

Title: An action networks model for pain reveals cortical neuromodulation targets

Authors: David P. Darrow^{1,2†*}; Alexander B. Herman^{2†}; Tariq Hattab¹; Seth König^{1,2}; Robert Hermosillo^{3,5}; Julia Moser^{3,5}; Sanju Koirala^{3,5}; Gracie Grimsrud³; Samuel R. Krimmel⁶; Ziad Nahas²; Oscar Miranda-Dominguez^{3,4}; Steven M. Nelson^{3,4}; Evan M. Gordon^{7,8}; Nico U.F. Dosenbach^{6,9-11}; Damien A. Fair^{2-5*}

Affiliations:

¹ Department of Neurosurgery, University of Minnesota; Minneapolis, MN, USA.

² Department of Psychiatry, University of Minnesota; Minneapolis, MN, USA.

³ Masonic Institute for the Developing Brain, University of Minnesota; Minneapolis, MN, USA.

⁴ Department of Pediatrics, University of Minnesota; Minneapolis, MN, USA.

⁵ Institute of Child Development, University of Minnesota; Minneapolis, MN, USA.

⁶ Department of Neurology, Washington University School of Medicine; St. Louis, MO, USA.

⁷ Department of Radiology, Washington University School of Medicine; St. Louis, MO, USA.

⁸ Department of Neuroscience, Washington University School of Medicine; St. Louis, MO, USA.

⁹ Department of Pediatrics, Washington University School of Medicine; St. Louis, MO, USA.

¹⁰ Department of Psychological & Brain Sciences, Washington University; St. Louis, MO, USA.

¹¹ Department of Biomedical Engineering, Washington University; St. Louis, MO, USA.

†These authors contributed equally to this work

*Corresponding authors: darro015@umn.edu (D.P.D.) and faird@umn.edu (D.A.F.)

Abstract

Chronic neuropathic pain is a debilitating condition, difficult to treat, and associated with poor outcomes, including addiction and suicide. Neuromodulation of primary motor cortex and dorsolateral prefrontal cortex (dlPFC) alleviates neuropathic pain in some cases, though the mechanism remains unknown. Recent advances in functional MRI led to the identification of the Somato-Cognitive Action Network (SCAN) within the primary motor cortex, and Action Mode Network (AMN) represented in the dlPFC. Both networks are important for pain perception, suggesting the previously baffling analgesic effects of motor cortex stimulation were likely due to modulation of action-relevant pain signals in these newly recognized networks. Inter-individual differences in SCAN and AMN provide a plausible explanation for the varied effectiveness of current neuromodulation targeting methods for chronic pain. Our novel action feedback-loop pain-control model suggests that personalized, precision targeting of the AMN and SCAN will improve chronic pain management, paving the way for future neuromodulatory treatments.

Introduction

Chronic pain, defined as pain persisting for more than three months, is one of the most common pervasive health issues, affecting approximately 20.4% (11-40%) of the US adult population¹. It is one of the most debilitating health conditions in the world, significantly reducing quality of life². Contrary to acute pain, which alerts the body to potential harm, chronic pain is better characterized as a maladaptive physiological condition with no apparent evolutionary benefit².

Neuropathic pain is a consequence of damage or disease affecting the somatosensory nervous system³. In clinical practice, neuropathic pain most commonly results from dysfunction in the peripheral nervous system, such as painful diabetic neuropathy and postherpetic neuralgia⁴. Less commonly, neuropathic pain can also result from diseases affecting the central nervous system, known as central neuropathic pain⁴. Central pain syndromes can result from conditions such as amputation, stroke, multiple sclerosis, or spinal cord injury⁵. Central pain syndromes are highly resistant to pharmacological treatments and often result in poor outcomes, typically requiring high doses of sedating medications and often lead to suicide⁶. The dearth of effective treatments, along with the desperation of patients and families, has also led to overprescription of opioids, resulting in misuse and contributing to the current opioid epidemic in adults^{1,7,8}, and even children^{8,9}. Improving our mechanistic understanding and treatment of central neuropathic pain has enormous implications for expanding therapeutic options for chronic pain syndromes overall, including those that lead to Opioid Use Disorder (OUD).

This overview examines non-pharmacological neuropathic pain management, focusing on neuromodulation. It highlights groundbreaking new research using precision functional brain mapping^{10,11}, which is providing a new perspective on how the cortex influences pain perception and control over the sensorimotor system (“action-control”). Synthesizing existing data with new insights, we propose an updated pain control model, in which the perception of pain serves as the most salient and urgent feedback signal for guiding action. This model suggests specific cortical nodes for imaging-guided, personalized, invasive, and non-invasive neuromodulation as a promising future direction for treating chronic neuropathic pain.

Current approaches to chronic neuropathic pain management are often insufficient

Nearly all chronic neuropathic pain patients go through traditional pharmacological treatment, including non-steroidal anti-inflammatories (NSAIDs), antidepressants (e.g., Tricyclic antidepressants (TCAs), Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)), and

anticonvulsants (e.g., gabapentin) ¹². However, these medications are effective in less than 50% of patients and associated with adverse effects that can be deleterious to the patient's quality of life ¹³. They carry well-known risks of gastrointestinal bleeding and cardiovascular events (NSAIDs), side effects like weight gain and cardiac complications (antidepressants), and dizziness or cognitive impairment (anticonvulsants). Using opioids to treat chronic pain carries the risks of opioid misuse (~25%) and addiction (10%) ⁷. Associated opioid overdose deaths total about ~85,000 per year in the US alone ¹⁴. About 23% of patients with persistent chronic pain will harbor suicidal ideation, and more than 15% will attempt suicide ¹⁵. As a result, the search for effective non-pharmacological chronic pain treatments, such as invasive and non-invasive neuromodulation, has become a top priority.

Neurostimulation methods for the treatment of chronic pain have been developed for targets throughout the central nervous system, including spinal cord stimulation (SCS), subcortical deep brain stimulation (DBS), and cortical stimulation (CS). In SCS, electrodes are implanted epidurally to deliver modulatory pulses to the spinal cord with the aim of reducing pain signaling in the dorsal root ganglia or higher levels ¹⁶. SCS is FDA-approved to manage chronic intractable pain of the trunk and limbs, including failed back surgery syndrome (FBSS), complex regional pain syndrome (CRPS) types 1 and 2, refractory angina pectoris (RAP), painful diabetic neuropathy, and nonsurgical back pain¹⁷. However, even with careful selection of patients refractory to maximum medical therapy, a substantial percentage do not respond (25-50%) ¹⁸. SCS carries a complication rate of 30-40%, including hardware-related problems such as lead migration or failure, as well as surgical risks such as infection, surgical site pain, erosions, or even spinal cord injury ¹⁹. SCS remains ineffective for central pain syndromes, and its precise mechanisms remain elusive ¹⁸.

Deep brain stimulation (DBS), successfully used to treat movement disorders such as Parkinson's disease and essential tremor, has also been explored as a potential pain treatment for over fifty years ²⁰. DBS was once thought a promising method for neuropathic pain control, even achieving FDA approval for pain management in 1977, albeit temporarily ²¹. Pain DBS targets have spanned the thalamus (ventral posterolateral/ventral posteromedial (VPL/VPM) nuclei, the internal capsule (IC), and the centromedian-parafascicular complex (CM-Pf)), the periaqueductal/periventricular gray matter (PAG/PVG), the anterior cingulate cortex (ACC), and ventral striatum ²²⁻²⁴. DBS's mechanism of action for neuropathic pain reduction is not fully understood. It has been hypothesized that stimulation of the thalamus's CM-Pf may provide pain relief through its action on inhibitory downstream targets, like the periaqueductal gray (PAG) ²³,

and indirectly the rostral ventromedial medulla (RVM)²⁵. These descending modulatory circuits are opioid-sensitive and have been known to promote the inhibition of nociceptive ascending pathways, which made them natural targets.

