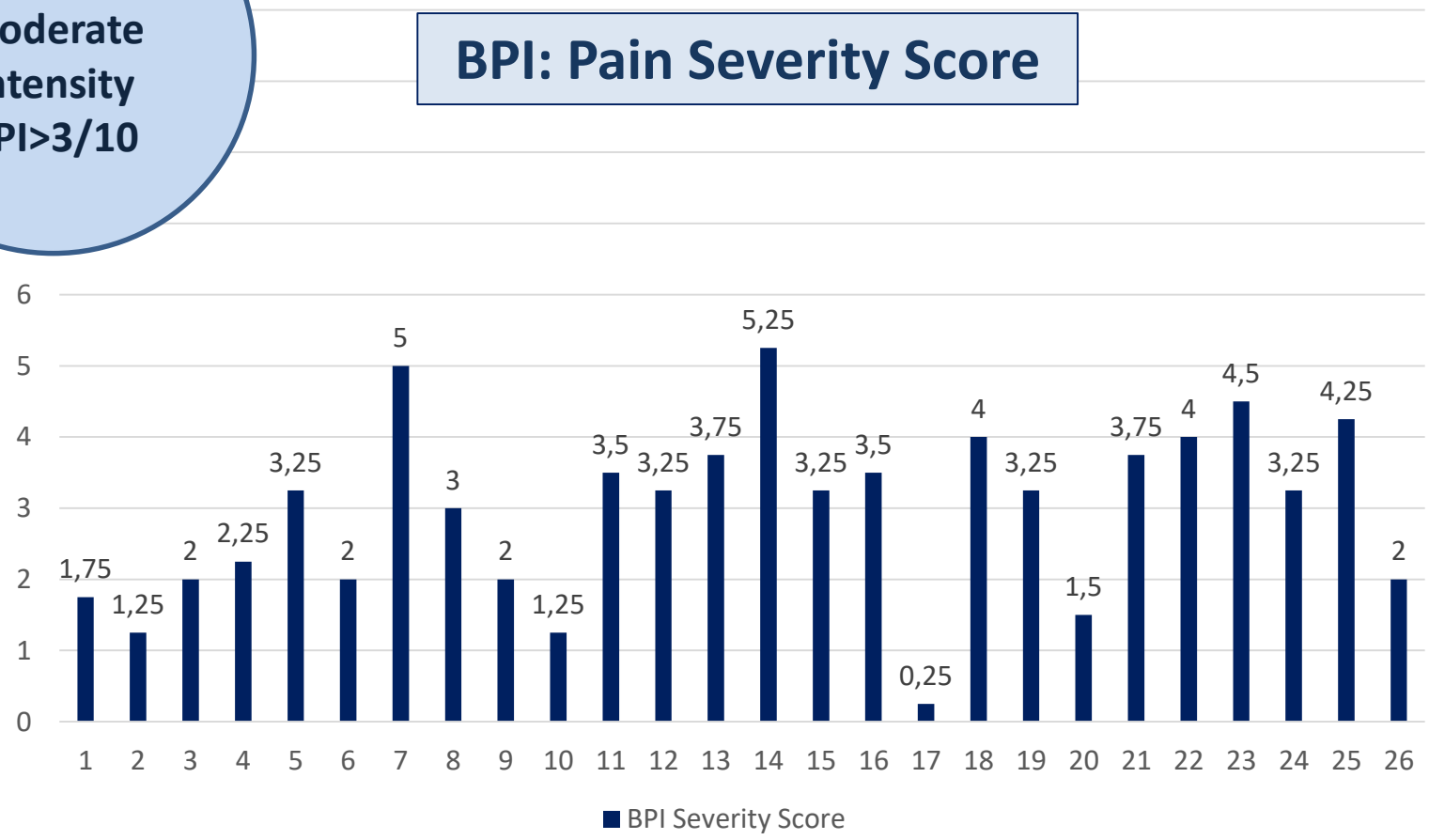
Leoni et al., 2019

Pain in RASopathies: results (7)

