PAIN MEDICINE

Brain Dynamics and Temporal Summation of Pain Predicts Neuropathic Pain Relief from Ketamine Infusion

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ABSTRACT

Background: Ketamine is an *N*-methyl-D-aspartate receptor antagonist that reduces temporal summation of pain and modulates antinociception. Ketamine infusions can produce significant relief of neuropathic pain, but the treatment is resource intensive and can be associated with adverse effects. Thus, it is crucial to select patients who might benefit from this treatment. The authors tested the hypothesis that patients with enhanced temporal summation of pain and the capacity to modulate pain *via* the descending antinociceptive brain pathway are predisposed to obtain pain relief from ketamine.

Methods: Patients with refractory neuropathic pain (n = 30) and healthy controls underwent quantitative sensory testing and resting-state functional magnetic resonance imaging and then completed validated questionnaires. Patients then received outpatient intravenous ketamine (0.5 to $2\,mg \cdot kg^{-1} \cdot h^{-1}$; mean dose $1.1\,mg \cdot kg^{-1} \cdot h^{-1}$) for 6h/day for 5 consecutive days. Pain was assessed 1 month later. Treatment response was defined as greater than or equal to 30% pain relief (*i.e.*, reduction in pain scores). We determined the relationship between our primary outcome measure of pain relief with pretreatment temporal summation of pain and with brain imaging measures of dynamic functional connectivity between the default mode network and the descending antinociceptive brain pathway.

Results: Approximately 50% of patients achieved pain relief (mean ± SD; Responders, 61 ± 35%; Nonresponders, 7 ± 14%). Pretreatment temporal summation was associated with the effect of ketamine ($\rho = -0.52$, $P = 0.003$) and was significantly higher in Responders (median [25th, 75th] = 200 [100, 345]) compared with Nonresponders (44 [9, 92]; $P = 0.001$). Pretreatment dynamic connectivity was also associated with the clinical effect of ketamine ($\rho = 0.51$, $P = 0.004$) and was significantly higher in Responders (mean ± SD, $0.55 ± 0.05$) compared with Nonresponders ($0.51 ± 0.03$; $P = 0.006$). Finally, the dynamic engagement of the descending antinociceptive system significantly mediated the relationship between pretreatment pain facilitation and pain relief (95% CI, 0.005 to 0.065).

Conclusions: These findings suggest that brain and behavioral measures have the potential to prognosticate and develop ketamine-based personalized pain therapy. (ANESTHESIOLOGY 2018; 129:1015-24)

NEUROPATHIC pain is a highly prevalent and often refractory chronic pain condition that is associated with substantial disability and deterioration in quality of life.[1] Accumulating evidence suggests that intravenous infusion of ketamine can result in significant relief of refractory neuropathic pain, when the dose is individually titrated to minimize adverse effects and maximize long-term analgesia.[2–5] However, approximately 50% of patients will not respond to this therapy. The factors that contribute to the analgesic effectiveness in some, but not in other patients, are unknown. Here we investigated whether there are noninvasive quantitative sensory testing or measures of brain function that point to aberrant pain mechanisms underlying refractory neuropathic pain that may have prognostic value regarding ketamine treatment.

Editor's Perspective

What We Already Know about This Topic

- Ketamine is an *N*-methyl-D-aspartate antagonist with growing use in the management of chronic pain
- Descending pain modulatory circuits are key modulators of chronic pain

What This Article Tells Us That Is New

- The infusion of ketamine resulted in meaningful pain relief in about 50% of patients with chronic neuropathic pain
- The magnitude of temporal summation of pain and the dynamic engagement of the descending pain modulatory circuit predicted treatment efficacy and point to mechanisms by which ketamine can relieve pain

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This article is featured in "This Month in Anesthesiology," page 1A. This article has an audio podcast. This article has a visual abstract available in the online version.

One mechanism responsible for refractory neuropathic pain is an upregulation of *N*-methyl-D-aspartate (NMDA) receptor activity, which leads to central sensitization and elevated temporal summation.[6,7] Ketamine produces analgesic effects primarily through inhibition of the NMDA receptor.[8,9] Thus, patients with NMDA-mediated central sensitization are likely to maximally benefit from treatment with ketamine. Temporal summation of pain is a sensory phenomenon that is known to reflect NMDA-mediated brain and spinal cord "wind-up" of nociceptive neurons.[10,11] The severity of temporal summation of pain is measured by administering repetitive brief painful stimuli at approximately 0.33 Hz to evoke a successive increase in perceived pain.[10,12–15] Temporal summation of pain is heightened in some patients with chronic pain, indicating enhanced sensitization, and it is inhibited by NMDA blockers or antagonists.[11,13,14] Therefore, pretreatment measures of temporal summation of pain could be useful in identifying patients who have enhanced NMDA-related central sensitization and thus are likely to benefit from intravenous ketamine.

