Silent Nerves, Loud Pain

New Insights Into Painful Diabetic Neuropathy

Gordon Sloan

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University of Sheffield

NHS
Sheffield Teaching Hospitals
NHS Foundation Trust

Declarations

I report the following potential duality/dualities of interest

I have received honoraria speaker fee from: Viatris, P&G Health and Eli Lilly

Outline

- An introduction to the current landscape of Painful-DPN
- Risk Factors for Painful-DPN
- Brain involvement in Painful-DPN
- Treating Painful-DPN
- Future perspectives on personalized treatment using neuroimaging

Outline

An introduction to the current landscape of Painful-DPN

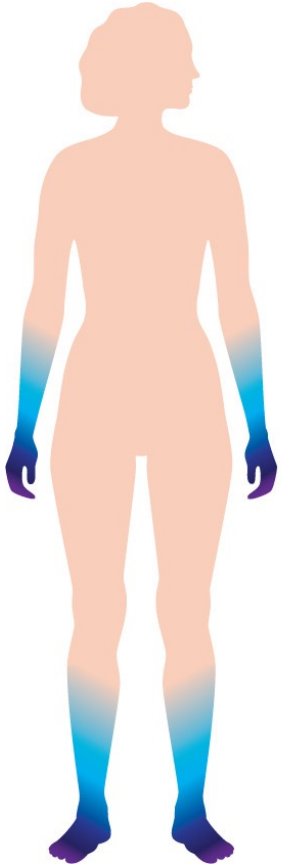
Risk Factors for Painful-DPN

Brain involvement in Painful-DPN

Treating Painful-DPN

Future perspectives on personalized treatment using neuroimaging

Diabetic Peripheral Neuropathy



TIME

Painful Neuropathy

Depression

Functional Impairment

Anxiety

Reduced Work Productivity

Cognitive Difficulties

Sleep impairment

Reduced Quality of Life

Social Isolation

Painful Diabetic Neuropathy

Depression

Unsteadiness

Foot Ulceration

Hypoglycaemia

Higher CVD Risk

Cognitive Difficulties

Functional Impairment

Autonomic Neuropathy

Nephropathy

Falls

Anxiety

Sleep impairment

Insulin

Retinopathy

Reduced Work Productivity

Reduced Quality of Life

Social Isolation

Painful Diabetic Neuropathy

Depression

Unsteadiness

Foot Ulceration

Higher CVD Risk

Cognitive Difficulties

Functional Impairment

Autonomic Neuropathy

Nephropathy

Falls

Anxiety

Sleep impairment

High level of heterogeneity among patients

Retinopathy

Reduced Work Productivity

Reduced Quality of Life

Social Isolation

Patient stratification in Painful-DPN

Non -Irritable Nociceptor Phenotype

Irritable Nociceptor Phenotype

Sloan et al. Nat Rev Endocrinol. 2021; Selvarajah et al Diabetes Care 2023; Teh et al Diabetologia 2021. 64(6)

There are many unanswered questions….

…. and consequently, treatments and are inadequate

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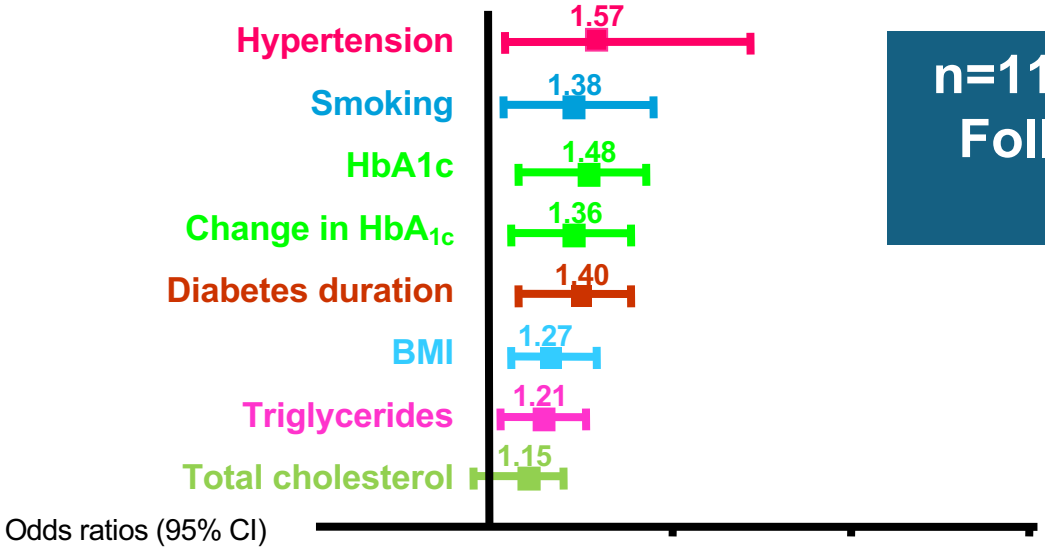
Future perspectives on personalized treatment using neuroimaging

The NEW ENGLAND JOURNAL of MEDICINE

Vascular Risk Factors and Diabetic Neuropathy

Solomon Tesfaye, M.D., Nish Chaturvedi, M.D., Simon E.M. Eaton, D.M.,
John D. Ward, M.D., Christos Manes, M.D., Constantin Ionescu-Tirgoviste, M.D.,
Daniel R. Witte, Ph.D., and John H. Fuller, M.A.,
for the EURODIAB Prospective Complications Study Group*



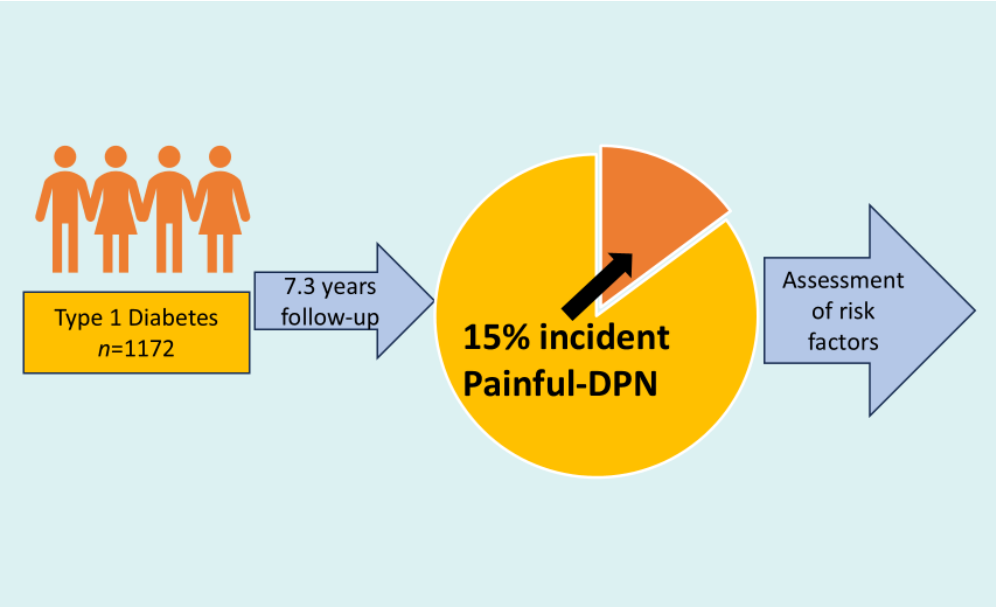
n=1101 with T1 DM; Follow-up 7.3±0.6 years

Tesfaye et al. NEJM 2005

Female sex is a risk factor for painful diabetic peripheral neuropathy: the EURODIAB prospective diabetes complications study

Diabetologia

Jackie Elliott[1,2] · Gordon Sloan[1,2] · Lynda Stevens[3] · Dinesh Selvarajah[1,2] · Giorgio Cruccu[4] · Rajiv A. Gandhi[1,2] · Peter Kempler[5] · John H. Fuller[6] · Nishi Chaturvedi[7] · Solomon Tesfaye[1,2] · for the EURODIAB Prospective Complications Study Group



Female sex a risk factor for Painful-DPN

Odds ratio of developing Painful-DPN for females was 2.69 (1.41, 6.23) vs. males

Variable	OR (95% CI)	*p* value
Adjustment for HbA_{1c} and duration of diabetes		
Female sex	2.69 (1.41, 6.23)	0.004
Height, cm	0.70 (0.49, 0.99)	0.04
WHR	0.69 (0.46, 1.03)	0.07
AER, µg/min[a]	0.59 (0.30, 0.95)	0.03
Micro- or macroalbuminuria, %	0.34 (0.13, 0.88)	0.03
Adjustment for HbA_{1c}, duration of diabetes and sex		
Height, cm	0.98 (0.61, 1.56)	0.9
WHR	0.91 (0.62, 1.34)	0.6
AER, µg/min[a]	0.60 (0.36, 1.00)	0.05
Micro- or macroalbuminuria, %	0.35 (0.13, 0.91)	0.03

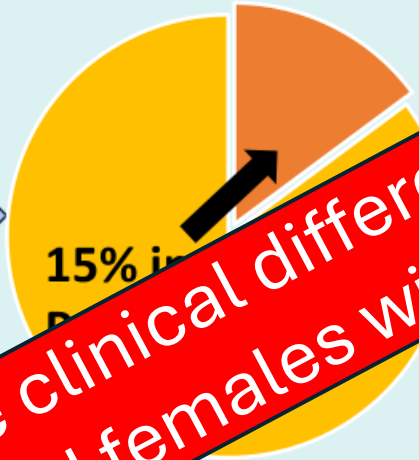
Standardised ORs are expressed per SD increase in each continuous risk factor

ORs for dichotomous variables have as a reference group those participants without the respective risk factor

[a]Log transformation was used

Type 1 Diabetes
n=1172

7.3 years follow-up



Risk f s for **Painful DPN**

nale Sex

Less incident albuminuria

This is in contrast to the risk factors for **DPN**

-HbA_{1c} -Diabetes duration -LDL-cholesterol	-Hypertension -Smoking -BMI -Triglycerides

Are there clinical differences between males and females with Painful-DPN?

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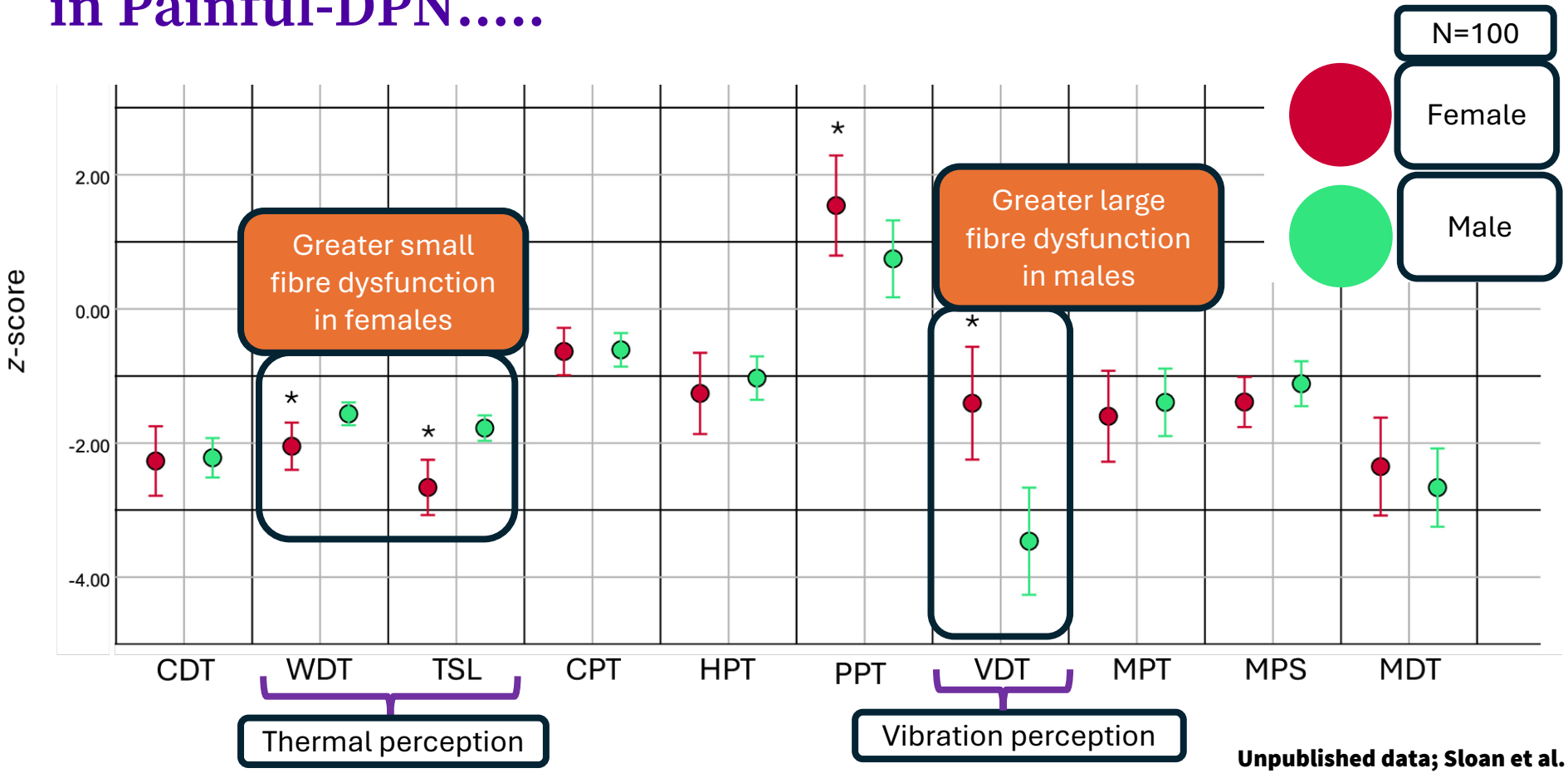
Females also have different nerve fibre involvement in Painful-DPN.....



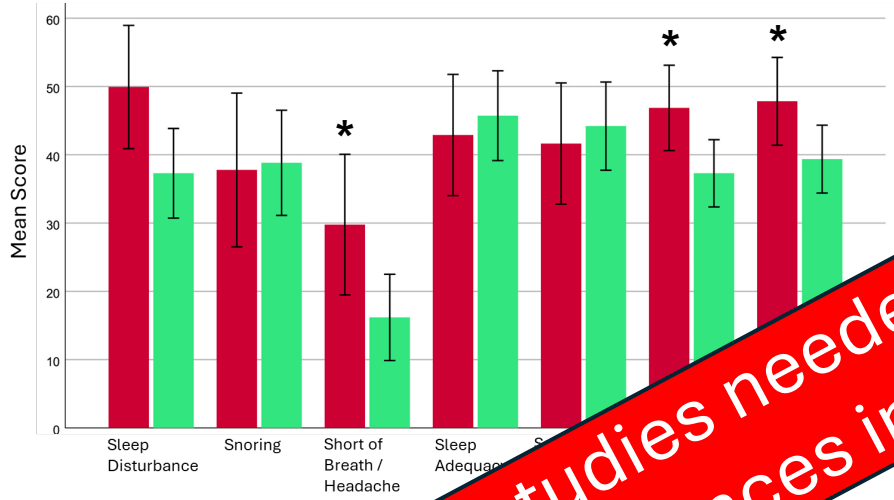
Unpublished data; Sloan et al.