INTENSITY
26/35 (74%) patients with AP fulfilled the BPI

62% moderate intensity BPI>3/10

BPI: Pain Severity Score

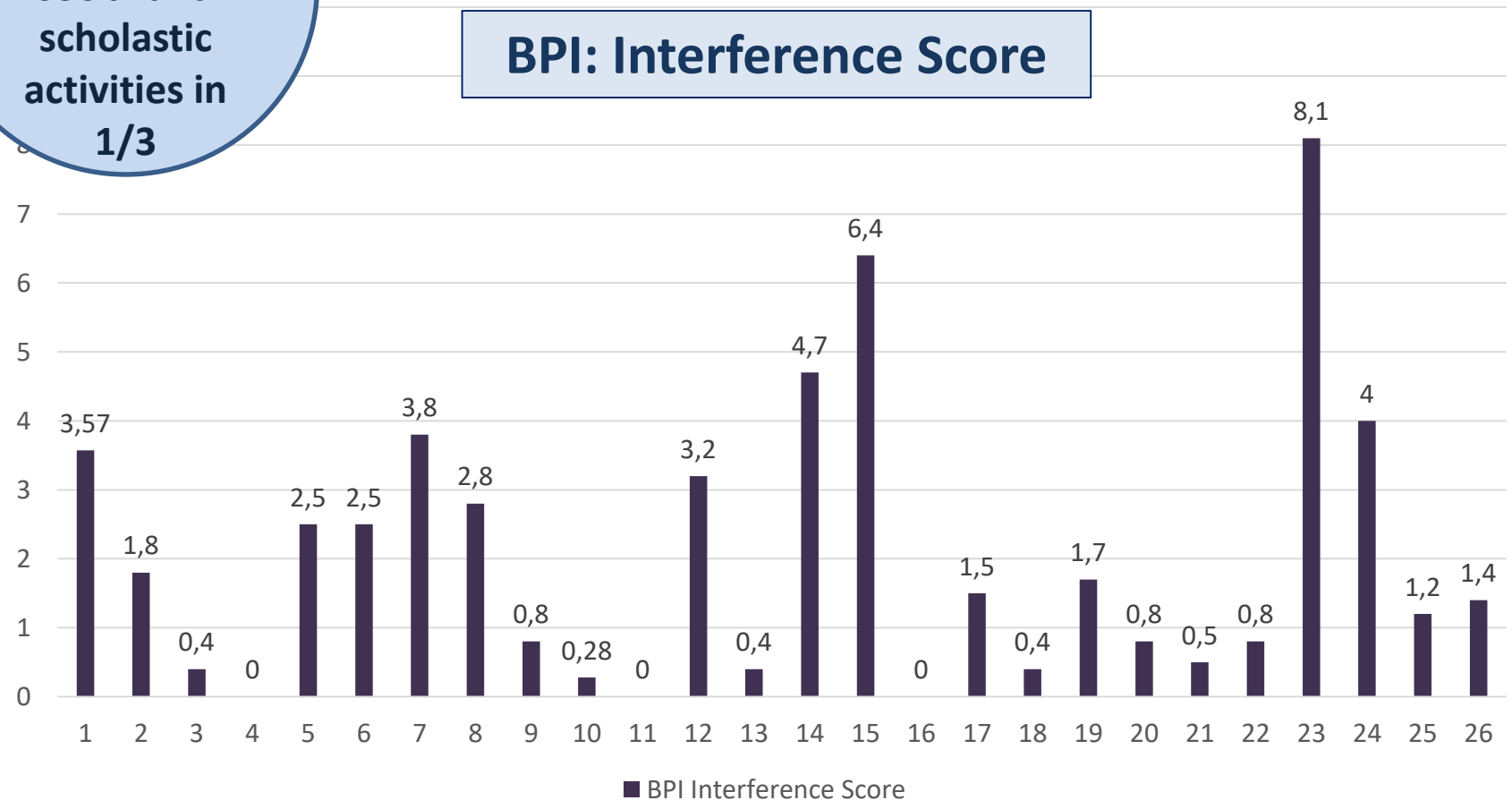


Leoni et al., 2019

Pain in RASopathies: results (7)