We recently demonstrated that intersubject variability in temporal summation of pain is associated with variability in the functionality of an individual's ascending nociceptive and descending pain-modulatory pathways.[16] Therefore, we propose that treatment response to ketamine also depends on an individual's capacity to modulate pain *via* antinociceptive pathways.

Pain modulation is inherently dynamic, and there are individual differences in one's ability to disengage attention from pain.[17,18] Compelling evidence suggests that neural fluctuations between networks, measured by dynamic functional connectivity between the default mode network (implicated in the intrinsic attention to pain[19]) and the descending antinociceptive pathway (implicated in endogenous analgesia), underlie this perceptual decoupling.[18] Specifically, greater dynamic functional connectivity between these two systems was associated with a greater ability to disengage attention from pain.[18] In patients with ongoing neuropathic pain, the capacity for this cognitive modulation involving interactions between the default mode network and descending antinociceptive pathway may be useful as predictive indicators and point to mechanisms by which ketamine relieves pain.

Thus, the aim of this study was to identify factors that predict the effect of ketamine treatment for neuropathic pain. Toward this aim, we tested the hypotheses that patients with (1) high temporal summation of pain and (2) enhanced fluctuations between networks and pathways that underlie the ability to disengage attention from pain will achieve sustained pain relief from treatment with ketamine.

Materials and Methods

Participants

Participants included 30 patients with refractory moderate-to-severe neuropathic pain (17 women, 13 men; mean age

± SD, 43.4 ± 13.8 yr) and 30 age- and sex-matched healthy controls (17 women, 13 men; mean age ± SD, 41.9 ± 12.6 yr). Data were collected between April 2015 and November 2017. Patients with neuropathic pain were recruited from the pain clinic at Toronto Western Hospital (Toronto, Ontario, Canada), and healthy controls were recruited from the community. All participants provided informed written consent to procedures approved by the University Health Network Research Ethics Board in accordance with the Declaration of Helsinki. The study is registered at ClinicalTrials.gov (NCT02373449). The inclusion criteria for patients were as follows: (1) sustained (3 months or longer) refractory neuropathic pain as diagnosed on the basis of history, examination, and relevant investigations, as well as a score of more than 4 on the Douleur Neuropathique 4 questionnaire[20]; (2) moderate-to-severe average daily pain (numerical rating scale for pain score of 4 of 10 or higher); and (3) insufficient analgesia from trials lasting 6 weeks or longer of at least three different pharmacologic groups of medications for neuropathic pain (*e.g.*, anticonvulsants, tricyclic antidepressants, serotonin noradrenaline reuptake inhibitors). The Douleur Neuropathique 4 was used as additional criteria to indicate the presence of neuropathic pain in our study. This instrument has a sensitivity of 83% and a specificity of 90% for detecting neuropathic pain.[21,22] Exclusion criteria included the following: (1) ketamine or lidocaine intravenous infusion within 6 months preceding study enrollment; (2) contraindications to ketamine (*e.g.*, allergy, raised intracranial pressure, severe coronary artery disease, uncontrolled hypertension or hyperthyroidism); (3) ongoing litigations issues related to the patient's pain that may affect reporting of pain and quality of life; (4) unstable medical or psychiatric conditions (anxiety with panic attacks, depression with suicidal ideation, psychosis, and schizophrenia); (5) contraindications for magnetic resonance imaging; and (6) inability to comply with the study protocol. The exclusion criteria for the health control participants were as follows: (1) history of neurologic disease or psychiatric or pain disorder and (2) contraindications for magnetic resonance imaging. All participants underwent behavioral testing and magnetic resonance imaging (details in "Psychophysical Assessment" and "Neuroimaging Acquisition" sections). Patients were then treated with intravenous ketamine infusion over 5 consecutive days (details in "Ketamine Infusion" section) followed by oral ketamine (0.5 mg · kg^{-1} three times daily for 6 weeks). Patients underwent a second test session 1 month after treatment.