…and suffer with higher disease burden

Female

Male

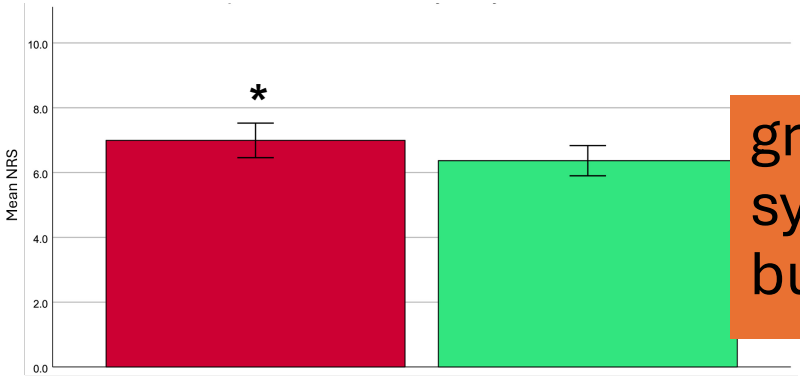
N=184



wors

Further studies needed to determine sex differences in Painful-DPN

more anxiety



greater symptom burden

Unpublished data; Sloan et al.

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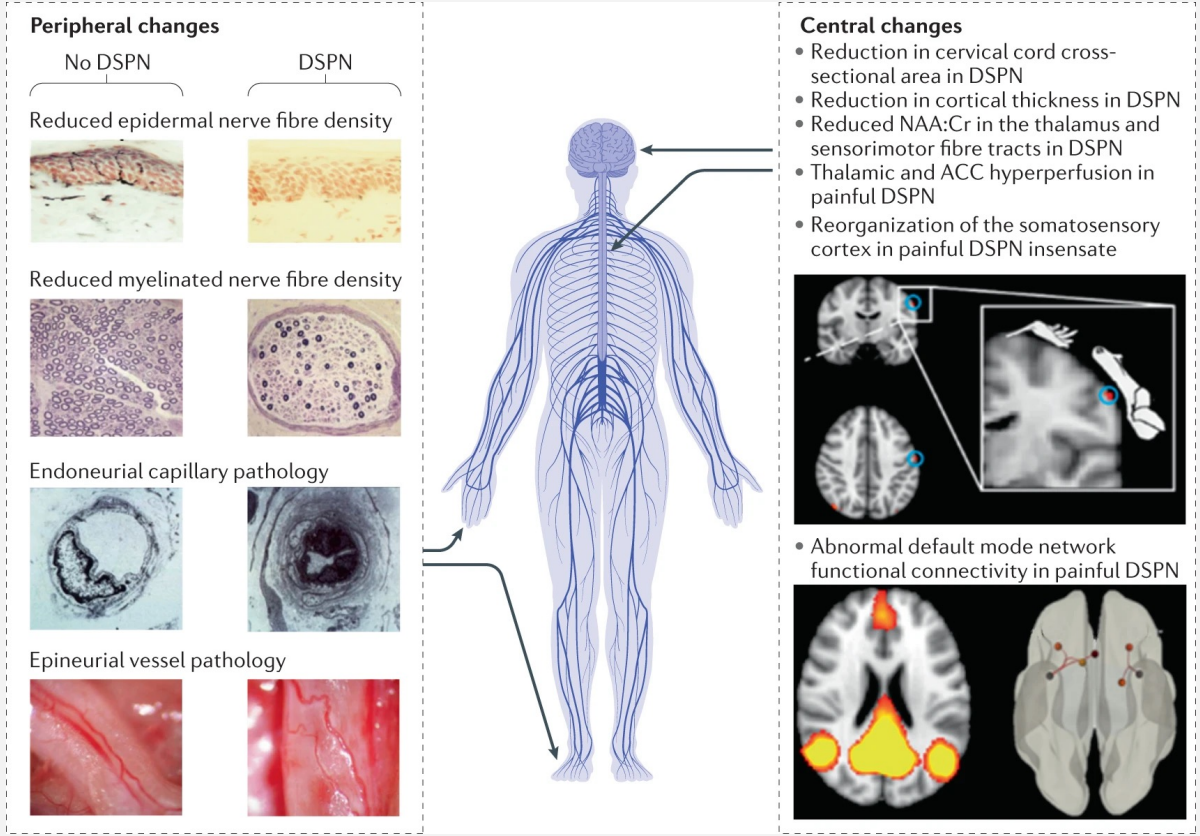
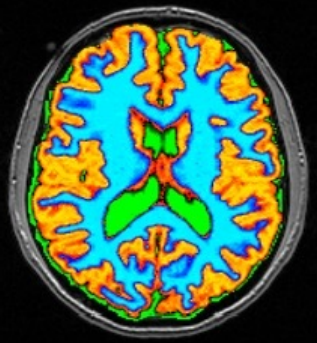
Diabetic Peripheral Neuropathy

Involves both the peripheral **and** central nervous system

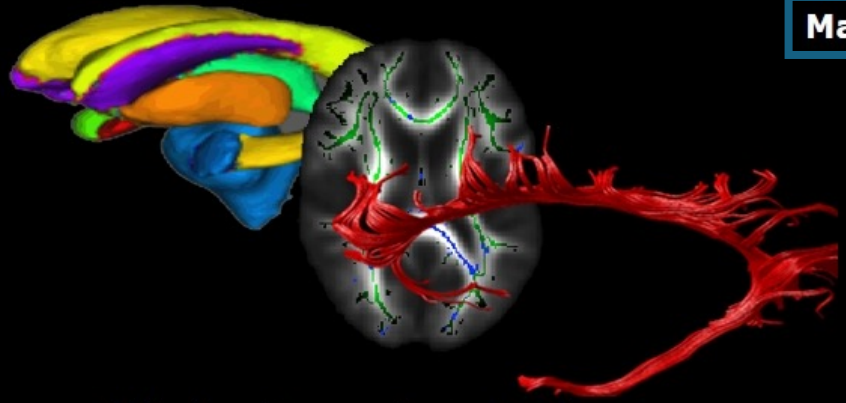


Sloan et al. Nat Rev Endo 2021

CNS involvement in Diabetic Polyneuropathy

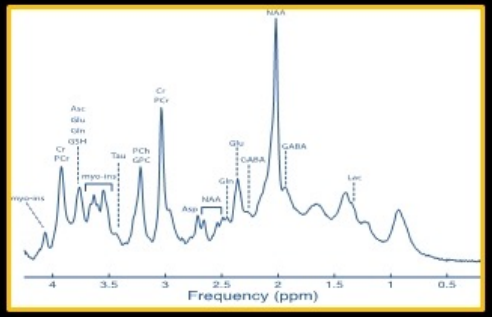


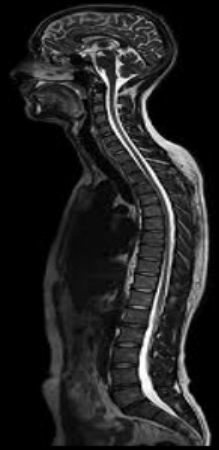
Volumetric measures

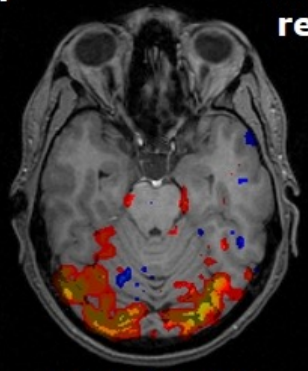


Diffusion Tensor Imaging/ Tractography

Magnetic Resonance Spectroscopy

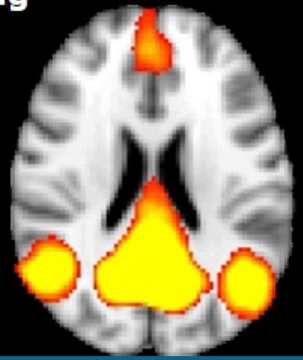






Task fMRI/ Perfusion Imaging

Functional magnetic resonance imaging



Resting fMRI

Structural Brain Alterations in Key Somatosensory and Nociceptive Regions in Diabetic Peripheral Neuropathy

n=277

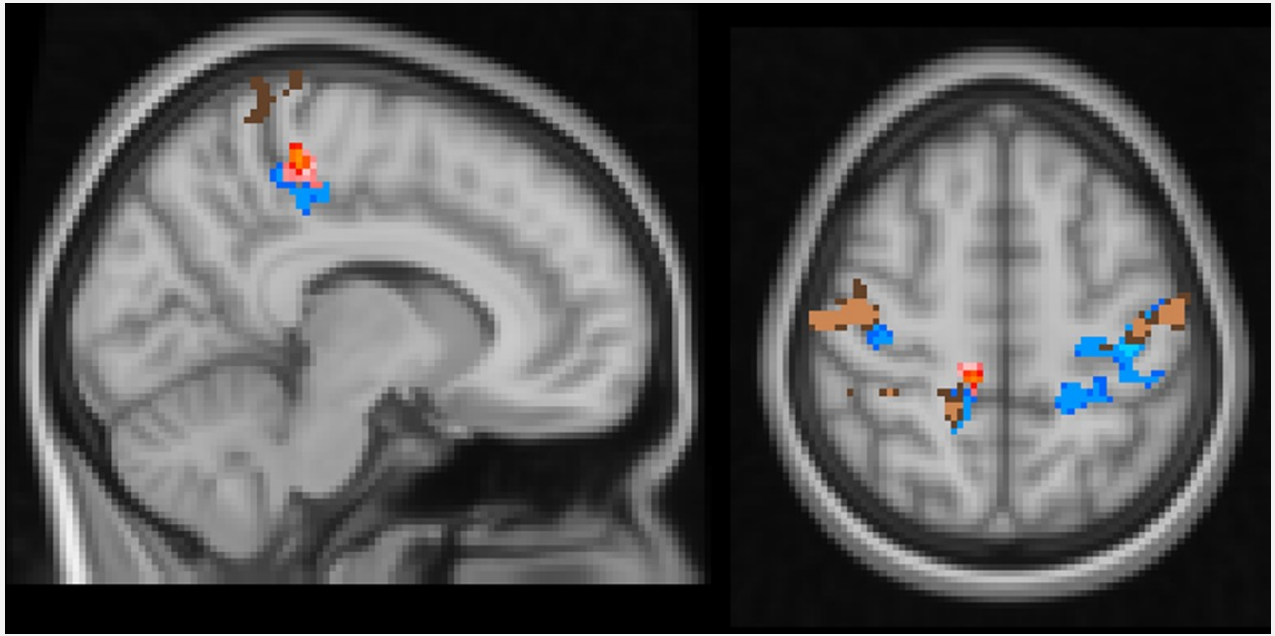
DPN groups reduced cortical thickness/volume:

-Primary somatosensory cortex

-Primary motor cortex

-Insular cortex

-Thalamus



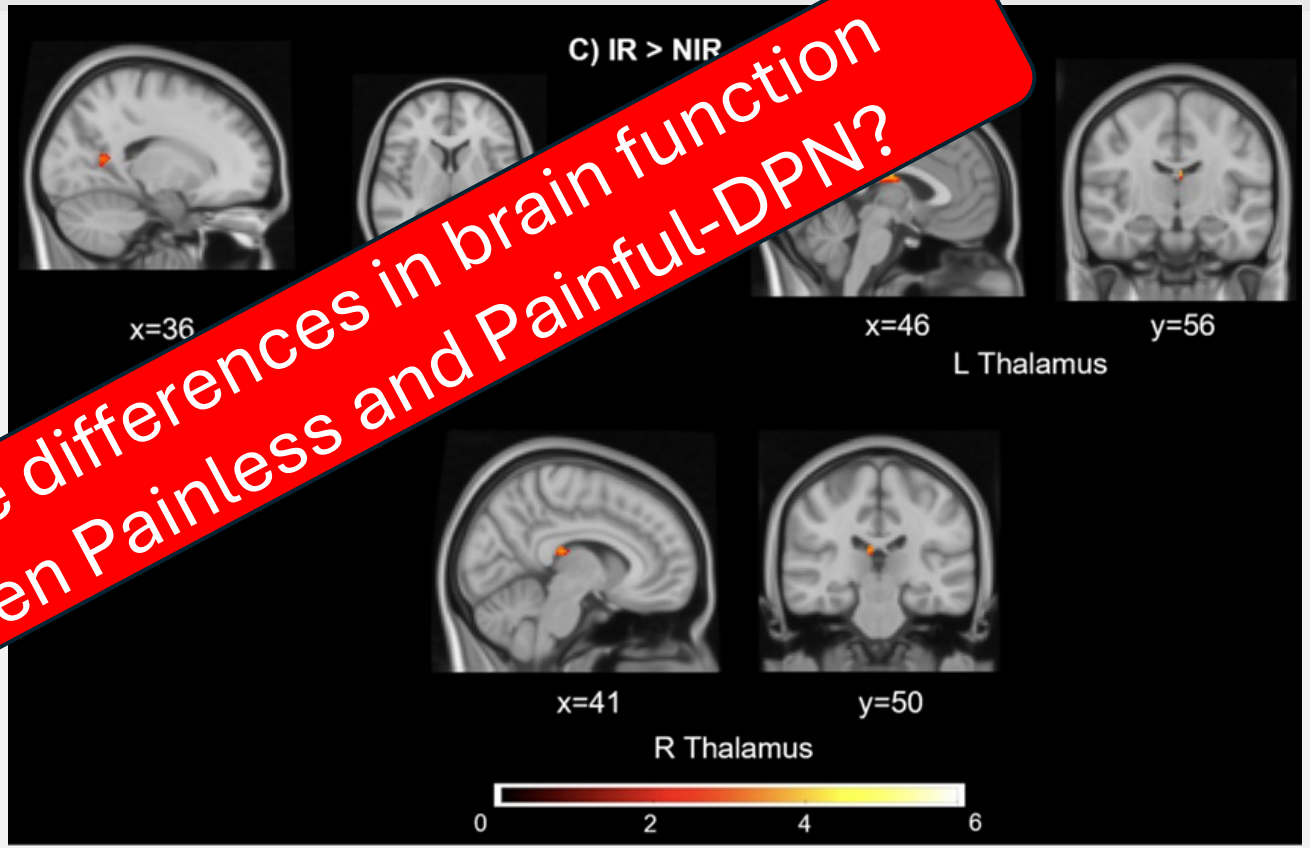
Diabetes Care

Selvarajah D / Sloan G. et al Diabetes Care 2023

Differences in brain structure between clinical phenotypes of Painful-DPN

NIR Painful-DPN: reduced primary somatosensory cortical, posterior cingulate cortical, and thalamic volume

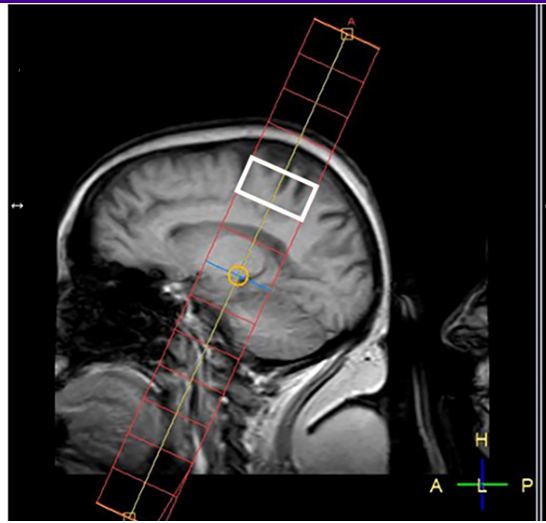
IR Painful-DPN: reduced anteri cingulate thicknes

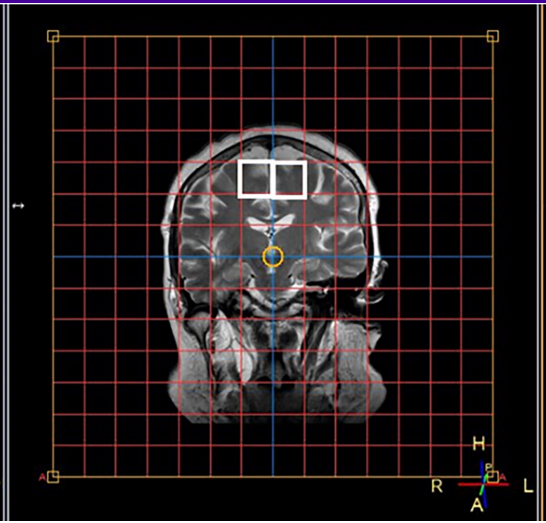


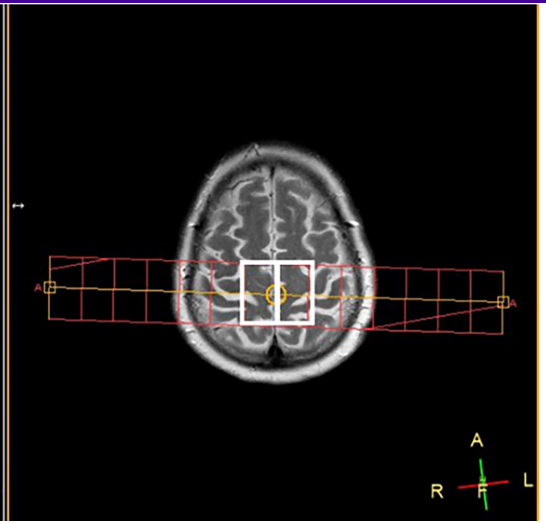
Are there differences in brain function between Painless and Painful-DPN?