Unfortunately, prospective DBS studies have yielded discouraging findings^{24,26,27}, and only limited relief, particularly for central pain^{24,26}. Nonetheless, DBS continues to be used off-label in the US and Europe for pain management in highly specialized centers^{22,28}. Commonly reported complications include intracranial hemorrhage (0.3 - 2%), seizures (<1%), stroke (<1%), and hardware-related complications (e.g., infection: 5 - 6.1%, erosions: 1.3%, lead migration: 5.1% of patients)^{22,29}. In light of these shortcomings, the ongoing quest for more effective pain treatments has shifted towards cortical neuromodulation.

Cortex can powerfully modulate pain perception

The cortex's role in modulating pain has been recognized for over a century. The first indications of the cortex's importance for pain control came from Nobel Prize-winning work by Sir Charles Sherrington, who originally coined the term nociception. By demonstrating an increase in nociceptive reflexes following spinal cord transection, Sherrington correctly postulated spinal cord transmission to be modulated via descending inhibition from the brain³⁰. This early discovery laid the groundwork for several impressive observations. In the 1940s, Beecher reported a remarkable attenuation of pain in soldiers returning from combat despite severe injuries, pointing towards emotional and cognitive influences on pain control³¹. We now know that the cerebral cortex's ability to modulate pain extends well beyond nociceptive reflexes and combat. Pain is attenuated in athletes who experience injury during competition³², during focused attention to tasks³³, in distinct contexts related to expectations (e.g., placebo)³⁴, during specific mood states³⁵, and more.

The discovery of motor cortex stimulation for treating neuropathic pain

Over the past 30 years, motor cortex stimulation (MCS) has seen periods of enthusiasm due to its potent effect on central neuropathic pain³⁶. The interest in MCS followed the realization that stimulating the somatosensory cortex was, surprisingly, ineffective and even worsened pain in some instances³⁷. The basis for treating pain with MCS was laid in 1991 by Tsubokawa and team³⁸, searching for alternative treatment targets in the cortex. Working with cat models of central sensory deafferentation pain, they discovered that hyperactivity near the lesion in the thalamus, considered to reflect the degree of pain sensation, was reduced by MCS. They

theorized that the activation of inhibitory pathways through MCS could dampen the transmission of pain signals and reduce the perception of pain³⁷. Within the year, they successfully demonstrated satisfactory pain control for patients with neuropathic pain, including those with central post-stroke pain syndrome (CPSP)³⁷. However, the striking counter-intuitiveness of targeting primary motor, instead of somatosensory cortex for pain, a presumed sensory issue, fueled skepticism about MCS.

Despite these concerns, several studies followed Tsubokawa et al.'s initial work. A systematic review of 14 studies comprising 210 heterogeneous patients showed good pain control, defined as >40-50% pain relief, in 45% of patients who were followed for at least a year³⁹. Nonetheless, such heterogeneity of outcomes has dampened momentum despite what many would see as a significant effect for a treatment-resistant population.

Effectiveness of cortical neuromodulation for pain varies across patients

The significant variability in outcomes has hampered progress in pain management via neuromodulation⁴⁰. This variability is due, in part, to the complex individual-specific topography of the brain⁴¹ and the inherent inter-individual variability in functional networks - meaning that traditional "one target fits all" approaches for targeting likely stimulate different functional units across patients. As a result, the evidence supporting cortical stimulation in neuropathic pain has remained variable and inconclusive⁴², necessitating a more personalized targeting approach. Such personalization has already improved outcomes from transcranial magnetic stimulation (TMS) for refractory depression⁴³. Chronic pain is positioned for a similar revolution in treatment approach and success.

Precision Functional Mapping (PFM) of pain-related networks for personalized targeting

A state-of-the-art neuroimaging technique known as precision functional mapping (PFM) with resting-state functional connectivity MRI (r-fMRI) offers innovative directions for personalizing chronic pain neuromodulation^{10,11}. PFM generates individualized functional brain maps to enhance the specificity and effectiveness of neuromodulation targeting and, ultimately, the therapeutic response. In contrast to more traditional fMRI methods, PFM eschews group-averaging data, because it blurs inter-individual differences important for precise targeting. Over the last few years, PFM has begun to unveil intricate, individual-specific connectomes that have implications for pain management^{11,44}. Individual-specific precision maps of two functional networks that link dlPFC with the motor cortex, the newly discovered

Somato-Cognitive Action Network ^{10,11} (SCAN; Figure **1A**) and the Action-Mode Network ⁴⁵ (AMN; Figure **1B,D**), empower personalized neuromodulation for chronic pain.

The Action-Mode Network (AMN) modulates pain

The AMN (previously referred to as the Cingulo-opercular network or CON ⁴⁵) was originally described in a series of task and resting fMRI publications in the late 2000s ^{46,47}. The AMN, encompassing a distributed set of regions that includes the dorsal anterior cingulate cortex (dACC), insula, premotor regions, and the dlPFC (**Figure 1B,D**), plays a central role in coordinating cognition and action ^{48,49}. Details of its topography are variable across individuals ^{10,11,44,50}. The AMN is remarkable for its consistent responses to most task paradigms with varying sensory and motor outputs, and sensory-motor transformations ^{46,47,10,47}. It has most commonly been thought of as a central contributor to higher order executive functions ^{46,47,10,47}. Importantly, the AMN has also been closely aligned with a host of autonomic functions, including heart rate and blood pressure regulation, respiration ⁵¹, gastrointestinal activity ⁵², and insulin modulation ⁵³. The topography of the AMN defined with resting-state fMRI data, strongly overlaps with maps of task fMRI responses to painful stimuli with a spatial correlation of $r = 0.73$ (**Figure 1B**) ^{54,55}. Within the AMN, the dACC and posterior insula are known to be highly responsive to pain and are likely to be involved with cognitive activities (attention tasks, placebo, mood states, etc) related to pain modulation noted above ⁵⁶. The dACC is involved in the emotional aspect of pain perception and has been implicated in the subjective experience of pain ⁵⁷. DBS targeting the dACC has achieved some success in treating pain, and follows a long history of cingulotomy for pain ²⁰. Likewise, the insula is associated with the integration of sensory, affective, and cognitive aspects of pain perception ⁵⁸. Top-down modulatory control of AMN regions in the dlPFC also shapes individual-specific responses to pain (**Figure 1D**) ⁵⁹. Despite such evidence, the AMN's role in pain processing has been emphasized less than its role in executive function. A recent discovery by Gordon et al. ¹⁰ has recalibrated this focus.

The Somato-Cognitive Action Network (SCAN) processes pain

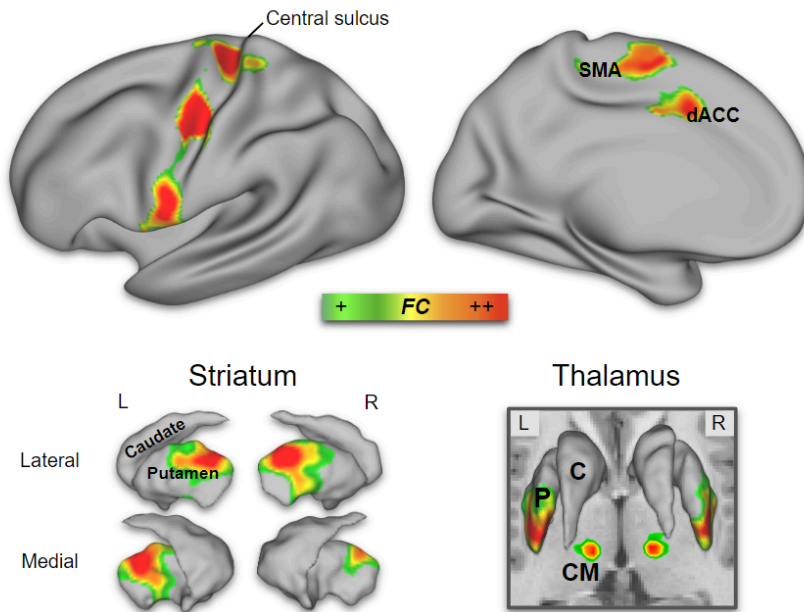
Leveraging PFM, Gordon et al. showed that a set of interconnected regions (i.e. Somato-Cognitive Action Network; SCAN) interrupts the somatotopic motor homunculus, overturning an organizational principle of the brain that had been taken as truth for over 90 years ¹⁰ (**Figure 1A**). These findings were subsequently confirmed with sEEG depth electrodes ⁶⁰. The SCAN's inter-effector regions have connectivity (**Figure 1C**), structure, and function clearly distinct from known effector-specific regions controlling the feet, hands, and mouth.