INTENSITY

Pain interfearing with daily social and scholastic activities in 1/3

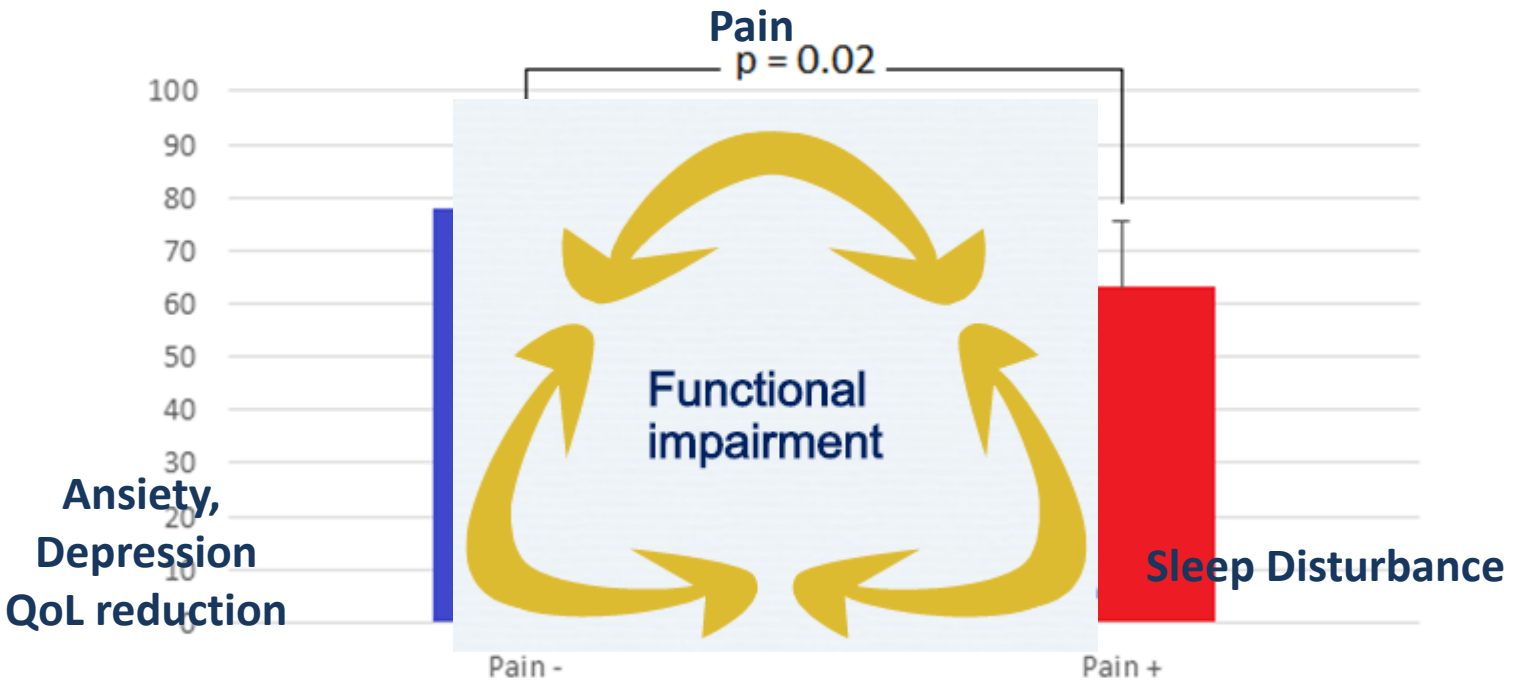


Leoni et al., 2019

Pain in RASopathies: results (9)

QoL and sleeping pattern

- Acute pain significantly impairs sleeping pattern
- Chronic pain significantly worsen QoL