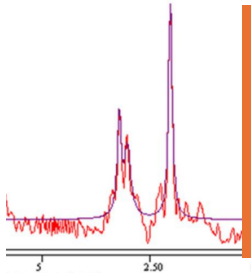
Selvarajah D / Sloan G. et al Diabetes Care 2023

Magnetic Resonance Spectroscopy

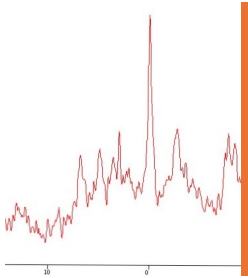




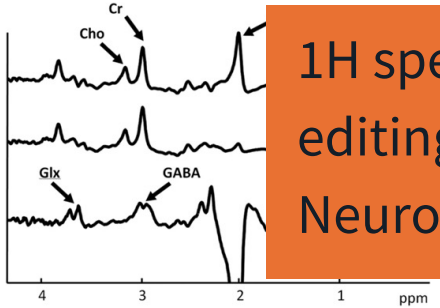




1H-MRS: Neuronal Function



31P-MRS: Cellular energetics

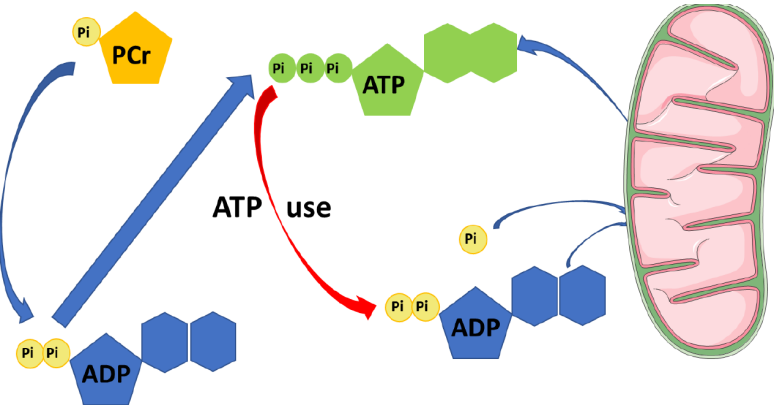


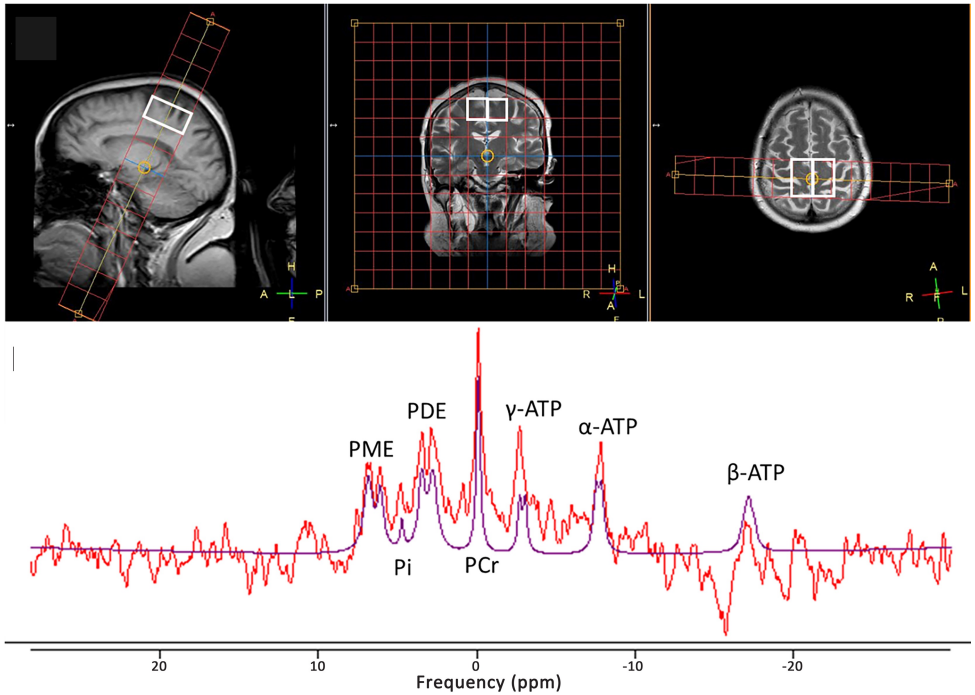
1H spectral editing: Neurotransmitters

Higher Sensory Cortical Energy Metabolism in Painful Diabetic Neuropathy: Evidence From a Cerebral Magnetic Resonance Spectroscopy Study

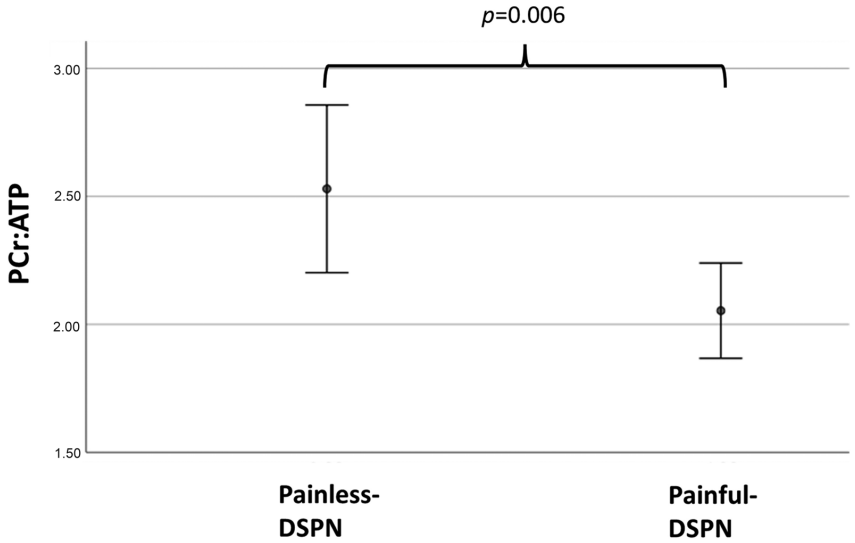
diabetes

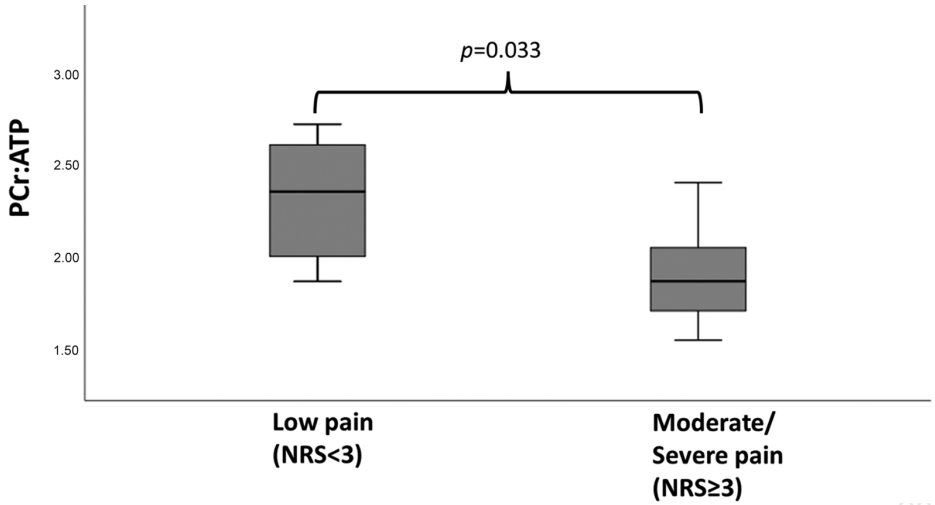
Gordon Sloan,[1,2] Adriana Anton,[3] Sharon Caunt,[1] Iain Wilkinson,[3] Dinesh Selvarajah,[2] and Solomon Tesfaye[2]





Greater energy usage in Painful- compared to Painless-DPN





Altered structure and function at the thalamus in Painful- compared to Painless-DPN

Neuronal hyperexcitability in Rodent models

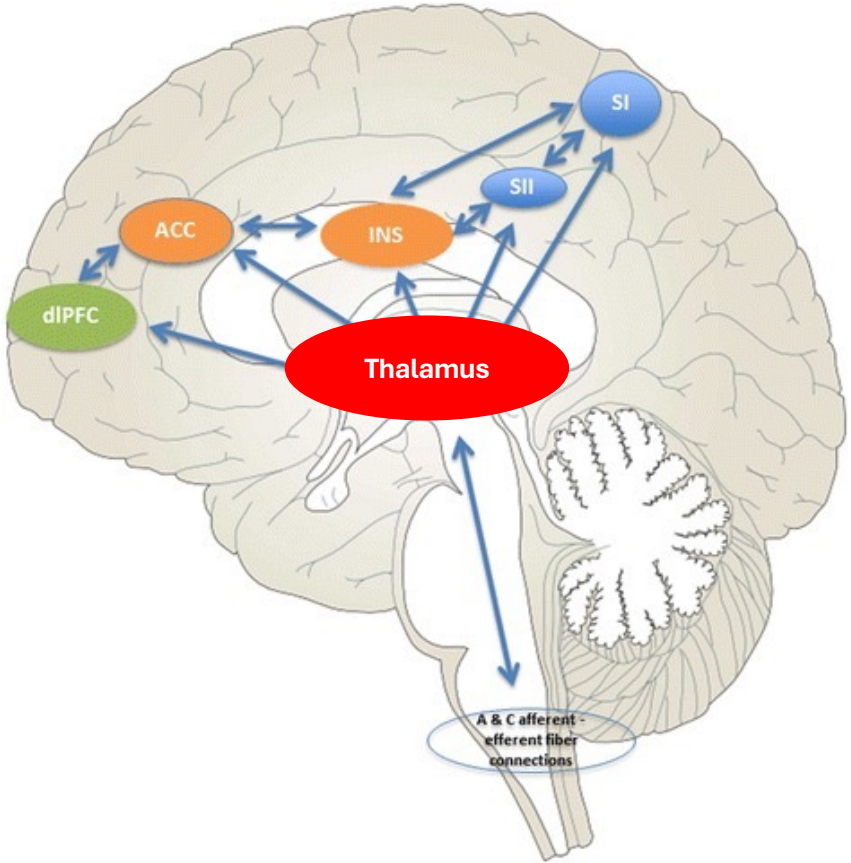
Fischer et al. 2009 Brain Res; Freeman et al. 2016 Eur J Neurosci

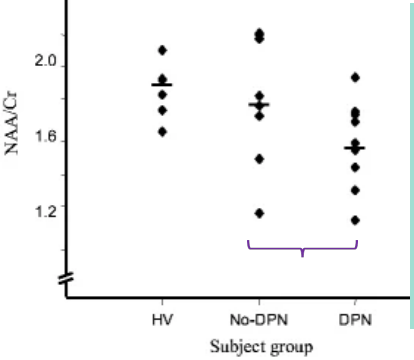
Hypervascularity

Selvarajah et al. Diabetes Care 2011.

Altered connectivity with other brain regions

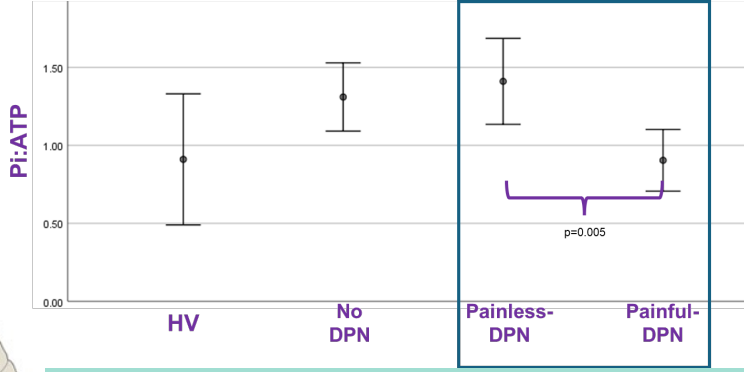
Croosu et al Diabetes Care 2023.