These inter-effectors lack movement specificity and are co-activated during action planning (coordination of hands and feet) and axial body movement (such as of the abdomen or eyebrows). The SCAN is also strongly connected to the action-mode network (AMN). The SCAN's connectivity to the CM nucleus of the thalamus (**Figure 1A**) is also notable ¹⁰, as lesions to CM can result in CPSP ⁶¹, and DBS research has highlighted CM as a potential target for pain modulation ⁶².

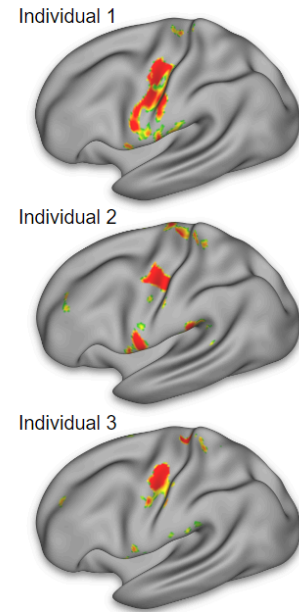
The realization that the primary motor cortex consists of alternating effector-specific motor regions and SCAN nodes, which process top-down and bottom-up action-relevant signals, including pain, suddenly made MCS – targeting motor cortex for a presumably sensory issue – seem less nonsensical. Many pain researchers, including those who had previously doubted MCS, immediately recognized that the SCAN discovery could explain why MCS was sometimes but not always effective. If MCS efficacy depended, in fact, on modulating SCAN rather than classical motor regions, then interventions lacking precise fMRI guidance could only succeed when the small, variable SCAN nodes were hit by pure chance.

The combination of a whole-body action control system within the motor strip (SCAN), linked to thalamic pain nuclei (CM) and the action-mode network (AMN), points to an action loop model that explains many previously unexplained phenomena, including the effectiveness of MCS for pain control. New observations of successful pain attenuation when selectively stimulating the SCAN and AMN provide further evidence for their role in pain modulation (**Figure 2**). Two illustrative cases are reviewed below.

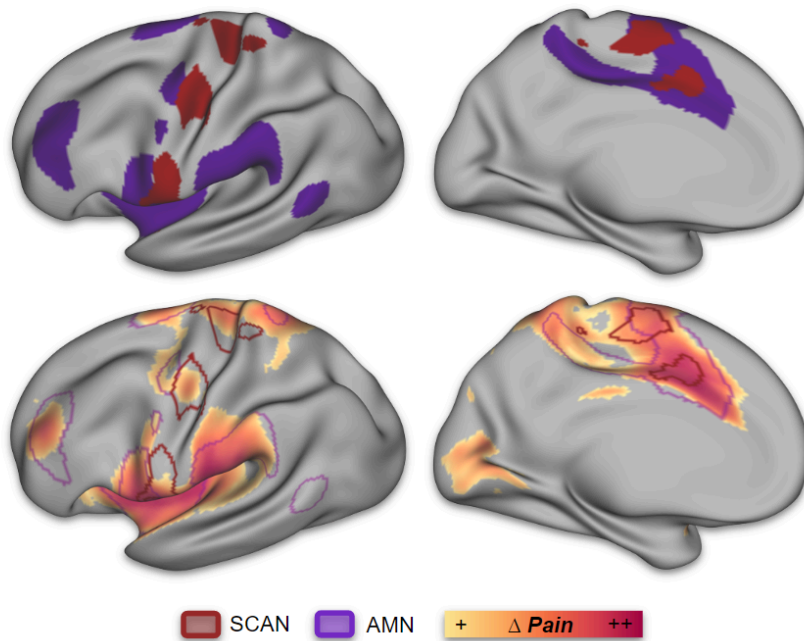
A. Somato-cognitive action network: SCAN



C. SCAN variability



B. SCAN/AMN and pain activations



D. AMN variability

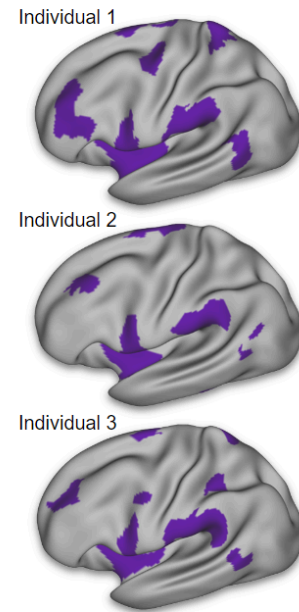


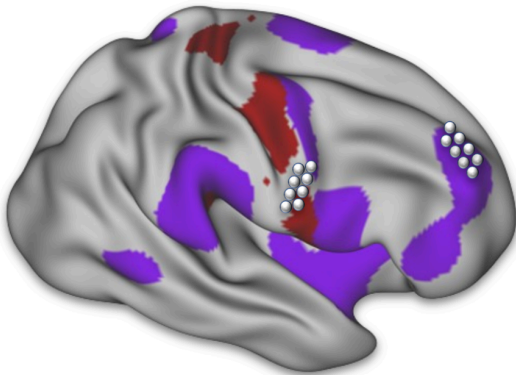
Figure 1: The Somato-Cognitive Action (SCAN) and Action-Mode (AMN) networks process pain signals. A) The Somatic-Cognitive Action Network (SCAN) has strong functional connectivity (FC) with regions in the dorsal Anterior Cingulate (dACC) and Supplementary Motor Area (SMA). Subcortically, connectivity extends to the posterior dorsal putamen and the centromedian (CM) thalamic nucleus ¹⁰. **B)** Overlay of task fMRI activations in response to painful stimuli ⁵⁹, over the outlines of the AMN (purple) ⁶³ and SCAN (burgundy) ¹⁰. The spatial correlation between the AMN and cortical pain maps is $r = 0.73$ ($p < 0.001$). **C)** Inter-individual variation in the SCAN, and **D)** AMN.

Stimulation of SCAN and AMN provides maximal pain relief

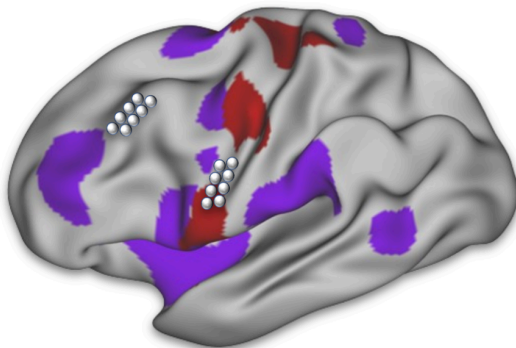
The SCAN discovery¹⁰, along with prior research on the AMN⁴⁵, might explain the outcome variability in MCS for neuropathic pain. Examination of extant data from two of our patients who underwent cortical stimulation for intractable chronic pain prior to the discovery of the SCAN highlights the path towards more effective neuromodulation. The first patient (P1) was a 45-year-old woman who developed unbearable left-sided facial pain after multiple thalamic strokes due to paradoxical emboli. P1's pain began as a cold sensation that progressed from her jaw up to her forehead. All previous pharmacologic and interventional treatments failed to mitigate the pain, leaving her incapacitated from pain and medication side effects. The second patient (P2) was a 53-year-old woman with recalcitrant trigeminal neuralgia who suffered from iatrogenic anesthesia dolorosa stemming from rhizotomies. Both patients (P1,2) had surface electrodes (8 contacts each) placed over the motor cortex and dlPFC through a single burr hole (**Figure 2A**). Stimulation parameters were selected using automated Bayesian optimization⁶⁴ to achieve maximal pain relief.