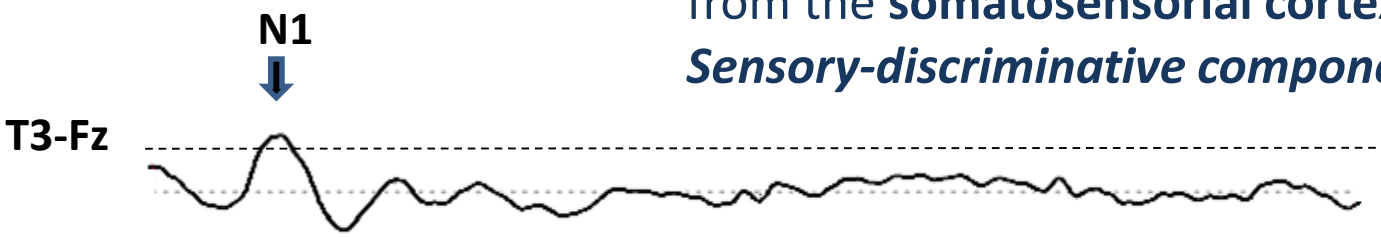


Leoni et al., 2019

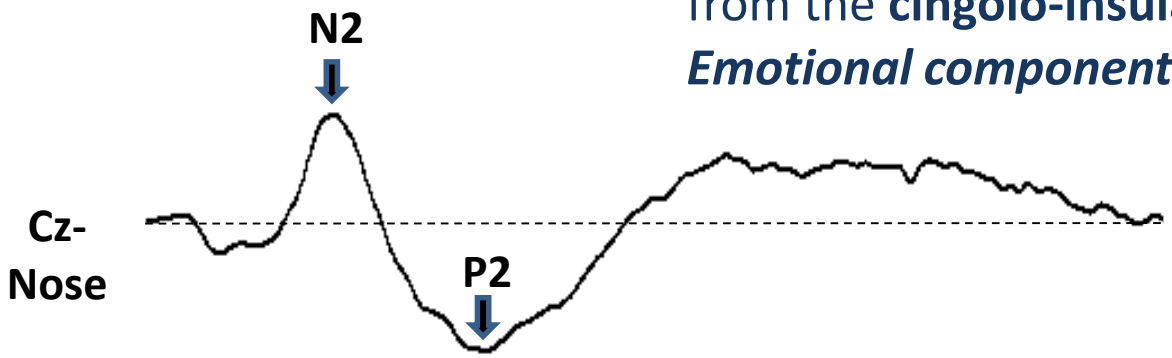
Pain in RASopathies: LEP results (10)

LEP: N1 potential and N2-P2 complex

N1 potential seems to originate from the **somatosensorial cortex.** ***Sensory-discriminative components of pain***

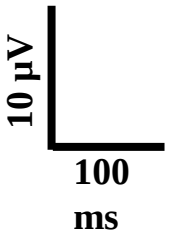


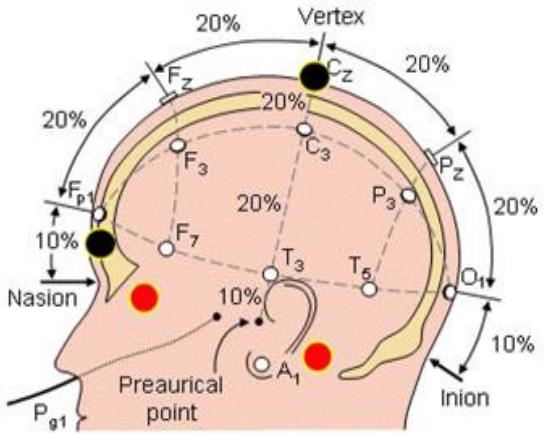
N2-P2 complex seems to originate from the **cingolo-insular region.** ***Emotional components of pain***



N1: S1 ed S2

N2-P2: cingulate cortex





Leoni et al., 2019

Pain in RASopathies: LEP results (10)