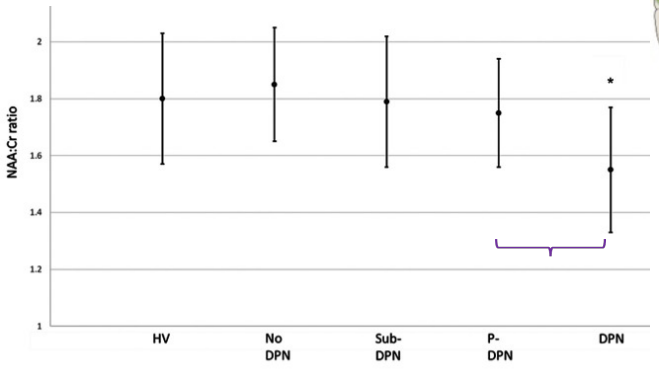


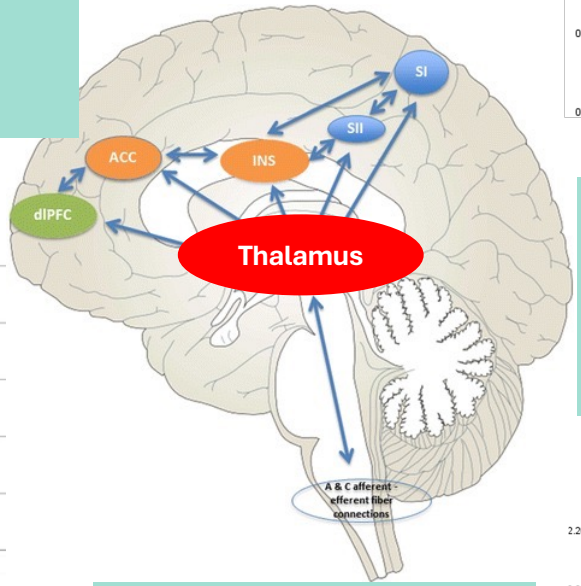


Thalamic neuronal dysfunction in DPN

Selvarajah et al. Diabetologia 2008







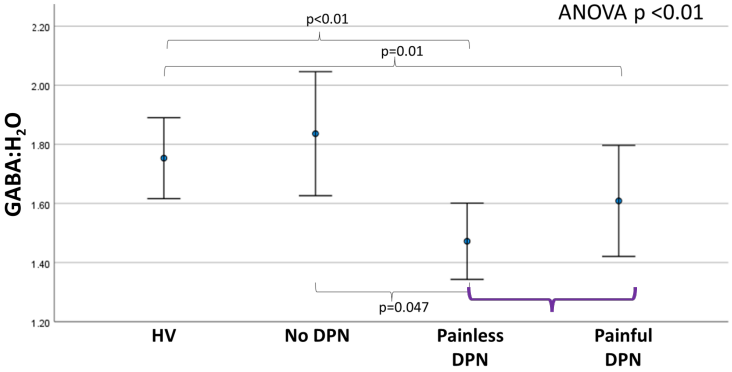
Normal levels of thalamic Pi:ATP in Painful-DPN, suggesting preserved **mitochondrial** function Sloan et al. unpublished

Normal levels of thalamic NAA in Painful-DPN, suggesting preserved **neuronal** function

Gandhi, Selvarajah, Sloan et al. Front Pain Res 2023

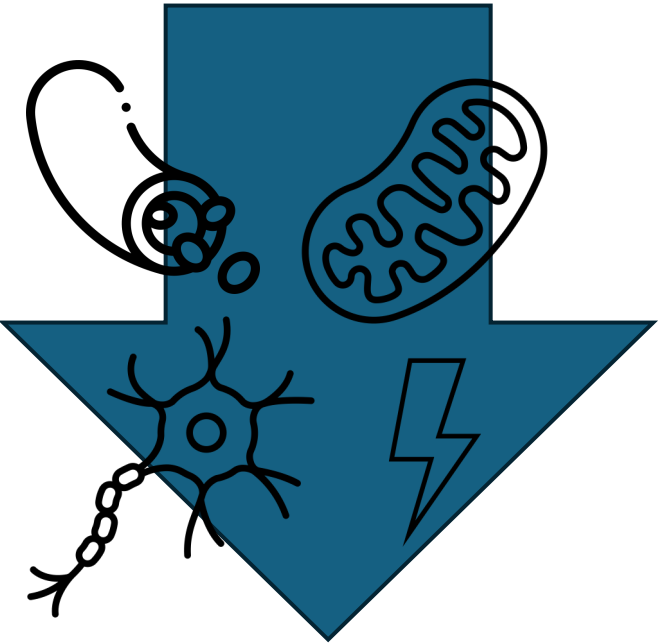
Partial preservation of GABA in Painful-DPN

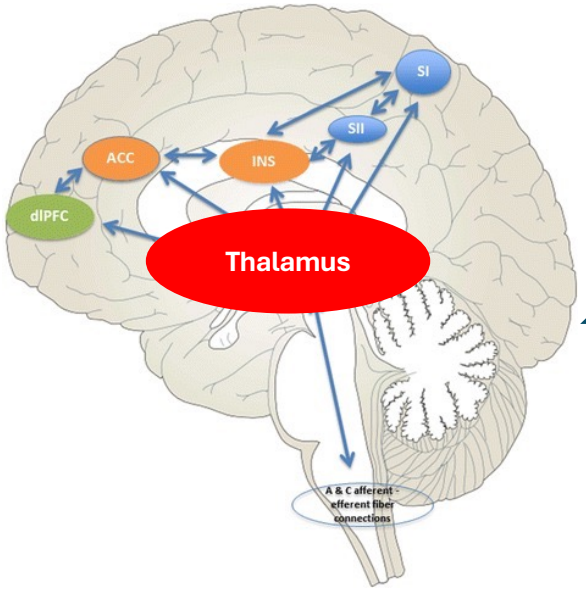
Shillo/Sloan et al. Diabetes 2024

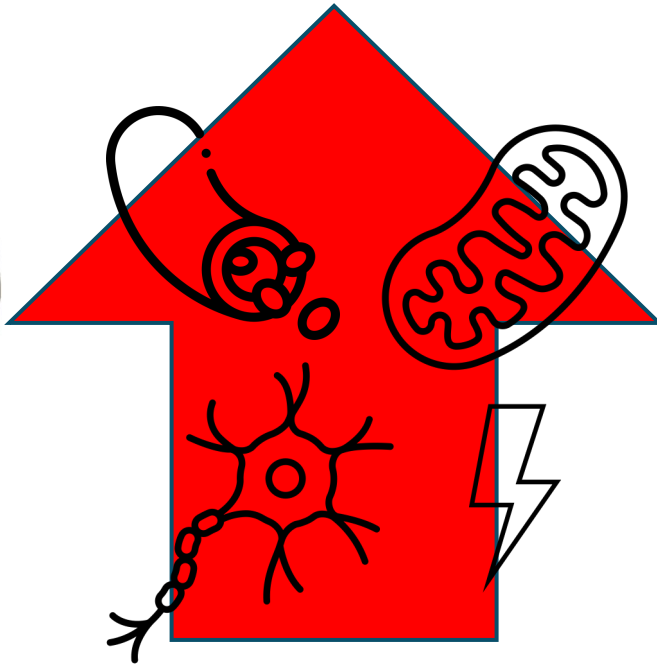


Thalamus preserved/hyperfunctioning in Painful-DPN

Painless - DPN







Painful - DPN

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An introduction to the current landscape of Painful-DPN

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Treating Painful-DPN

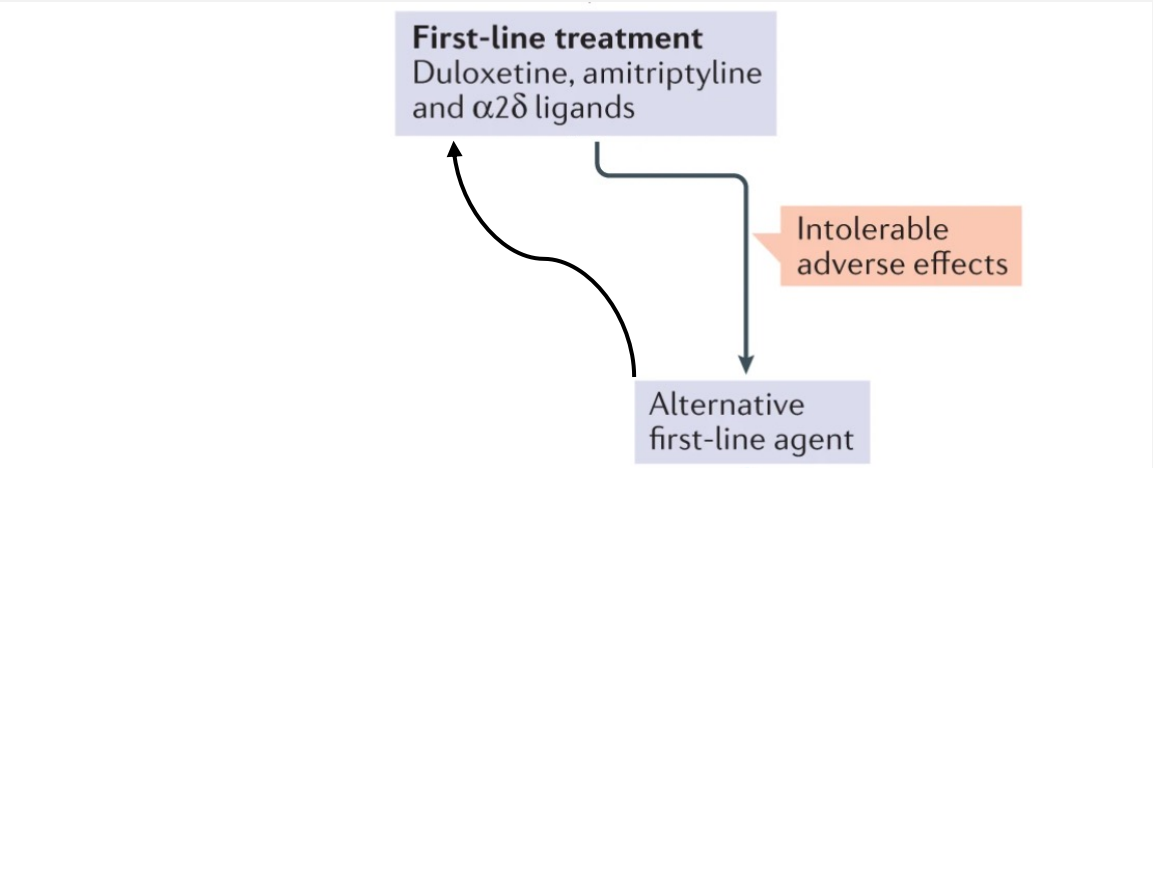
Future perspectives on personalized treatment using neuroimaging

Treatment of Painful-DPN

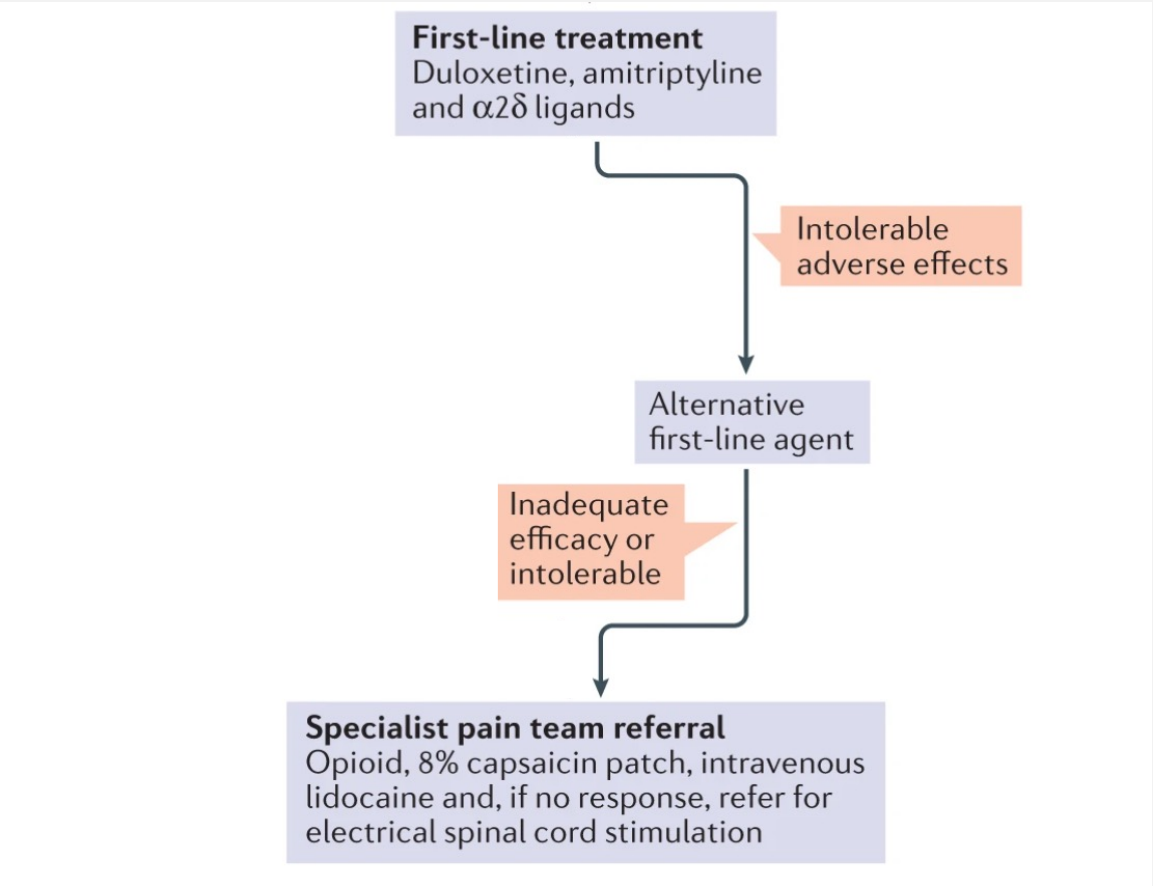
First-line treatment
Duloxetine, amitriptyline and α2δ ligands