A. Location of electrodes

Patient 1: Thalamic stroke, 45F

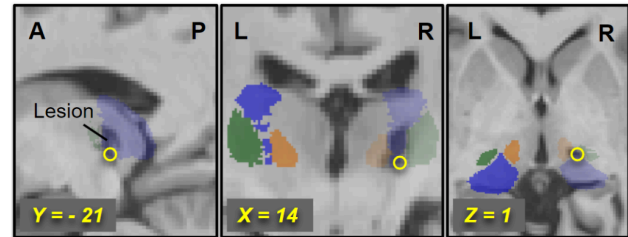


Patient 2: TN and anesthesia dolorosa, 53F



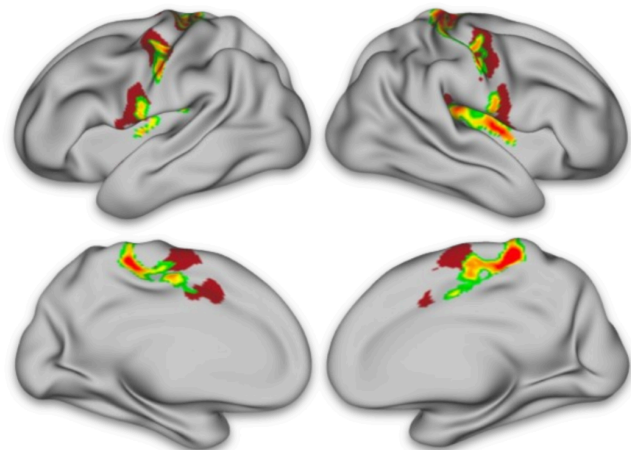
SCAN AMN Electrode Contact

B. Thalamic lesion: Patient 1



LP VPL CM Subcortical seed

C. Lesion connectivity: Patient 1



SCAN + FC ++

Figure 2: Cortical surface neuromodulation for central neuropathic pain. **A)** In P1 electrodes were placed (without individual-specific precision targeting) over the AMN in dIPFC and over the SCAN in the precentral gyrus. In P2 the dIPFC electrodes missed the AMN, but the precentral electrodes were likely placed over the inferior SCAN node. P1 had much greater pain relief than P2. **B)** P1 central thalamus lesion, secondary to stroke, causing intractable facial neuropathic pain. Centromedian (CM; gray), lateral posterior (LP; blue) and ventral posterolateral (VPL; green) nuclei of the thalamus are based on the THOMAS atlas⁶⁵. The functional connectivity for P1's stroke lesion seed (yellow; MNI coordinates: 14,-21,1) is shown in panel C. **C)** Functional connectivity map (group-averaged Human Connectome Project data; n = 897) seeded from the location of P1's central thalamic stroke (shown in yellow in panel B). Group connectivity of the lesion seed shows overlap with the SCAN, highlighting its role in pain modulation. Abbreviations: **TN**: trigeminal neuralgia, **SCAN**: somato-cognitive action network, **AMN**: action-mode network, **LP**: lateral posterior (Pulvinar) nucleus, **VPL**: ventral posterolateral nucleus, **CM**: centromedian nucleus, **FC**: functional connectivity.

For P1, both motor cortex and dIPFC stimulation resulted in pain relief. Combining motor cortex and dIPFC stimulation provided the greatest pain reduction. However, in P2, pain relief was only achieved with stimulation over presumed motor cortex, while dIPFC stimulation did not affect her pain. Scrutiny of the electrode placement in relation to previously published probabilistic

functional network maps ⁶⁶ (**Figure 2A**) revealed that pain relief scaled with modulating both AMN and SCAN nodes in P1. Stimulating either SCAN or AMN provided only partial pain relief. The finding that simultaneous stimulation of the AMN (dIPFC) and SCAN (motor cortex) led to superior pain relief suggests a synergistic interaction between these networks in managing neuropathic pain ⁶⁴. As with P1, in P2 by chance one electrode was placed over the most inferior SCAN node and successfully alleviated pain. However, stimulating the dIPFC electrode in P2, which missed the AMN, failed to reduce pain (**Figure 2A**) – highlighting the AMN's importance in pain reduction, but also suggesting that while both networks can optimally reduce pain perception, one network may be sufficient

The functional connectivity of the thalamic lesion site that caused P1's chronic pain provided additional insights into the SCAN's role in pain regulation (**Figure 2B**). P1's central post-stroke pain (CPSP; or Dejerine-Roussy) syndrome seems to have been caused by a lesion affecting the intersection of the CM-pf, VPL, and Pulvinar nuclei, consistent with prior studies ^{61,67}. As discussed above, the CM-pf and VPL have been previously suggested as DBS targets in chronic central pain ^{21,23,68}, and lesions in this particular part of the thalamus have historically led to post-stroke neuropathic pain ^{61,67}. One theory is that the CM-Pf complex ^{23,25} and VPL ²⁵ serve as 'gatekeepers', allowing pain signals through to the cortex only under certain conditions. We observed that this thalamic lesion location, likely corresponding to the intersection of the CM-pf and VPL, is selectively functionally connected to the SCAN (**Figure 2C**), suggesting that P1's CPSP was likely caused by disruption of her SCAN circuitry.

P1 and P2 did not have any adverse events, but in general cortical neuromodulation with implanted electrodes carries similar risks as as DBS: intracranial hemorrhage, CSF leak, seizures, stroke, and hardware-related complications (e.g., infection, erosions, lead migration) ^{22,29}. Cortical stimulation specifically involves drilling into the skull and placing an electrode epidurally or subdurally, which takes about 1-2 hours when a target has been predefined. Most of the surgical time is spent routing wires under the skin to an implanted subcutaneous battery similar to DBS or SCS. Based on the limited existing data, these risks are weighed against an efficacy rate of approximately 50%, without precision targeting, in a treatment-resistant population.

Non-invasive cortical stimulation techniques, such as repetitive Transcranial Magnetic Stimulation (rTMS) do not carry the surgical risks of implanting electrodes ⁶⁹. Seizures are the

most serious rTMS side effect (<1%)⁷⁰ and it can occur even in patients without a history of epilepsy, which is a relative contraindication⁷⁰. The FDA has approved TMS for several indications (depression, OCD, migraine) but currently considers rTMS investigational for pain, despite its approval in the EU for neuropathic pain⁷¹. In 2020, a panel of European experts found level A evidence (definite benefit) for high-frequency rTMS over the motor cortex in neuropathic pain⁷². A 2021 rTMS trial without precision targeting, compared M1, dIPFC and sham stimulation (total n = 149) in the treatment of neuropathic pain⁶⁹. This trial found M1, but not dIPFC stimulation to be significantly better than sham rTMS. The most common side effect in the study was headache (34.7%; vs 27.1% in sham)⁶⁹. The main distinction along the spectrum of cortical stimulation invasiveness (i.e., rTMS to implanted electrodes) are logistical considerations about facilitating treatments session (e.g.: every weekday for 6 weeks for TMS in depression) and it is unknown how often rTMS will need to be dosed for a persistent and robust effect in treating pain.

The past outcome variability of non-invasive and invasive MCS and dIPFC stimulation for chronic pain can be explained by failing to deliberately target SCAN and AMN nodes. Prior MCS and dIPFC stimulation seem to have succeeded only when unwittingly finding SCAN and/or AMN regions by chance. Task fMRI (**Figure 1B**), direct electrocortical stimulation (**Figure 2A**) and lesion data (**Figure 2B**) all show that the SCAN/AMN action circuitry is critically important for pain processing. The efficacy of dIPFC and precentral gyrus stimulation for pain relief appears to be dependent on modulation of the AMN and SCAN, which are also strongly functionally connected to each other¹⁰. These novel insights forced us to update our model of central pain processing and our clinical approach to treating patients with intractable central neuropathic pain.