LEPs A delta-hand								
	A d fibers-hand							
		N2 Latency	N2 Amplitude	P2 Latency	P2 Amplitude	N1 Latency	N1 Amplitude	N2-P2 Amplitude
No Chronic Pain Group	average	234,62	9,06	360,11	13,48	165,28	12,04	22,54
	SD	83,95	4,05	80,76	5,62	45,5	6,07	9,28
Chronic Pain Group	average	237,76	12,34	368,1	17,11	175,33	11,8	29,45
	SD	46,57	4,91	56,84	11,17	34,54	6,39	12,41
Total	average	237,1	11,65	366,42	16,35	173,21	11,85	28
	SD	53,51	4,84	60,09	10,23	35,93	6,15	11,94

LEPs C fibers-head								
	C fibers- head							
		N2 Latency	N2 Amplitude	P2 Latency	P2 Amplitude	N1 Latency	N1 Amplitude	N2-P2 Amplitude
No Chronic Pain Group	average	252,44	11,15	435,67	17,02	178,96	9,82	28,17
	SD	58,98	11,47	67,17	5,98	27,95	2,9	13,82
Chronic Pain Group	average	244,82	12,77	410,29	20,66	172,52	14,67	33,42
	SD	40,4	10,51	54,66	10,08	25,81	9,27	12,9
Total	average	246,42	12,43	415,63	19,89	173,88	13,65	32,32
	SD	43,12	10,41	56,47	9,34	25,61	8,51	12,89

p=0.02

Leoni et al., 2019

Pain in RASopathies: Conclusions

- **Pain is highly prevalent** among RASopathies
- It has a **multifactorial origin** with muscle-skeletal and gastrointestinal systems being most involved
- **Abdominal pain** and **functional GI disorders** are highly prevalent in RASopathies
- AP significantly **impairs sleeping pattern**
- Intensity and severity of CP pain significantly **impacts on QoL**
- Sensory (perceptive) component of pain is normal in individuals with RASopathies
- An **altered emotional component** has been recorded: impaired elaboration of painful stimuli at a central level (**pain memory**)
- **No therapies** are available to treat pain and GI disorders in individuals with RASopathies different from those used for the general population
- A better understanding of characteristics and etiology of pain in RASopathies is required to provide a consensus on the **personalized stepped-care approach** for treatment of acute and chronic pain

Pain in RASopathies: project ongoing

Ministero della Salute Direzione Generale della Ricerca Sanitaria e Biomedica e della Vigilanza sugli Enti **BANDO RICERCA FINALIZZATA 2019** **esercizio finanziario anni 2018-2019**	**Project Title:** Pain in RASopathies: new investigative techniques and possible treatments
Project Code: GR-2019-12371203	**Principal Investigator:** leoni chiara

- ✓ Aumentare la coorte di pazienti arruolata nel progetto pilota
- ✓ Confermare i dati ottenuti: prevalenza, caratterizzazione e localizzazione del dolore
- ✓ Analizzare biomarcatori del dolore (prelievo ematico)
- ✓ Ampliare lo studio con nuove tecniche diagnostiche strumentali
- ✓ Diffondere i dati attraverso il registro Nazionale RASopatie