University of Sheffield

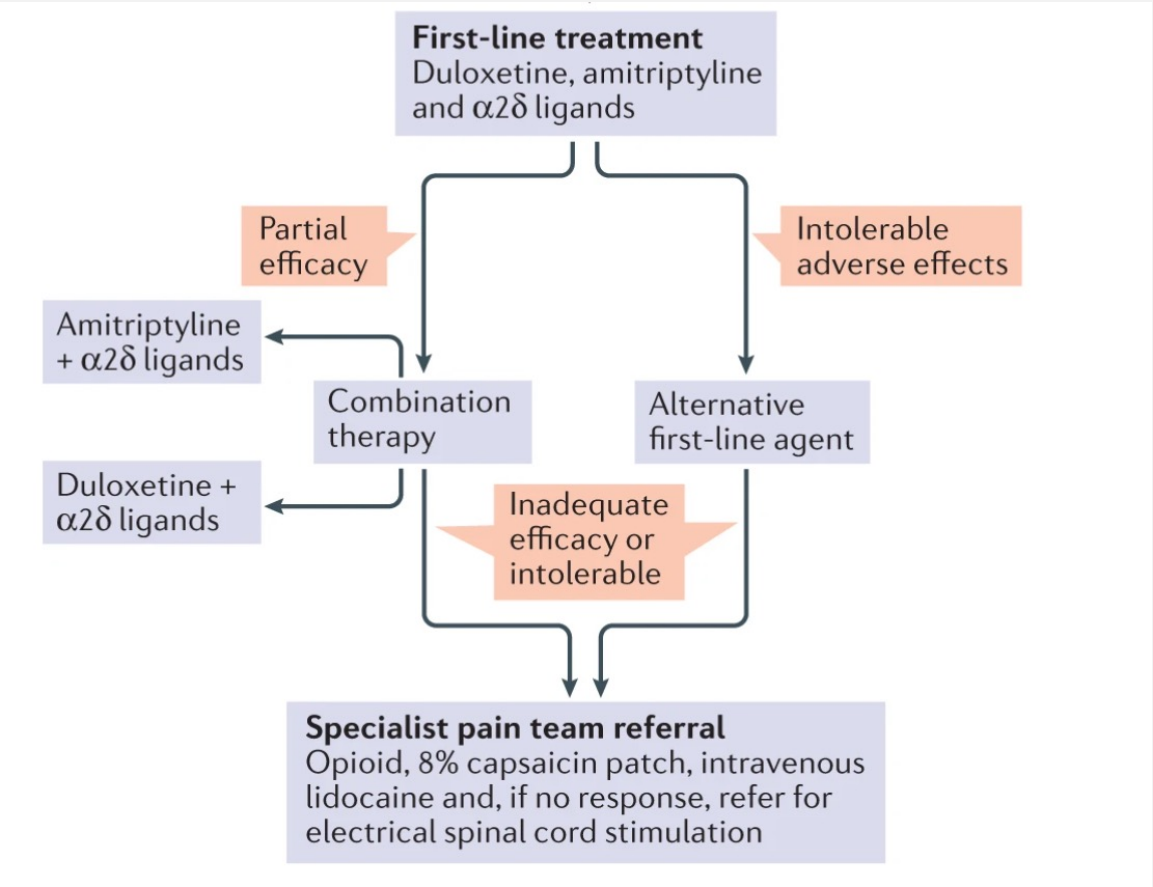
Treatment of Painful-DPN



Treatment of Painful-DPN



Treatment of Painful-DPN



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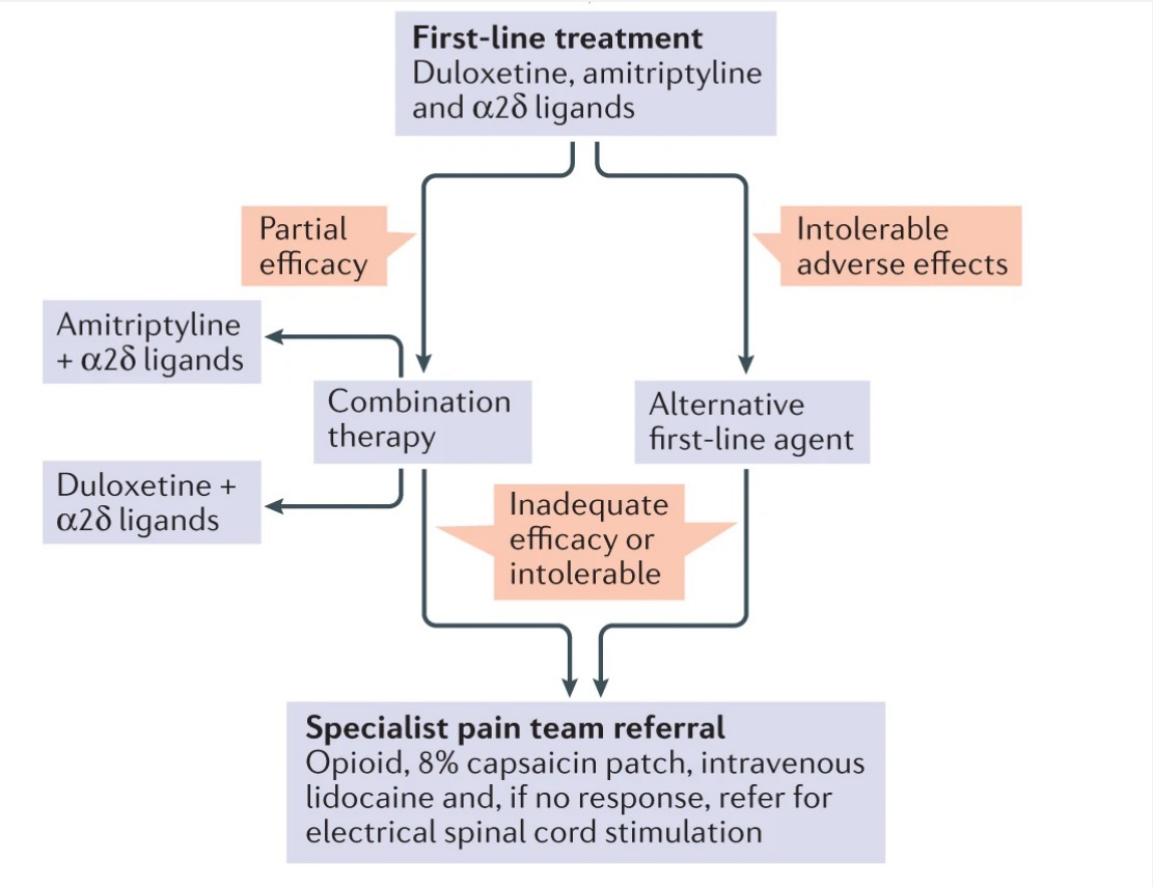
Sloan et al. Nat Rev Endo 2021

Treatment of Painful-DPN

Are any of the first line agents more effective?

Is there a combination of agents which is most effective?



THE LANCET

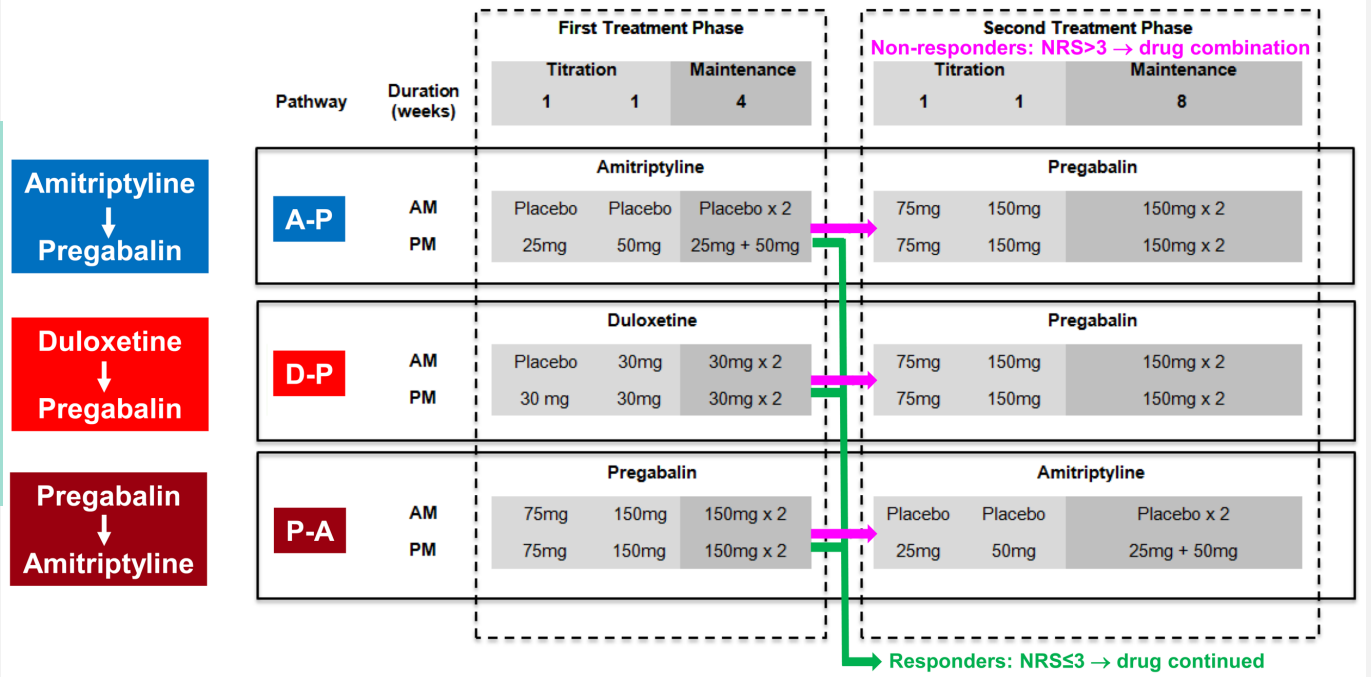
FUNDED BY
NIHR | National Institute for Health Research

Comparison of amitriptyline supplemented with pregabalin, pregabalin supplemented with amitriptyline, and duloxetine supplemented with pregabalin for the treatment of diabetic peripheral neuropathic pain (OPTION-DM): a multicentre, double-blind, randomised crossover trial

Solomon Tesfaye, Gordon Sloan, Jennifer Petrie, David White, Mike Bradburn, Stephen Julious, Satyan Rajbhandari, Sanjeev Sharma, Gerry Rayman, Ravikanth Gouni, Uazman Alam, Cindy Cooper, Amanda Loban, Katie Sutherland, Rachel Glover, Simon Waterhouse, Emily Turton, Michelle Horspool, Rajiv Gandhi, Deirdre Maguire, Edward B Jude, Syed H Ahmed, Prashanth Vas, Christian Hariman, Claire McDougall, Marion Devers, Vasileios Tsatlidis, Martin Johnson, Andrew S C Rice, Didier Bouhassira, David L Bennett, Dinesh Selvarajah, on behalf of the OPTION-DM trial group

OPTION-DM study

Aim: to assess the efficacy and tolerability of different combinations of first-line drugs for treatment of Painful-DPN



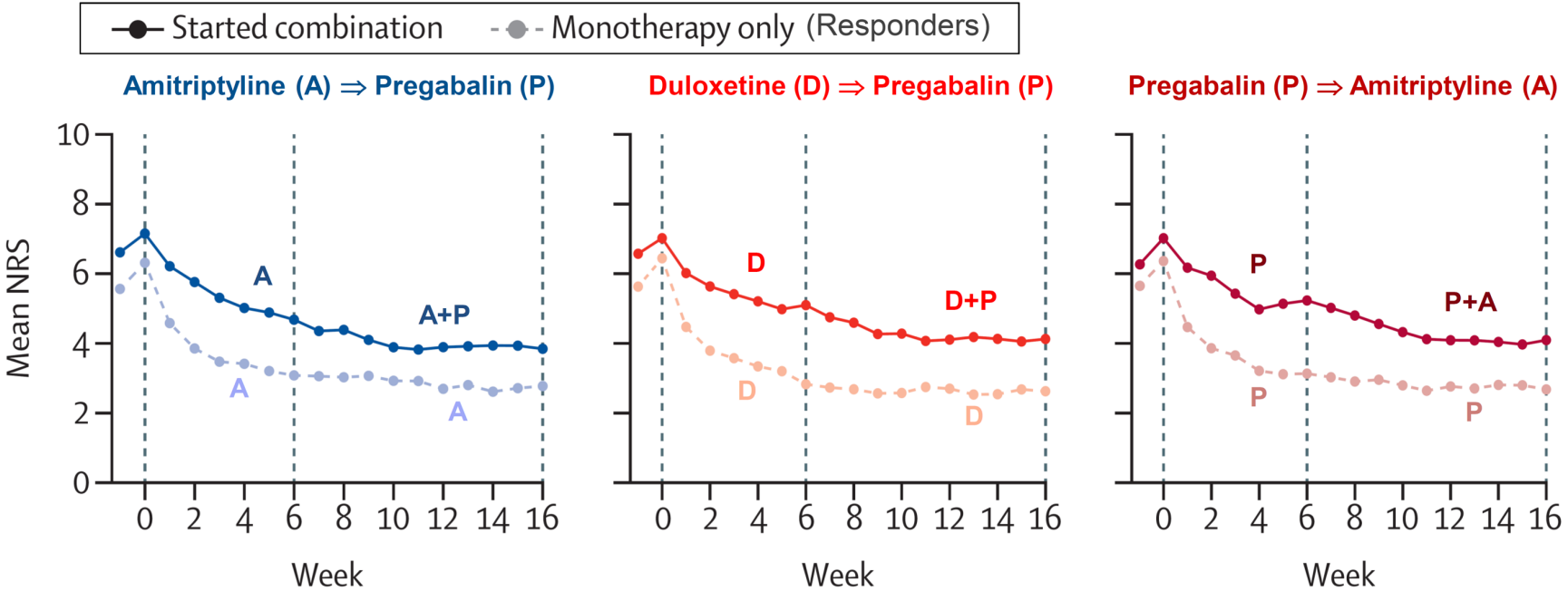
A, amitriptyline; D, duloxetine; DPNP, diabetic peripheral neuropathic pain; P, pregabalin.

1. Tesfaye S, Sloan G, Petrie J et al; OPTION-DM trial group. Comparison of amitriptyline supplemented with pregabalin, pregabalin supplemented with amitriptyline, and duloxetine supplemented with pregabalin for the treatment of diabetic peripheral neuropathic pain (OPTION-DM): a multicentre, double-blind, randomised crossover trial. *Lancet* 2022;400(10353):680–90.

OPTION-DM results

UK, 13 centers, n=130

Numerical rating scale (NRS) at week 16:	6.6 → 3.3
Mean difference between sequences:	0, -0.1, -0.1
Mean reduction for combo vs mono:	1.0 vs 0.2



1. Tesfaye S, Sloan G, Petrie J et al; OPTION-DM trial group. Comparison of amitriptyline supplemented with pregabalin, pregabalin supplemented with amitriptyline, and duloxetine supplemented with pregabalin for the treatment of diabetic peripheral neuropathic pain (OPTION-DM): a multicentre, double-blind, randomised crossover trial. *Lancet* 2022;400(10353):680–90.

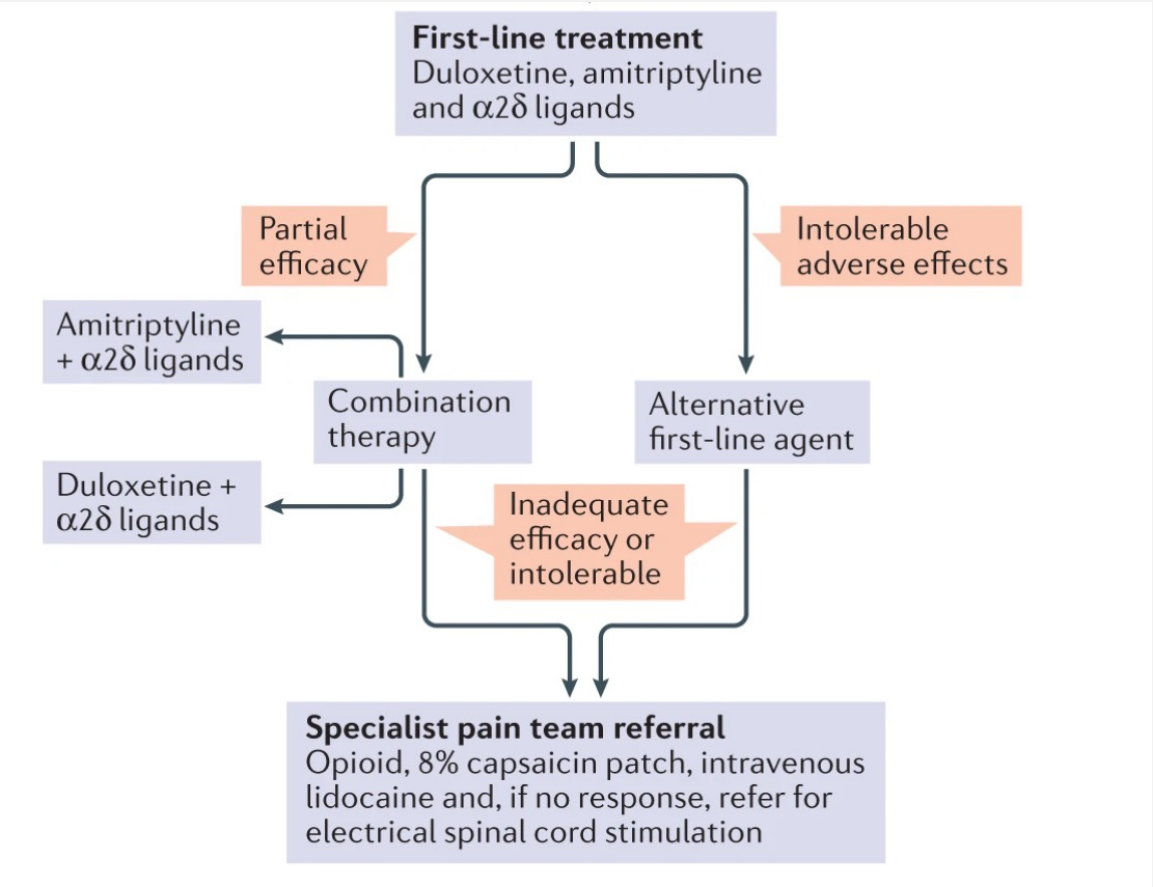
OPTION-DM summary of conclusions

- Amitriptyline (**A**), duloxetine (**D**) and pregabalin (**P**) are equally efficacious
- **A-P, D-P** and **P-A** pathways are equally efficacious
- Compared to monotherapy, combination therapy leads to:
  - a further NRS drop of 1
  - 14% more >50% pain relief (40%→54%)
  - 18% greater achievement of NRS <3 (36%→54%)
- Combination therapy is well-tolerated, with AEs well recognized for the drugs
- The **P-A** pathway had the fewest monotherapy discontinuation due to TEAEs (p=0.031) and was numerically the preferred pathway (**A-P** 24%, **D-P** 33% and **P-A** 43%, p=0.26)

AE, adverse events; NRS, numerical rating scale; TEAEs, treatment-emergent adverse events.