The action feedback model of pain control

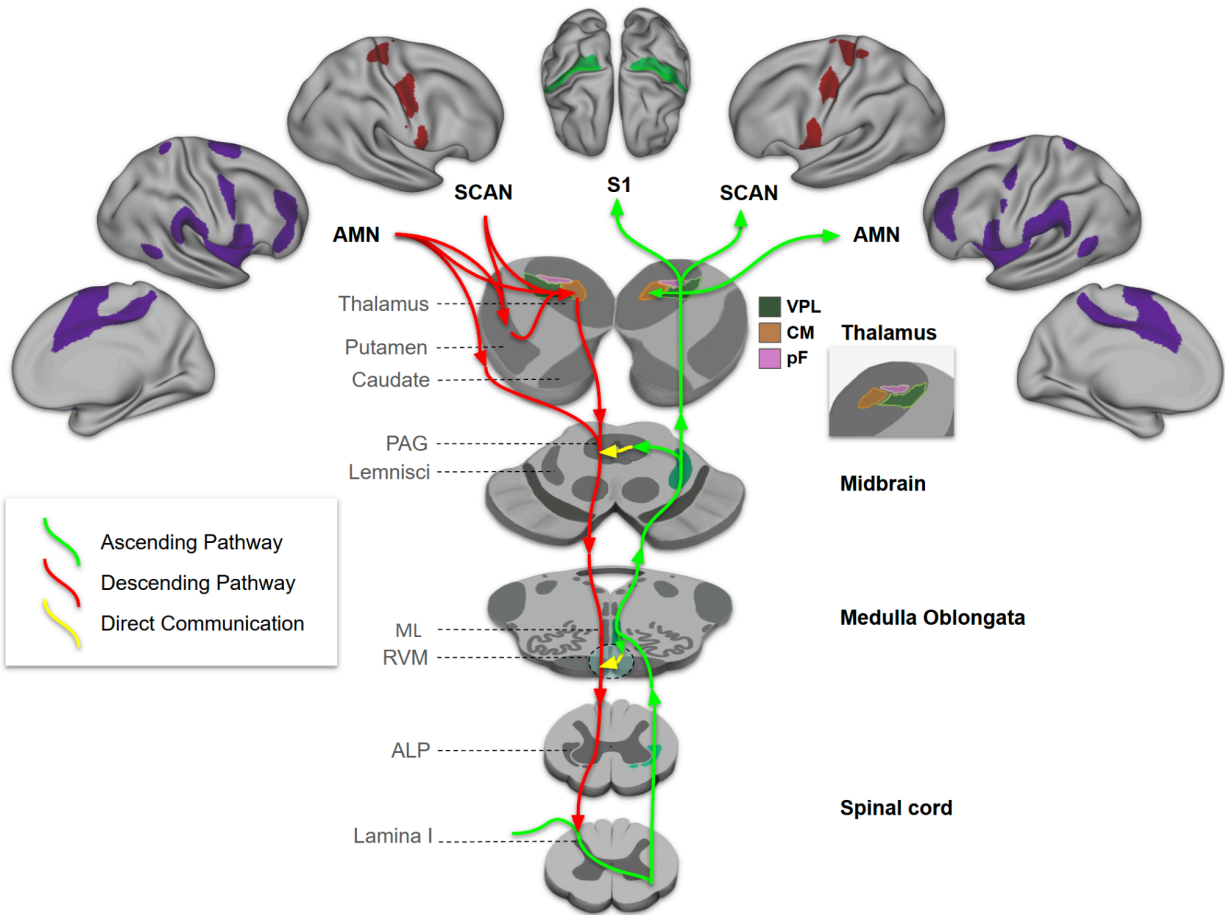


Figure 3: Pain processing pathways. The ascending pathway is shown in green, while the descending pathway is shown in red. Direct communications between the two are shown in yellow. Abbreviations: **ALP**: Anterolateral pathway, **RVM**: Rostral ventral medulla, **ML**: medial lemniscus, **PAG**: periaqueductal gray matter, **pF**: parafascicular nucleus, **CM**: central medial nucleus, **VPL** = ventroposterolateral nucleus, **AMN**: action-mode network, **SCAN**: somato-cognitive action network, **S1**: primary somatosensory cortex.

Combining new findings with existing knowledge allowed us to outline a model of pain as the most important feedback about our actions. This framework paves the way for improving the efficacy of non-invasive (e.g., rTMS, focused ultrasound) and invasive neuromodulation (Direct Cortical Stimulation; DCS) for pain control. At the heart of this model are the SCAN and AMN, primary targets for neuromodulation (**Figure 3**).

The ascending spinothalamic tract (STT) transmits nociceptive information and has both direct and indirect connectivity with several structures in the midbrain and thalamus as it ascends (**Figure 3**). These structures include aforementioned pain modulation centers, such as the RVM

and the PAG⁷³. The STT also provides input to the VPL nucleus of the thalamus, which relays somatosensory information to cortex (S1)⁷³. Other STT projections are CM-pf, which sends projections to the caudate and putamen, both of which are critical structures in pain processing²⁵. The midbrain and thalamus are critical relay and integration centers for nociceptive information (**Figure 3**).

These pain modulatory centers all have direct and indirect connectivity with both AMN (dACC, insula, premotor, dIPFC) and SCAN (i.e., M1) regions. Pain modulation can then occur via descending modulatory inputs coming from the AMN and SCAN cortical endpoints. For example, regions of the AMN (dACC, insula, premotor⁷⁴) feed into the PAG, with outputs to the RVM that modulate pain⁷⁵. These same AMN regions also project to the thalamus including the CM-pf²⁵, further highlighting their modulatory potential in pain perception. The fact that the SCAN (and M1 generally) also includes functional connectivity¹⁰ and direct monosynaptic anatomical connections²⁵ to the CM highlights the proposed synergies between the SCAN and AMN in pain control. Both SCAN and AMN have direct connectivity to striatal regions (e.g., posterior dorsal putamen)¹⁰ that, in turn, also have heavy direct and indirect projections into CM-pf²⁵, completing an additional modulatory loop for pain. While this brief overview cannot cover the full intricacy of pain circuits, such as the amygdala's role in the emotional dimension of pain^{25,76}, it highlights the pivotal role of the AMN and SCAN action networks. While this model does not rule out other cortical and subcortical systems involved with pain, the AMN and SCAN contain several readily identifiable and accessible cortical targets for pain neuromodulation.

Precision neuromodulation targeting for personalized pain treatment

There are several important considerations for future invasive (e.g., DBS, DCS) and non-invasive (e.g., rTMS and focused ultrasound (FUS)) neuromodulation trials and treatments targeting the AMN and SCAN in chronic pain. Both the AMN and SCAN vary from person-to-person in the exact location of specific nodes (**Figure 1C & 1D**). Since functional network topography is individual-specific, success rates will be greatest with fMRI-based patient-specific PFM for the most precise neuromodulation targeting. Personalized precision targeting, which combines principled neuroanatomical priors with cutting-edge functional brain mapping techniques, can improve the safety and greatly improve the efficacy of neuromodulation for chronic pain.

Patient-specific PFM currently still requires high-quality functional MRI data and advanced image-processing know-how, currently only available at a subset of top-tier medical institutions. However, most centers now have use of an MRI machine and can acquire the necessary raw data. The increased frequency⁷⁷ and advances in MRI access have the potential to put precision-targeted neuromodulation within reach of most pain clinicians and patients (for some details see⁷⁸). In addition, based on large research brain MRI data sets, population statistics and probabilistic atlases of the intended targets have also been developed⁶³. Targeting invasive or non-invasive technologies via a population-based atlas of the SCAN and AMN target nodes when advanced functional MRI cannot be obtained is still more precise than current, ad-hoc stimulation standards, which are devoid of any imaging guidance⁶³. With the ability to upload individualized functional network maps and probabilistic atlases into neuronavigation software, implementing personalized precision neuromodulation is no longer science fiction but imminently achievable. New research priorities and trials leveraging precision neuromodulation in clinical workflows will speed up the exploration, verification and adoption of new targets, thus maximizing the reach and impact of the proposed action loop model of pain treatment. Along with direct cortical stimulation for treating intractable neuropathic pain, numerous neuromodulation technologies are poised to play a role in the future of noninvasive treatments and trials such as TMS, focused ultrasound (FUS)⁷⁹, transcranial alternating current stimulation (TACS)⁸⁰, and even temporally interfering electric fields⁸¹.