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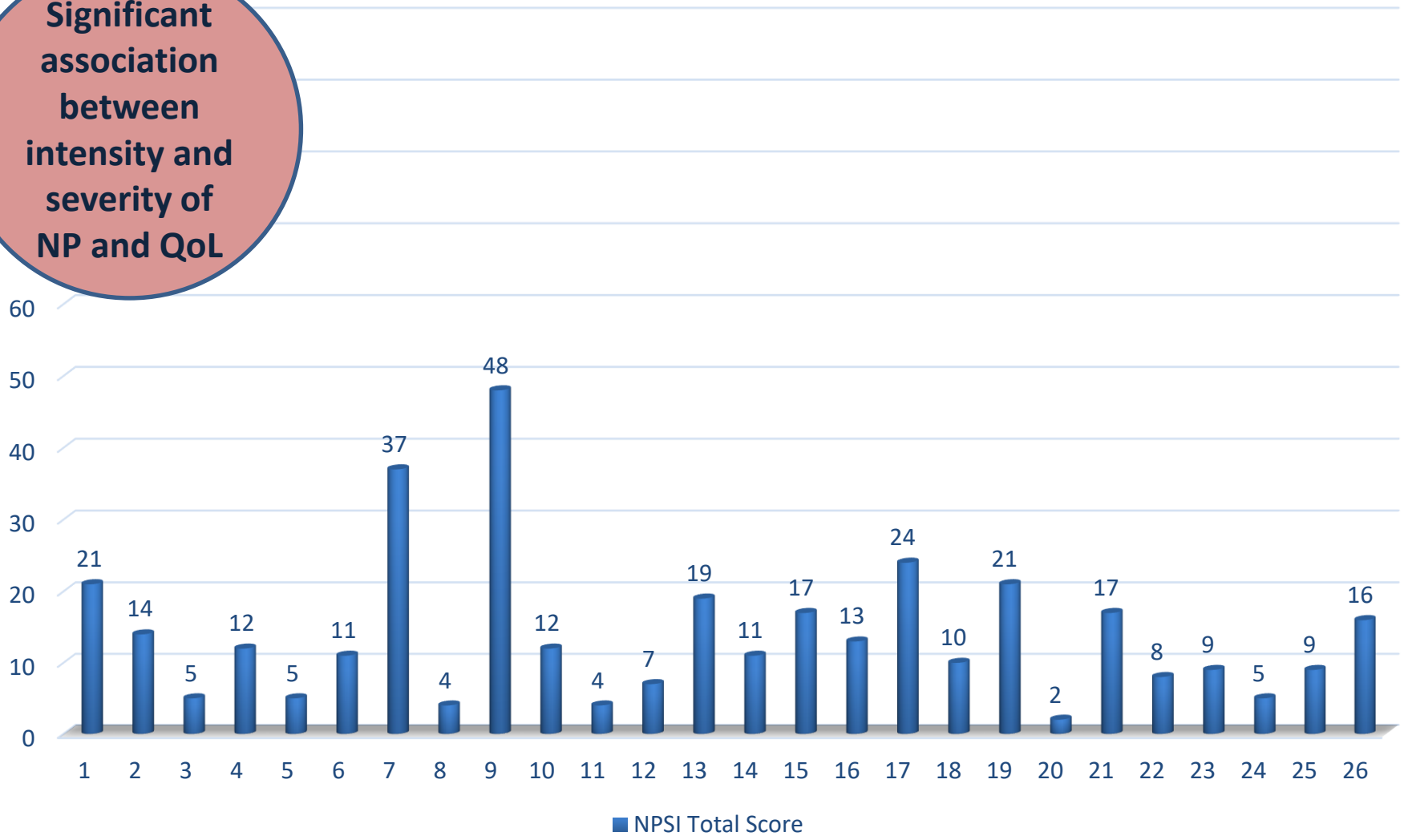
Grazie per l'attenzione

Pain in RASopathies: results (8)

NEUROPATHIC PAIN (NP)

Significant association between intensity and severity of NP and QoL



Leoni et al., 2019

< 3 anni	-Scala FLACC
3-8 anni con deficit cognitivo da assente a medio	-Scala di Wong-Baker e Scala Numerica -Questionari NPSI e BPI -Scala di valutazione dei disturbi del sonno SDSC -PEDS-QL
> 3 anni con deficit cognitivo grave-profondo	-Questionario NCCPC-R -Scala di valutazione dei disturbi del sonno SDSC -PEDS-QL
> 8 anni con deficit cognitivo da assente a grave	-Scala di WONG-BAKER e Scala Numerica -Questionari NPSI e BPI -Scala di valutazione dei disturbi del sonno SDSC -PEDS-QL -SF36 (per pz di età > 18 anni con deficit cognitivo al massimo lieve)