1. Tesfaye S, Sloan G, Petrie J et al; OPTION-DM trial group. Comparison of amitriptyline supplemented with pregabalin, pregabalin supplemented with amitriptyline, and duloxetine supplemented with pregabalin for the treatment of diabetic peripheral neuropathic pain (OPTION-DM): a multicentre, double-blind, randomised crossover trial. *Lancet* 2022;400(10353):680–90.

Treatment of Painful-DPN



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Sloan et al. Nat Rev Endo 2021

Outline

An introduction to the current landscape of Painful-DPN

Risk Factors for Painful-DPN

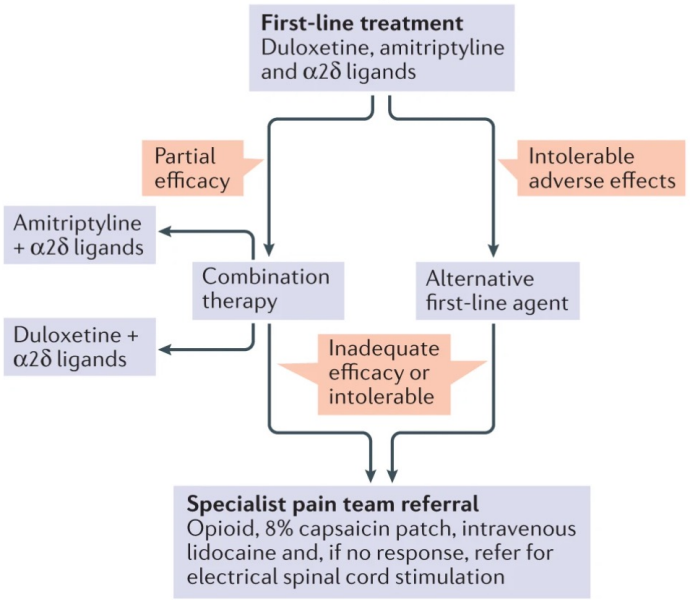
Brain involvement in Painful-DPN

Treating Painful-DPN

Future perspectives on neuroimaging biomarkers for Painful-DPN

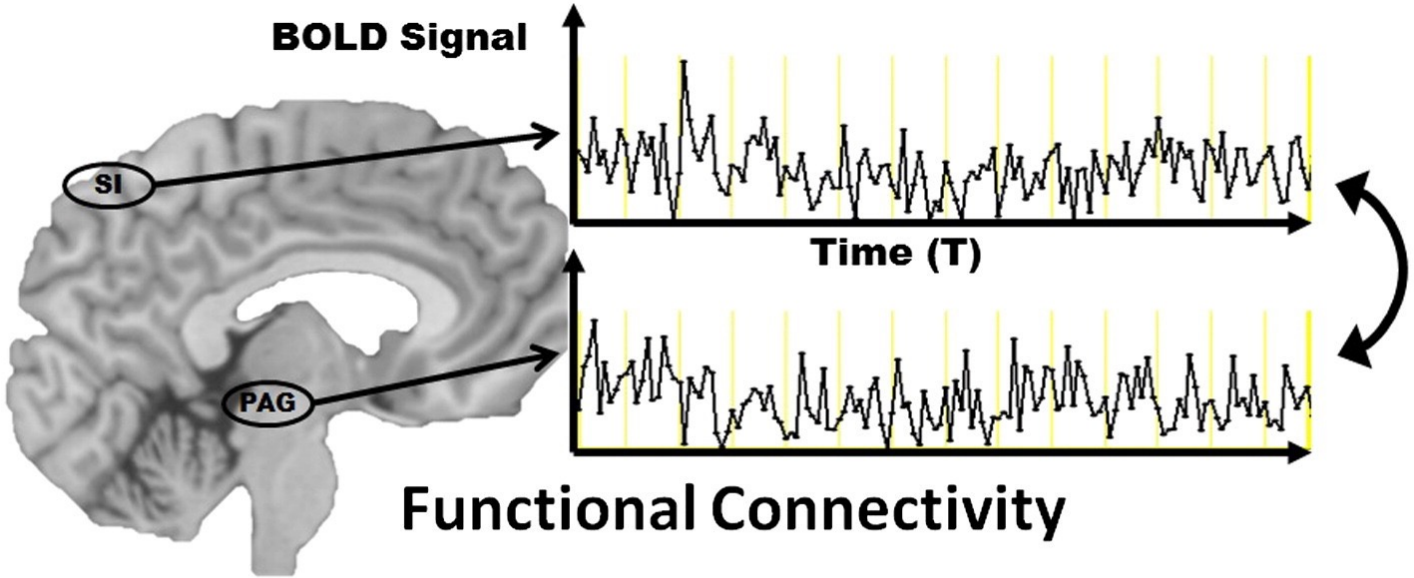
Why do we need biomarkers of Painful-DPN

- Treatment of Painful-DPN inadequate
- Treatments used empirically
- Heterogeneity of clinical features
- Clinical outcomes in pain trials subjective and susceptible to bias



Jensen TS, et al. Diab Vasc Dis Res. 2006

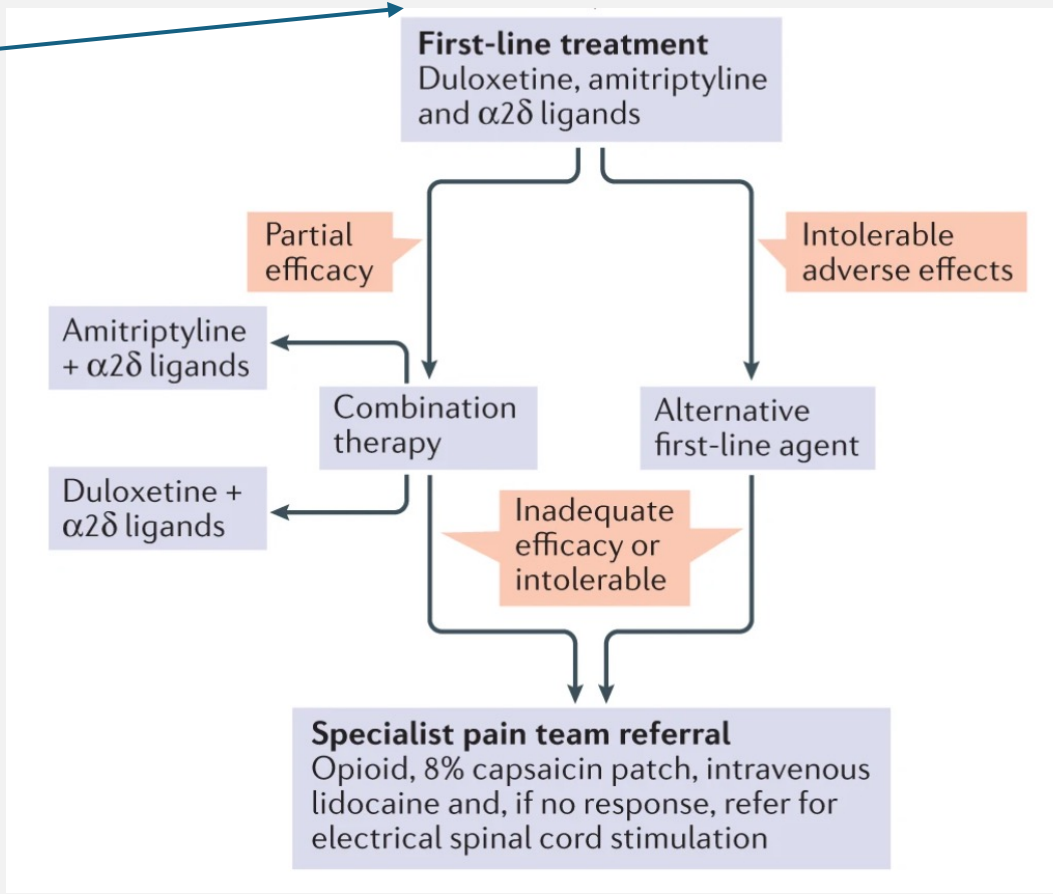
Resting state functional MRI



Gay et al. 2014 J Manipulative Physiol Ther

How neuroimaging biomarkers might improve the management of Painful-DPN

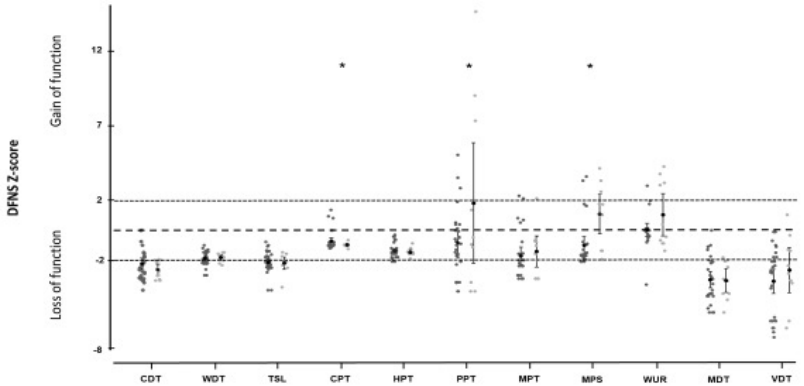
- Determining phenotypes of Painful-DPN

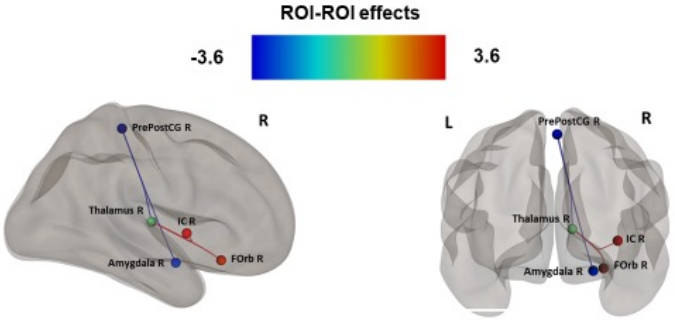


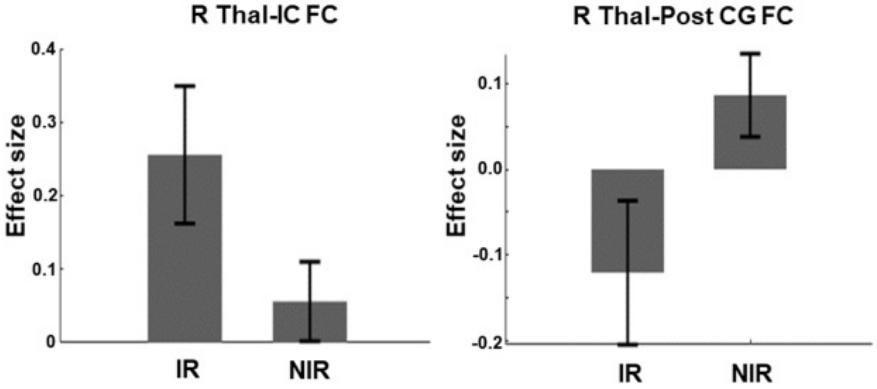
Somatosensory network functional connectivity differentiates clinical pain phenotypes in diabetic neuropathy

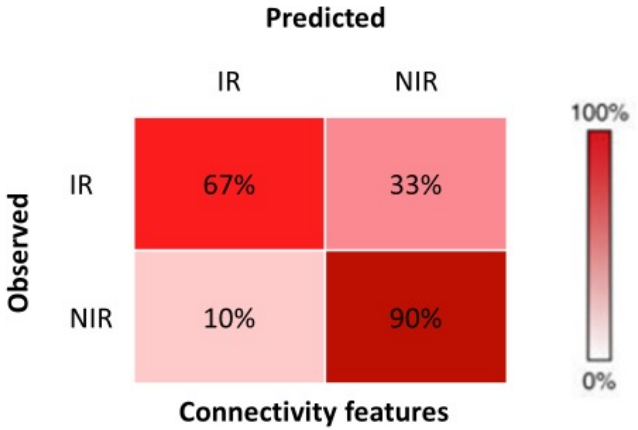
Diabetologia

Kevin Teh[1] · Iain D. Wilkinson[1] · Francesca Heiberg-Gibbons[2] · Mohammed Awadh[2] · Alan Kelsall[3] · Shillo Pallai[3] · Gordon Sloan[3] · Solomon Tesfaye[3] · Dinesh Selvarajah[2]



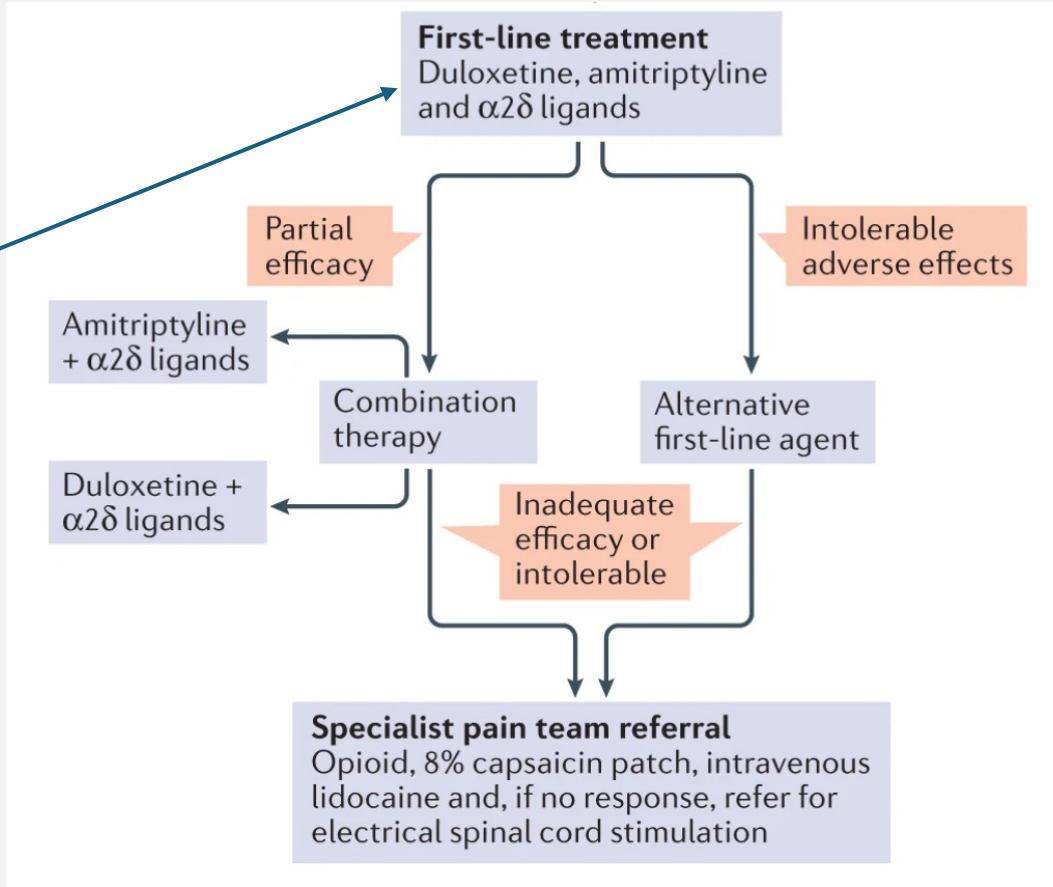






How neuroimaging biomarkers might improve the management of Painful-DPN

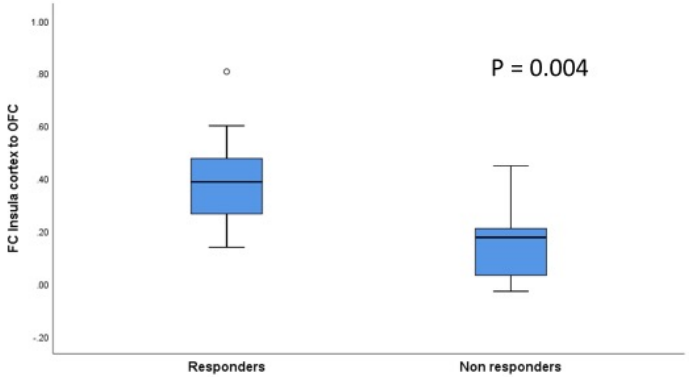
- Determining phenotypes of Painful-DPN
- Stratifying patients to treatments