The future of pain treatments

Deciphering the complexities of neuropathic pain has enormous implications for our society. By increasing the effectiveness of pain treatments and reducing the variability in patient responses through the adoption of a comprehensive patient-centered pain management framework, we can significantly improve patient outcomes and quality of life. Our new understanding of the person-specific cortical functional centers involved in pain modulation, namely the SCAN¹⁰ and AMN, is paving the way for the next generation of neuromodulation treatments and clinical trials, which is the next stage in advancing such therapies for chronic neuropathic pain. The potential of these innovative, non-pharmacological approaches to pain management—achievable through both invasive and non-invasive cortical neuromodulation—is vast and sets the stage for rapid progress in the years to come.

Search strategy and selection criteria

In this review, we searched PubMed, Embase, and Cochrane Library for articles published in English from January 1, 2014, to May 31, 2024, using the following keywords: "chronic pain," "neuropathic pain," "neuroimaging," "functional MRI," "neuromodulation," "precision functional mapping" and "transcranial magnetic stimulation." We included randomized controlled trials, cohort studies, systematic reviews, and meta-analyses that investigated the application of neuroimaging and neuromodulation techniques in the assessment and treatment of chronic and neuropathic pain. Studies were excluded if they focused solely on animal models, if they lacked primary clinical data, or if they were published before 2014. Additional articles were identified through manual searches of the reference lists of the selected studies and relevant review articles. No restrictions were applied regarding the age, gender, or underlying conditions of the study populations.

Glossary of Terms:

- **Neuromodulation:** A therapeutic approach that uses electrical or magnetic stimulation to alter nervous system activity.
- **Spinal Cord Stimulation (SCS):** An invasive method of neuromodulation where electrodes are placed in the epidural space behind the spinal cord to modulate pain signals
- **Deep Brain Stimulation (DBS):** An invasive neuromodulation technique that uses electrodes implanted within the brain parenchyma to deliver electrical stimulation to specific areas.
- **Direct Cortical Stimulation (DCS):** An invasive neuromodulation technique that uses electrodes to deliver electrical stimulation to the surface of specific areas in the brain.
- **Motor Cortex Stimulation (MCS):** DCS targeting the primary motor cortex.
- **Transcranial Magnetic Stimulation (TMS):** A non-invasive neuromodulation technique that uses external magnetic fields to stimulate specific areas in the brain.
- **Resting-State Functional MRI (r-fMRI):** A type of MRI that measures brain activity by detecting changes associated with blood flow, often used to map brain networks at rest (e.g., while watching a movie or while looking at a crosshair).
- **Precision Functional Mapping (PFM):** A personalized brain-mapping technique using 30-40 minutes of high-quality resting-state functional MRI to identify individual-specific variations in brain networks.

CRedit author statement

David P. Darrow: Conceptualization, Writing-review & editing, Supervision; **Alexander B. Herman:** Writing-review & editing; **Tariq Hattab:** Conceptualization, Writing-original draft, Writing-review & editing, Visualization; **Seth König:** Writing-review & editing; **Robert Hermosillo:** Writing-review & editing, Visualization; **Julia Moser:** Writing-review & editing; **Sanju Koirala:** Writing-review & editing; **Gracie Grimsrud:** Writing-review & editing; **Samuel R. Krimmel:** Writing-review & editing; **Ziad Nahas:** Writing-review & editing; **Oscar Miranda-Dominguez:** Writing-review & editing; **Steven M. Nelson:** Writing-review & editing; **Evan M. Gordon:** Writing-review & editing, Visualization; **Nico U.F. Dosenbach:** Conceptualization, Writing-review & editing, Visualization; **Damien A. Fair:** Conceptualization, Supervision, Writing-original draft, Writing-review & editing, Visualization.

Author ORCID

David Darrow: <https://orcid.org/0000-0001-9335-0584>
Alex Herman: <https://orcid.org/0000-0001-6229-433X>
Tariq Hattab: <https://orcid.org/0000-0001-8207-2160>
Seth König: <https://orcid.org/0000-0002-1600-0342>
Robert Hermosillo: <https://orcid.org/0000-0003-2959-8483>
Julia Moser: <https://orcid.org/0000-0002-6219-415X>
Sanju Koirala: <https://orcid.org/0000-0001-8844-4586>
Gracie Grimsrud: <https://orcid.org/0000-0001-7167-4289>
Samuel R. Krimmel: <https://orcid.org/0000-0002-5198-1545>
Ziad Nahas: <https://orcid.org/0000-0002-8391-5673>
Oscar Miranda-Dominguez: <https://orcid.org/0000-0002-3622-0166>
Steven M. Nelson: N/A
Evan M. Gordon: <https://orcid.org/0000-0002-2276-5237>
Nico U.F. Dosenbach: <https://orcid.org/0000-0002-6876-7078>
Damien A. Fair: <https://orcid.org/0000-0001-8602-393X>

Declaration of interests statement

Damien Fair and Nico Dosenbach are patent holders on the Framewise Integrated Real-Time Motion Monitoring (FIRMM) software. They are also co-founders of Turing Medical Inc, which licenses this software. The nature of this financial interest has been reviewed by two committees at Washington University and the University of Minnesota. They have put in place a plan to help ensure that this work is not affected by the financial interest. David Darrow reports unrelated consulting with neuro1 and unrelated grant funding from Abbott Labs as well as research funding from Turing. Ziad Nahas reports consulting with Turing Medical Inc, and other unrelated consulting with Liva Nova, MECTA, MOTIF and Magnus Medical.

Funding source statement

Research reported in this publication was supported by the University of Minnesota's MnDRIVE (Minnesota's Discovery, Research and Innovation Economy) initiative and the Institute for Translational Neuroscience (ITN; D.P.D.); National Institute of Drug Addiction (# 5K23DA050909; A.B.H.); the Brain & Behavior Research Foundation under NARSAD Young Investigator Award (# 28426; A.B.H.); DFG Deutsche Forschungsgemeinschaft (German Research Foundation; 493345456; J.M.); National Institutes of Health (NIH) grants MH121276 (N.U.F.D., E.M.G., D.A.F.), MH096773 (D.A.F., N.U.F.D.), MH122066 (D.A.F., E.M.G., N.U.F.D.), MH124567 (D.A.F., E.M.G., N.U.F.D.), NS129521 (E.M.G., D.A.F., N.U.F.D.) and NS088590 (N.U.F.D.); the National Spasmodic Dysphonia Association (E.M.G.); the Intellectual and Developmental Disabilities Research Center (N.U.F.D.); by the Kiwanis Foundation (N.U.F.D.); the Washington University Hope Center for Neurological Disorders (E.M.G., N.U.F.D.) and by Mallinckrodt Institute of Radiology pilot funding (E.M.G., N.U.F.D.).

References

- 1 Dahlhamer J, Lucas J, Zelaya C, *et al.* Prevalence of Chronic Pain and High-Impact Chronic Pain Among Adults - United States, 2016. *MMWR Morb Mortal Wkly Rep* 2018; **67**: 1001–6.
- 2 Cohen SP, Vase L, Hooten WM. Chronic pain: an update on burden, best practices, and new advances. *Lancet* 2021; **397**: 2082–97.
- 3 Bouhassira D. Neuropathic pain: Definition, assessment and epidemiology. *Rev Neurol* 2019; **175**: 16–25.
- 4 Cavalli E, Mammana S, Nicoletti F, Bramanti P, Mazzon E. The neuropathic pain: An overview of the current treatment and future therapeutic approaches. *Int J Immunopathol Pharmacol* 2019; **33**: 2058738419838383.
- 5 Finnerup NB, Kuner R, Jensen TS. Neuropathic pain: From mechanisms to treatment. *Physiol Rev* 2021; **101**: 259–301.
- 6 Dydyk AM, Givler A. Central Pain Syndrome. StatPearls Publishing, 2023.
- 7 Vowles KE, McEntee ML, Julnes PS, Frohe T, Ney JP, van der Goes DN. Rates of opioid misuse, abuse, and addiction in chronic pain: a systematic review and data synthesis. *Pain* 2015; **156**: 569–76.
- 8 Volkow ND, Blanco C. The changing opioid crisis: development, challenges and opportunities. *Mol Psychiatry* 2021; **26**: 218–33.
- 9 Miech R, Johnston L, O'Malley PM, Keyes KM, Heard K. Prescription Opioids in Adolescence and Future Opioid Misuse. *Pediatrics* 2015; **136**: e1169–77.
- 10 Gordon EM, Chauvin RJ, Van AN, *et al.* A somato-cognitive action network alternates with

- effector regions in motor cortex. *Nature* 2023; **617**: 351–9.
- 11 Gordon EM, Laumann TO, Gilmore AW, *et al.* Precision Functional Mapping of Individual Human Brains. *Neuron* 2017; **95**: 791–807.e7.
 - 12 Finnerup NB, Attal N, Haroutounian S, *et al.* Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. *Lancet Neurol* 2015; **14**: 162–73.
 - 13 Colloca L, Ludman T, Bouhassira D, *et al.* Neuropathic pain. *Nat Rev Dis Primers* 2017; **3**: 17002.
 - 14 Tanz LJ, Jones CM, Davis NL, *et al.* Trends and Characteristics of Buprenorphine-Involved Overdose Deaths Prior to and During the COVID-19 Pandemic. *JAMA Netw Open* 2023; **6**: e2251856.
 - 15 Kirtley OJ, Rodham K, Crane C. Understanding suicidal ideation and behaviour in individuals with chronic pain: a review of the role of novel transdiagnostic psychological factors. *Lancet Psychiatry* 2020; **7**: 282–90.
 - 16 Sdrulla AD, Guan Y, Raja SN. Spinal Cord Stimulation: Clinical Efficacy and Potential Mechanisms. *Pain Pract* 2018; **18**: 1048–67.
 - 17 Rock AK, Truong H, Park YL, Pilitsis JG. Spinal Cord Stimulation. *Neurosurg Clin N Am* 2019; **30**: 169–94.
 - 18 Joosten EA, Franken G. Spinal cord stimulation in chronic neuropathic pain: mechanisms of action, new locations, new paradigms. *Pain* 2020; **161 Suppl 1**: S104–13.
 - 19 Eldabe S, Buchser E, Duarte RV. Complications of Spinal Cord Stimulation and Peripheral Nerve Stimulation Techniques: A Review of the Literature. *Pain Med* 2016; **17**: 325–36.
 - 20 Boccard SGJ, Pereira EAC, Aziz TZ. Deep brain stimulation for chronic pain. *J Clin Neurosci* 2015; **22**: 1537–43.
 - 21 Gildenberg PL. History of Electrical Neuromodulation for Chronic Pain. *Pain Med* 2006; **7**: S7–13.
 - 22 Pereira EAC, Green AL, Aziz TZ. Chapter 23 - Deep brain stimulation for pain. In: Lozano AM, Hallett M, eds. *Handbook of Clinical Neurology*. Elsevier, 2013: 277–94.
 - 23 Ilyas A, Pizarro D, Romeo AK, Riley KO, Pati S. The centromedian nucleus: Anatomy, physiology, and clinical implications. *J Clin Neurosci* 2019; **63**: 1–7.
 - 24 Lempka SF, Malone DA Jr, Hu B, *et al.* Randomized clinical trial of deep brain stimulation for poststroke pain. *Ann Neurol* 2017; **81**: 653–63.
 - 25 Jones EG. *The Thalamus*. Springer US.
 - 26 Rasche D, Rinaldi PC, Young RF, Tronnier VM. Deep brain stimulation for the treatment of various chronic pain syndromes. *Neurosurg Focus* 2006; **21**: E8.
 - 27 Coffey RJ. Deep brain stimulation for chronic pain: results of two multicenter trials and a structured review. *Pain Med* 2001; **2**: 183–92.

- 28 Cruccu G, Aziz TZ, Garcia-Larrea L, *et al.* EFNS guidelines on neurostimulation therapy for neuropathic pain. *Eur J Neurol* 2007; **14**: 952–70.
- 29 Hamani C, Lozano AM. Hardware-related complications of deep brain stimulation: a review of the published literature. *Stereotact Funct Neurosurg* 2006; **84**: 248–51.
- 30 Sherrington CS. New Haven, CT, US: Yale University Press The integrative action of the nervous system., 1906.
- 31 Beecher HK. Pain in Men Wounded in Battle. *Ann Surg* 1946; **123**: 96–105.
- 32 Meeusen R, Watson P. Amino acids and the brain: do they play a role in ‘central fatigue’? *Int J Sport Nutr Exerc Metab* 2007; **17 Suppl**: S37–46.
- 33 Bantick SJ, Wise RG, Ploghaus A, Clare S, Smith SM, Tracey I. Imaging how attention modulates pain in humans using functional MRI. *Brain* 2002; **125**: 310–9.
- 34 Wager TD, Atlas LY. The neuroscience of placebo effects: connecting context, learning and health. *Nat Rev Neurosci* 2015; **16**: 403–18.
- 35 Rhudy JL, Meagher MW. Fear and anxiety: divergent effects on human pain thresholds. *Pain* 2000; **84**: 65–75.
- 36 Maarrawi J, Peyron R, Mertens P, *et al.* Motor cortex stimulation for pain control induces changes in the endogenous opioid system. *Neurology* 2007; **69**: 827–34.
- 37 Tsubokawa T, Katayama Y, Yamamoto T, Hirayama T, Koyama S. Chronic motor cortex stimulation for the treatment of central pain. *Acta Neurochir Suppl* 1991; **52**: 137–9.
- 38 Tsubokawa T, Katayama Y, Yamamoto T, Hirayama T, Koyama S. Treatment of thalamic pain by chronic motor cortex stimulation. *Pacing Clin Electrophysiol* 1991; **14**: 131–4.
- 39 Fontaine D, Hamani C, Lozano A. Efficacy and safety of motor cortex stimulation for chronic neuropathic pain: critical review of the literature. *J Neurosurg* 2009; **110**: 251–6.
- 40 Attia M, McCarthy D, Abdelghani M. Repetitive Transcranial Magnetic Stimulation for Treating Chronic Neuropathic Pain: a Systematic Review. *Curr Pain Headache Rep* 2021; **25**: 48.
- 41 Miranda-Dominguez O, Mills BD, Grayson D, *et al.* Bridging the gap between the human and macaque connectome: a quantitative comparison of global interspecies structure-function relationships and network topology. *J Neurosci* 2014; **34**: 5552–63.
- 42 Cruccu G, Garcia-Larrea L, Hansson P, *et al.* EAN guidelines on central neurostimulation therapy in chronic pain conditions. *Eur J Neurol* 2016; **23**: 1489–99.
- 43 Cole EJ, Stimpson KH, Bentzley BS, *et al.* Stanford Accelerated Intelligent Neuromodulation Therapy for Treatment-Resistant Depression. *Am J Psychiatry* 2020; **177**: 716–26.
- 44 Cui Z, Pines AR, Larsen B, *et al.* Linking Individual Differences in Personalized Functional Network Topography to Psychopathology in Youth. *Biol Psychiatry* 2022; **92**: 973–83.