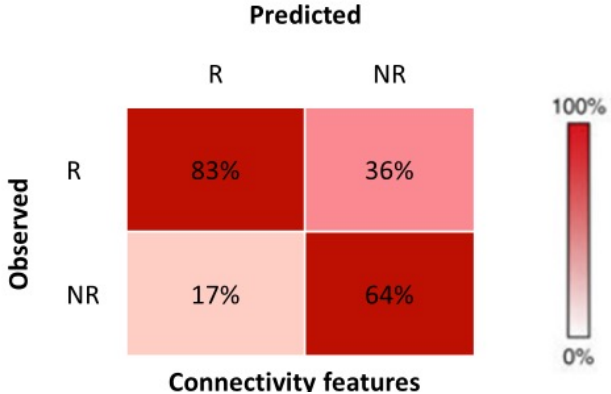


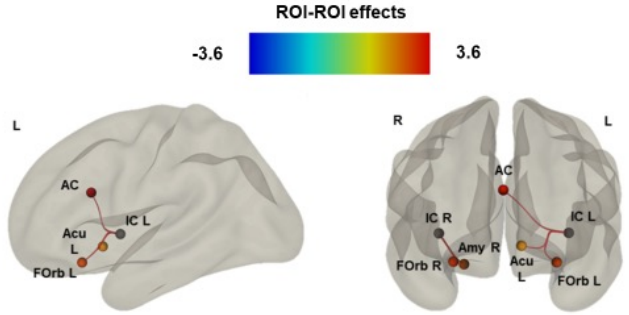
Determinants of Treatment Response in Painful Diabetic Peripheral Neuropathy: A Combined Deep Sensory Phenotyping and Multimodal Brain MRI Study

diabetes

Iain David Wilkinson,[1] Kevin Teh,[1] Francesa Heiberg-Gibbons,[2] Mohammad Awadh,[2] Alan Kelsall,[3] Pallai Shillo,[3] Gordon Sloan,[3] Solomon Tesfaye,[3] and Dinesh Selvarajah[2]





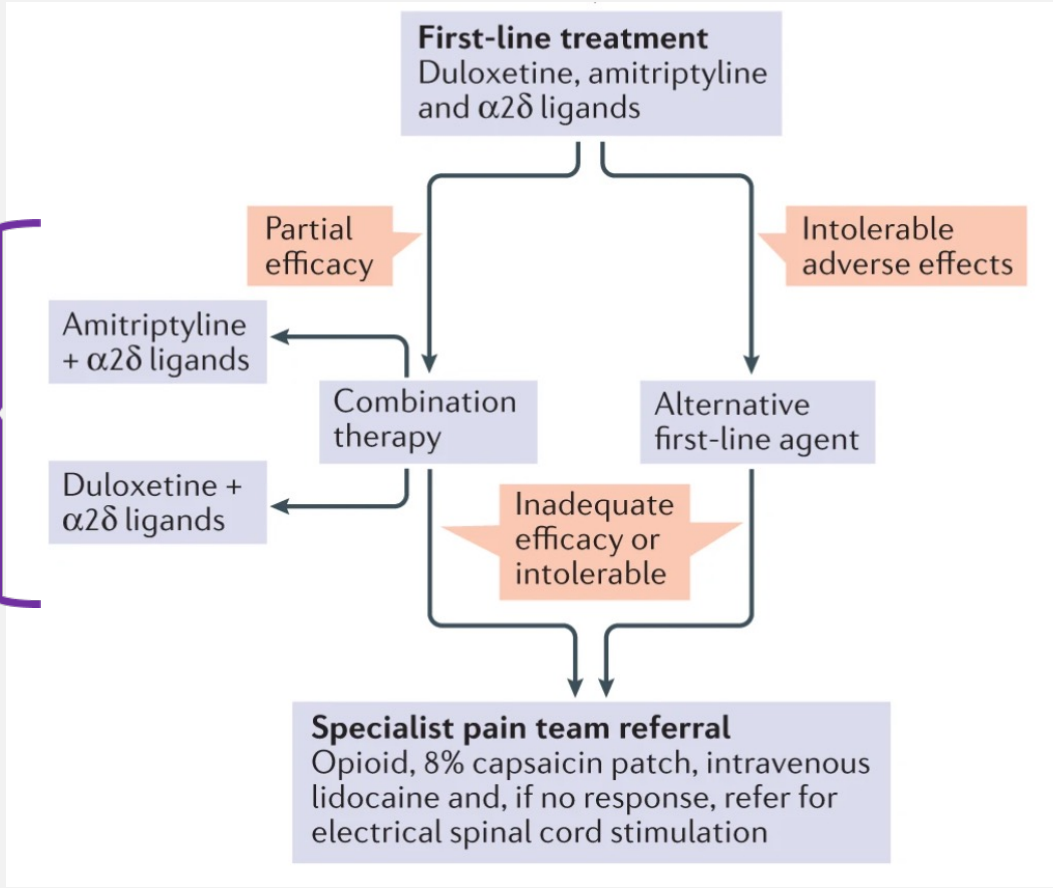


Individual differences in treatment response could be related to at least two factors:

1. Diagnostic heterogeneity
2. Variable brain 'wiring' patterns (i.e. capacity for target engagement)

How neuroimaging biomarkers might improve the management of Painful-DPN

- Determining phenotypes of Painful-DPN
- Stratifying patients to treatments
- Developing surrogate outcomes for clinical trials



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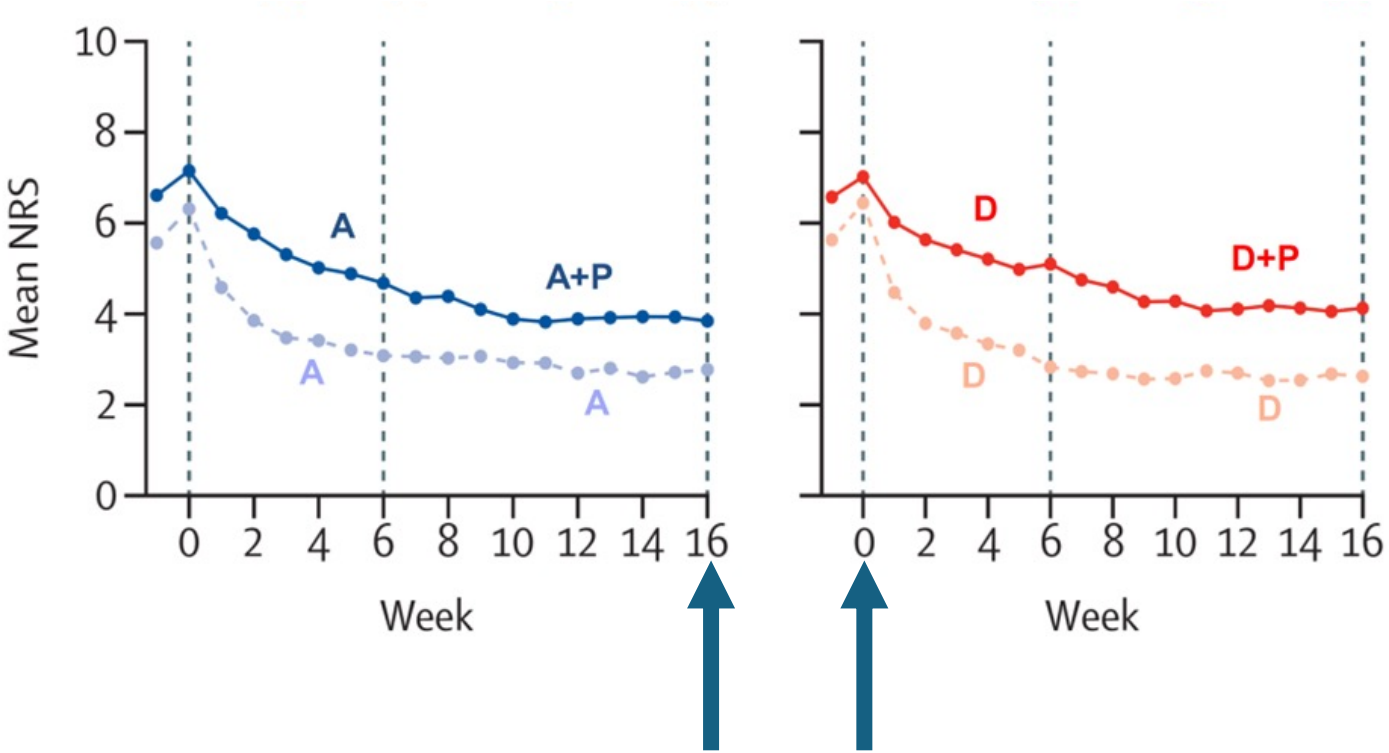
Increased Thalamocortical Functional Connectivity on Discontinuation of Treatment in Painful Diabetic Peripheral Neuropathy

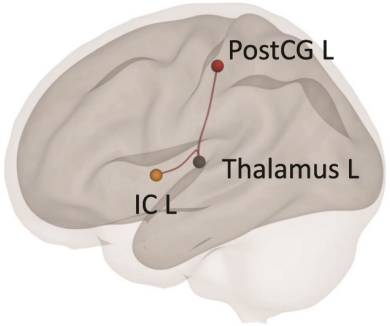
diabetes

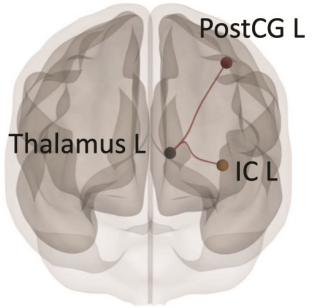
Gordon Sloan,[1,2] Kevin Teh,[3] Sharon Caunt,[2] Iain Wilkinson,[3] Dinesh Selvarajah,[1,2] and Solomon Tesfaye[1,2]



Thalamocortical engagement associated with a rise in pain intensity

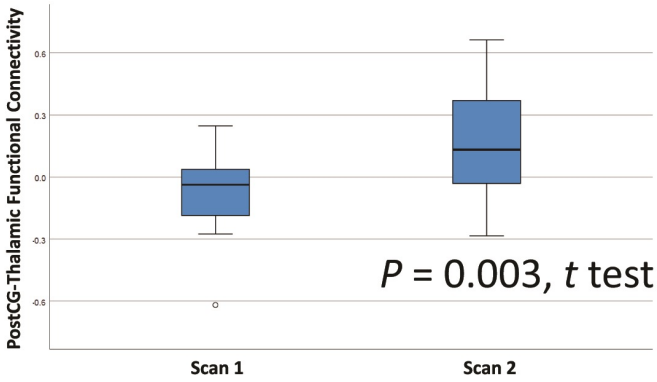
Greater functional connectivity between the thalamus and primary somatosensory and insular cortex on stopping analgesia

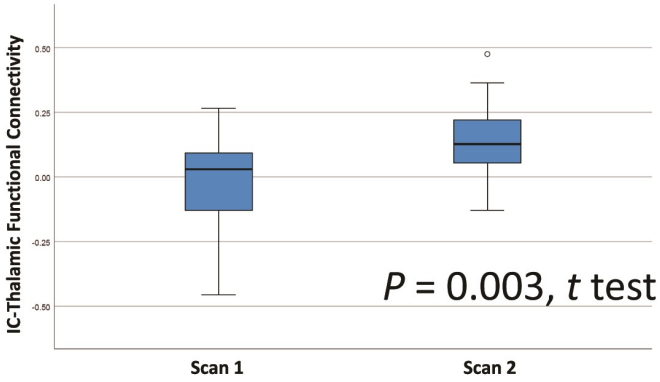




ROI-to-ROI effects:

-3.57 3.57





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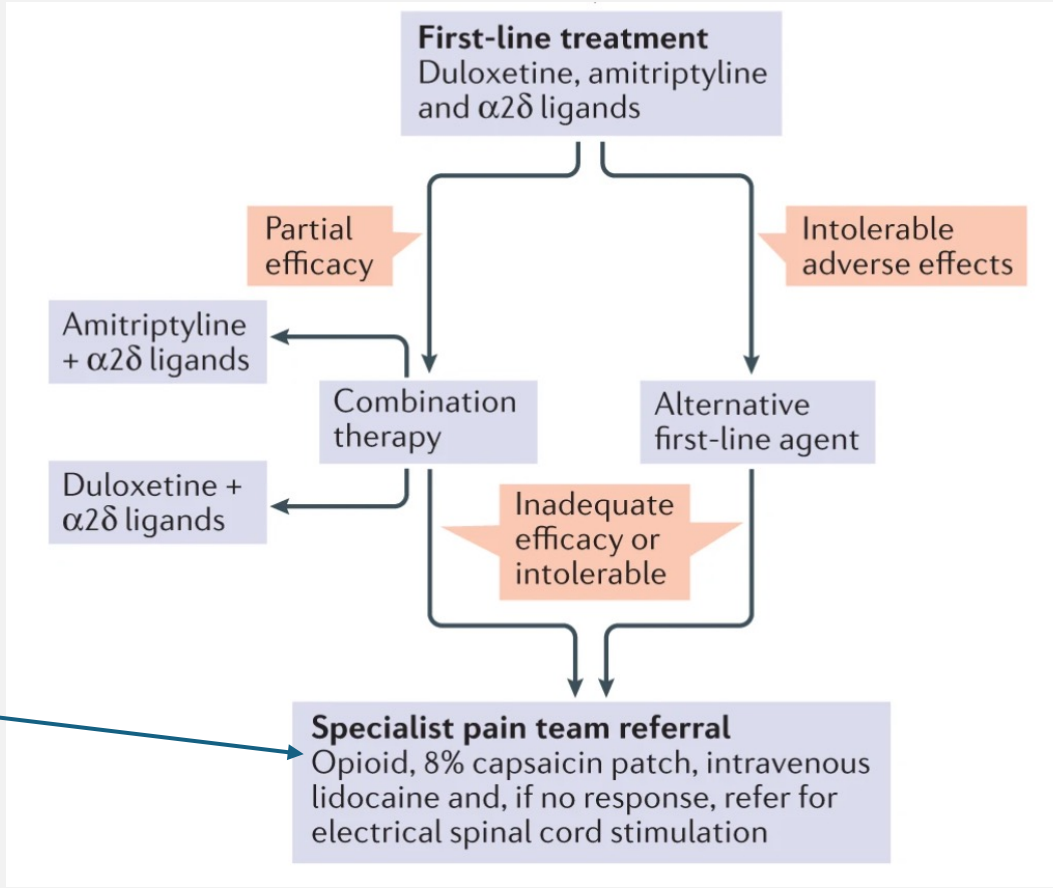
How neuroimaging biomarkers might improve the management of Painful-DPN