- 45 Dosenbach NUF, Raichle ME, Gordon EM. The brain's cingulo-opercular action-mode network. <https://osf.io/2vt79/download> (accessed Feb 11, 2024).
- 46 Dosenbach NUF, Fair DA, Miezin FM, *et al.* Distinct brain networks for adaptive and stable task control in humans. *Proc Natl Acad Sci U S A* 2007; **104**: 11073–8.
- 47 Dosenbach NUF, Fair DA, Cohen AL, Schlaggar BL, Petersen SE. A dual-networks architecture of top-down control. *Trends Cogn Sci* 2008; **12**: 99–105.
- 48 Posner MI, Petersen SE. The attention system of the human brain. *Annu Rev Neurosci* 1990; **13**: 25–42.
- 49 Fair DA, Dosenbach NUF, Church JA, *et al.* Development of distinct control networks through segregation and integration. *Proc Natl Acad Sci U S A* 2007; **104**: 13507–12.
- 50 DiNicola LM, Buckner RL. Precision Estimates of Parallel Distributed Association Networks: Evidence for Domain Specialization and Implications for Evolution and Development. *Curr Opin Behav Sci* 2021; **40**: 120–9.
- 51 Critchley HD, Mathias CJ, Josephs O, *et al.* Human cingulate cortex and autonomic control: converging neuroimaging and clinical evidence. *Brain* 2003; **126**: 2139–52.
- 52 Mayer EA. Gut feelings: the emerging biology of gut-brain communication. *Nat Rev Neurosci* 2011; **12**: 453–66.
- 53 Kaneto A, Miki E, Kosaka K, Okinaka S, Nakao K. Effects of stimulation of the cingulate gyrus on insulin secretion. *Endocrinology* 1965; **77**: 617–24.
- 54 Peyron R, Laurent B, García-Larrea L. Functional imaging of brain responses to pain. A review and meta-analysis (2000). *Neurophysiol Clin* 2000; **30**: 263–88.
- 55 Wager TD, Atlas LY, Lindquist MA, Roy M, Woo C-W, Kross E. An fMRI-based neurologic signature of physical pain. *N Engl J Med* 2013; **368**: 1388–97.
- 56 Lieberman MD, Eisenberger NI. The dorsal anterior cingulate cortex is selective for pain: Results from large-scale reverse inference. *Proc Natl Acad Sci U S A* 2015; **112**: 15250–5.
- 57 Shackman AJ, Salomons TV, Slagter HA, Fox AS, Winter JJ, Davidson RJ. The integration of negative affect, pain and cognitive control in the cingulate cortex. *Nat Rev Neurosci* 2011; **12**: 154–67.
- 58 Wiech K, Lin C-S, Brodersen KH, Bingel U, Ploner M, Tracey I. Anterior insula integrates information about salience into perceptual decisions about pain. *J Neurosci* 2010; **30**: 16324–31.
- 59 Hoeppli ME, Nahman-Averbuch H, Hinkle WA, *et al.* Dissociation between individual differences in self-reported pain intensity and underlying fMRI brain activation. *Nat Commun* 2022; **13**: 3569.
- 60 Jensen MA, Huang H, Valencia GO, *et al.* A motor association area in the depths of the central sulcus. *Nat Neurosci* 2023; **26**: 1165–9.
- 61 Sprenger T, Seifert CL, Valet M, *et al.* Assessing the risk of central post-stroke pain of

- thalamic origin by lesion mapping. *Brain* 2012; **135**: 2536–45.
- 62 Abdallat M, Saryyeva A, Blahak C, *et al.* Centromedian-Parafascicular and Somatosensory Thalamic Deep Brain Stimulation for Treatment of Chronic Neuropathic Pain: A Contemporary Series of 40 Patients. *Biomedicines* 2021; **9**. DOI:10.3390/biomedicines9070731.
 - 63 Hermosillo RJM, Moore LA, Fezcko E, *et al.* A Precision Functional Atlas of Network Probabilities and Individual-Specific Network Topography. *bioRxiv.* 2022; : 2022.01.12.475422.
 - 64 Dastin-van Rijn EM, König SD, Carlson D, *et al.* Personalizing Dual-Target Cortical Stimulation with Bayesian Parameter Optimization Successfully Treats Central Post-Stroke Pain: A Case Report. *Brain Sci* 2021; **12**. DOI:10.3390/brainsci12010025.
 - 65 Su JH, Thomas FT, Kasoff WS, *et al.* Thalamus Optimized Multi Atlas Segmentation (THOMAS): fast, fully automated segmentation of thalamic nuclei from structural MRI. *Neuroimage* 2019; **194**: 272–82.
 - 66 Hermosillo RJM, Moore LA, Feczko E, *et al.* A precision functional atlas of personalized network topography and probabilities. *Nat Neurosci* 2024; published online March 26. DOI:10.1038/s41593-024-01596-5.
 - 67 Klit H, Finnerup NB, Jensen TS. Central post-stroke pain: clinical characteristics, pathophysiology, and management. *Lancet Neurol* 2009; **8**: 857–68.
 - 68 Kiefe TM, Nüssel M, Zhao Y, Stadlbauer A, Buchfelder M, Krauss JK. P 30 Stereotactic Deep Brain Modulation Targeting the Somatosensory and Affective Pain Circuits of the Thalamus. *Clin Neurophysiol* 2022; **137**: e31.
 - 69 Attal N, Poindessous-Jazat F, De Chauvigny E, *et al.* Repetitive transcranial magnetic stimulation for neuropathic pain: a randomized multicentre sham-controlled trial. *Brain* 2021; **144**: 3328–39.
 - 70 Stultz DJ, Osburn S, Burns T, Pawlowska-Wajswol S, Walton R. Transcranial Magnetic Stimulation (TMS) Safety with Respect to Seizures: A Literature Review. *Neuropsychiatr Dis Treat* 2020; **16**: 2989–3000.
 - 71 Knotkova H, Hamani C, Sivanesan E, *et al.* Neuromodulation for chronic pain. *Lancet* 2021; **397**: 2111–24.
 - 72 Lefaucheur J-P, Aleman A, Baeken C, *et al.* Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS): An update (2014-2018). *Clin Neurophysiol* 2020; **131**: 474–528.
 - 73 Basbaum AI, Bautista DM, Scherrer G, Julius D. Cellular and molecular mechanisms of pain. *Cell* 2009; **139**: 267–84.
 - 74 Harrison R, Gandhi W, van Reekum CM, Salomons TV. Conditioned pain modulation is associated with heightened connectivity between the periaqueductal grey and cortical regions. *Pain Rep* 2022; **7**: e999.
 - 75 Tracey I, Mantyh PW. The cerebral signature for pain perception and its modulation. *Neuron*

2007; **55**: 377–91.

- 76 Ossipov MH, Dussor GO, Porreca F. Central modulation of pain. *J Clin Invest* 2010; **120**: 3779–87.
- 77 Smith-Bindman R, Miglioretti DL, Larson EB. Rising use of diagnostic medical imaging in a large integrated health system. *Health Aff* 2008; **27**: 1491–502.
- 78 Moser J, Nelson SM, Koirala S, *et al.* Multi-echo acquisition and thermal denoising advances precision functional imaging. *Imaging Neuroscience* 2024; published online Dec 16. DOI:10.1162/imag_a_00426.
- 79 Darrow DP. Focused Ultrasound for Neuromodulation. *Neurotherapeutics* 2019; **16**: 88–99.
- 80 Helfrich RF, Schneider TR, Rach S, Trautmann-Lengsfeld SA, Engel AK, Herrmann CS. Entrainment of brain oscillations by transcranial alternating current stimulation. *Curr Biol* 2014; **24**: 333–9.
- 81 Grossman N, Bono D, Dedic N, *et al.* Noninvasive Deep Brain Stimulation via Temporally Interfering Electric Fields. *Cell* 2017; **169**: 1029–41.e16.