- Determining phenotypes of Painful-DPN
- Stratifying patients to treatments
- Developing surrogate outcomes for clinical trials
- Monitoring of negative consequences of potentially harmful treatments



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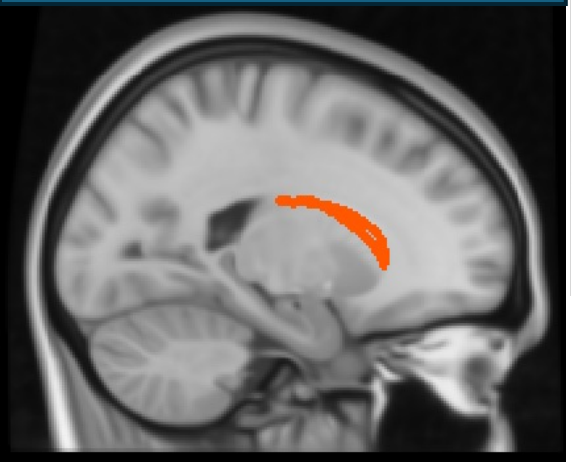
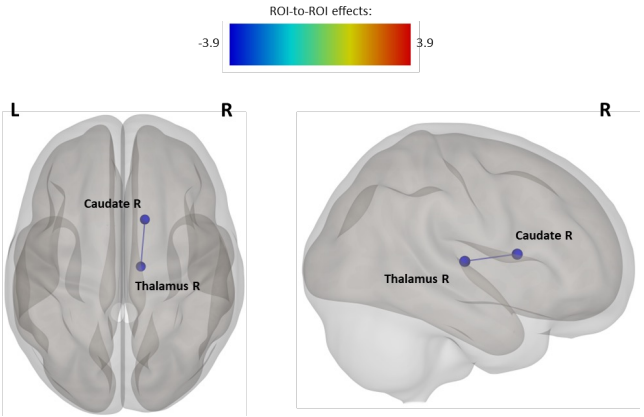
Beyond pain relief: the effects of chronic opioid use on brain structure and function in diabetic neuropathy—a multimodal neuroimaging study

Diabetologia

Gordon Sloan[1,2] · Kevin Teh[2] · Marni Greig[1] · Pallai Shillo[1] · Sharon Caunt[1] · Iain D. Wilkinson[2] · Solomon Tesfaye[2] · Dinesh Selvarajah[2]

Greater caudate volume



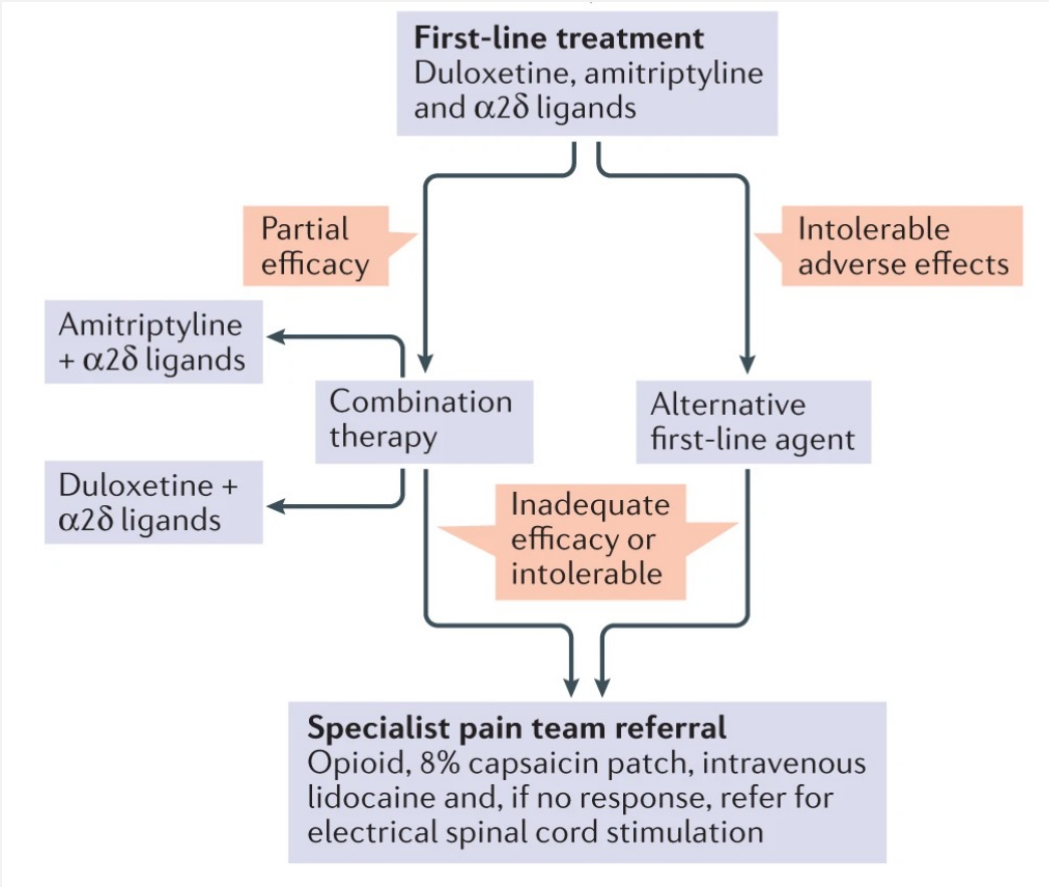


Altered connectivity in dopaminergic pathways

Disruption of dopaminergic pathways may reflect alterations in reward and stimulus-response systems

How neuroimaging biomarkers might improve the management of Painful-DPN

- Determining phenotypes of Painful-DPN
- Stratifying patients to treatments
- Developing surrogate outcomes for clinical trials
- Monitoring of negative consequences of potentially harmful treatments



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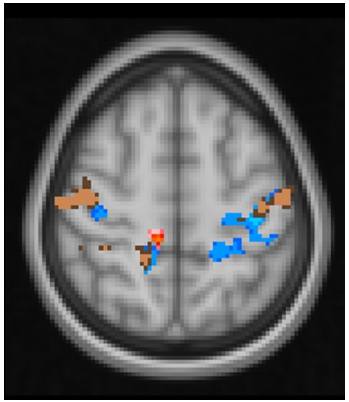
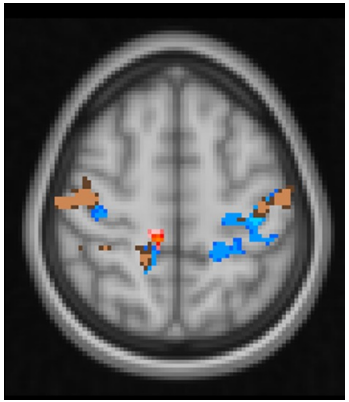
Conclusions

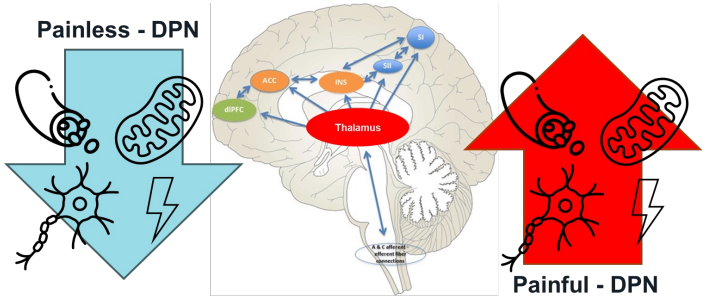


CNS involvement in DPN

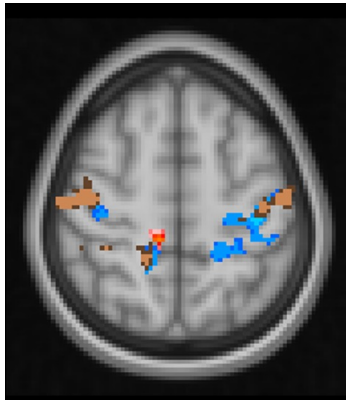
Conclusions

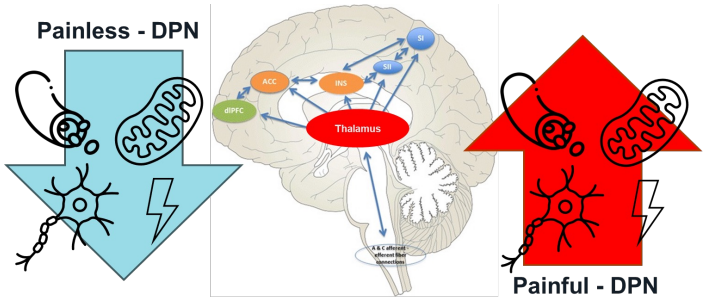


Brain function differentiates Painful- and Painless-DPN

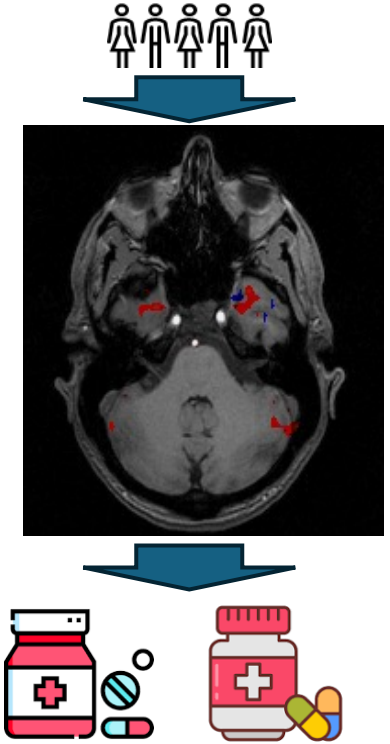


Conclusions

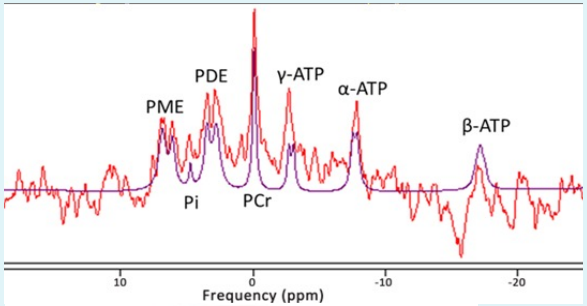


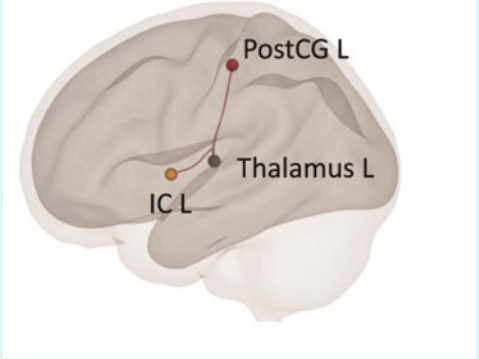


Neuroimaging measures could act as biomarkers in Painful-DPN



Investigating the efficacy of neuroimaging biomarkers for neuropathic pain in DPN

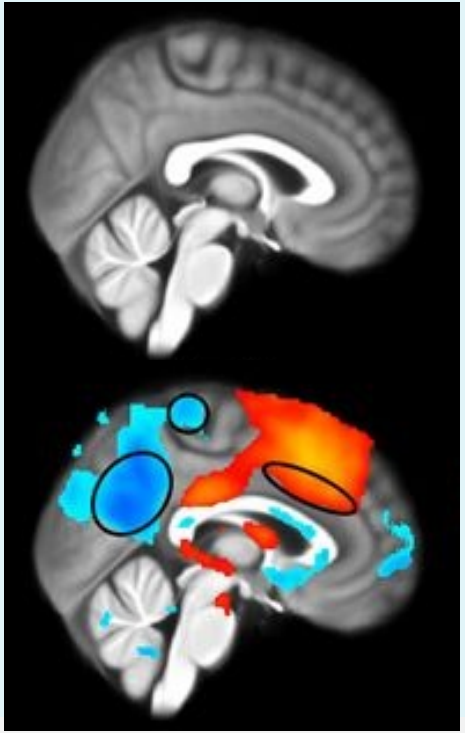




N=50

On analgesia

After analgesia washed out



Aim: To develop dynamic biomarkers of Painful-DPN

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NHS
Sheffield Teaching Hospitals
NHS Foundation Trust

NIHR | National Institute for Health Research

EFSD European Foundation for the Study of Diabetes

Breakthrough T1D™
Formerly JDRF

DIABETES CARE TRUST

Association of British Clinical Diabetologists

P&G

Sheffield Hospitals Charity

Collaborators

Sheffield

- Kevin Teh
- Adriana Anton
- Shillo Pallai
- Marni Greig
- Shaan Goonoo
- Jackie Elliott
- Rajiv Gandhi
- Clinical Research facility staff
- Clinical Trials research Unit
- Division of Imaging

Imperial College London:
Praveen Anand

Nottingham Trent University:
Richard Hulse

The Johns Hopkin University School of Medicine:
Richard Edden

Philippines:
Pepito Dela Pena
Aimee Andag-Silva

University College London:
Lynda Stevens and EURODIAB complications group

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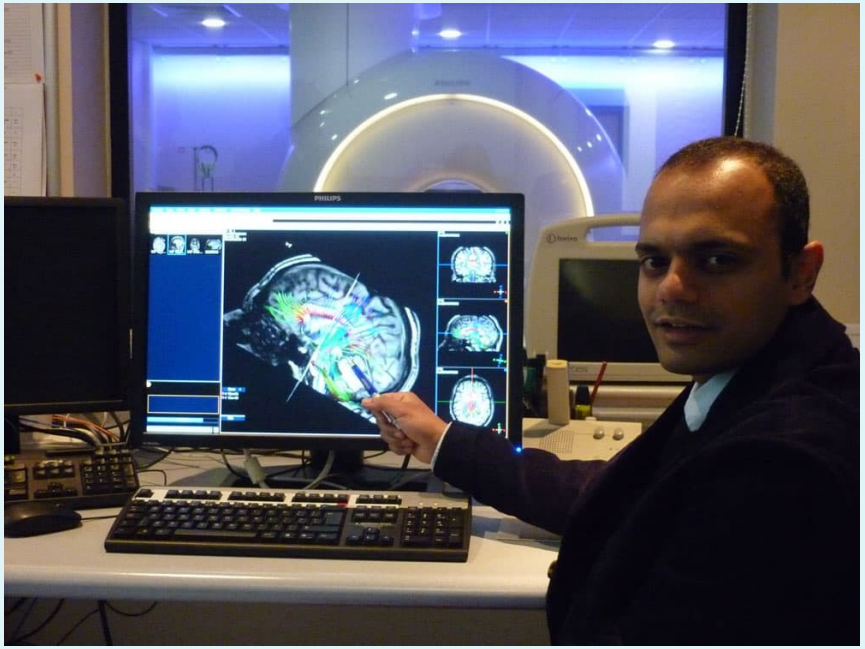
Sheffield Teaching Hospitals
NHS Foundation Trust

University of Sheffield

Professor Solomon Tesfaye

Dr Dinesh Selvarajah



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