Ketamine Infusion

Ketamine treatment consisted of an intravenous infusion for 6 h/day over 5 consecutive days. The target therapeutic range was 0.5 to 2.0 mg · kg^{-1} · h^{-1} (mean dose 1.1 mg · kg^{-1} · h^{-1}). The dose was adjusted in each patient to achieve maximal pain relief while minimizing adverse effects to a tolerable level. Intravenous midazolam (0.03 mg · kg^{-1}), ondansetron (0.1 mg · kg^{-1} to a maximum dose of 8 mg), and dexamethasone (0.1 mg · kg^{-1} to a maximum dose of 8 mg)

were administered to mitigate the common adverse effects of ketamine (*e.g.*, nausea, vomiting, increased heart rate). Further doses of midazolam (1 to 2 mg) were administered to treat psychoactive adverse effects of ketamine (*e.g.*, hallucinations, agitation).

Questionnaires

All participants completed the Hospital Anxiety and Depression Scale (subscores above 8 are considered clinically relevant),[23] the Pain Catastrophizing Scale,[24] and the Resilience Scale.[25] Patients also completed the Brief Pain Inventory (each item on a 0 to 10 scale),[26,27] and pain relief was calculated as a percentage of change from posttreatment compared with pretreatment rating of "pain now." Patients who achieved 30% or greater reduction in numerical rating scale pain scores at 1 month after the infusion were classified as treatment Responders, and those unable to achieve this outcome were classified as treatment Nonresponders. Pain and psychologic data were compared between controls, Responders, and Nonresponders using a one-way ANOVA and *post hoc* Tukey pairwise comparisons.

Psychophysical Assessment

All participants underwent a psychophysical assessment that included quantitative sensory tests. Thermal stimuli were delivered to the test sites by a computer-controlled Peltier device (Q-sense, 3- × 3-cm thermode, Medoc Ltd., Israel). Temperatures were adjusted until the stimulus-evoked pain intensity was rated as 50 of 100, and this temperature was then used to assess temporal summation of pain. The temporal summation of pain protocol consisted of 10 thermal stimuli manually applied to the skin of the volar forearm every 3 s (*i.e.*, 0.33 Hz; stimulus duration = 2 s). Participants were instructed to rate their pain immediately after each stimuli. Temporal summation of pain was calculated as a percentage of change of the peak pain rating from the pain evoked by the first stimulus.

Neuroimaging Acquisition

All study participants underwent a magnetic resonance imaging (3T GE) neuroimaging session to acquire a high-resolution T_1-weighted anatomical scan (1 × 1 × 1-mm³ voxels, matrix = 256 × 256, 180 axial slices, repetition time = 7.8 s, echo time = 3 ms, inversion time = 450 ms) and a T_2*-weighted resting-state functional magnetic resonance imaging scan (3.125 × 3.125 × 4-mm³ voxels, matrix = 64 × 64, 36 axial slices, repetition time = 2 s, echo time = 30 ms, flip angle = 85°, 277 volumes, total scan time = 9 min, 14 s). For the resting-state scan, participants were instructed to "close your eyes; do not try to think about anything in particular; do not fall asleep."

Preprocessing of Resting-state Functional Magnetic Resonance Imaging Data

We performed all preprocessing of the resting-state functional magnetic resonance imaging data using the FEAT

(functional magnetic resonance imaging expert analysis tool) toolbox in Oxford Centre of Functional Magnetic Resonance Imaging of the Brain's (FMRIB's) Software Library (FSL).[28] The first four volumes of the resting-state functional magnetic resonance imaging scan were removed, nonbrain tissues were removed using the Brain Extract Tool, and motion correction was performed using Motion Correction FMRIB's Linear Image Registration Tool (MCFLIRT). Linear registration between each participant's resting-state functional magnetic resonance imaging data to their skull-stripped (opti–Brain Extract Tool[29]), high-resolution anatomical image was followed by nonlinear registration to MNI152-2mm space using FMRIB's Non-linear Image Registration Tool (FNIRT). Scanner-related and physiologic noise was removed by means of applying aCompCor[30,31] as described previously.[18] Finally, spatial smoothing was applied using a 4-mm full-width at half-maximum kernel, and temporal filtering was performed in FSL to retain the signal between 0.01 to 0.1 Hz.

Dynamic Functional Connectivity

To examine whether dynamics in brain function were associated with the clinical effect of treatment, we calculated dynamic functional connectivity between the components of the dynamic pain connectome as follows. (1) We generated regions of interest from key regions of the default mode network and the descending antinociceptive pathway. The default mode network included 6-mm seeds in the posterior cingulate cortex ($x = -2$, $y = -46$, $z = 28$) and the medial prefrontal cortex ($x = 4$, $y = 54$, $z = 2$), whereas the descending antinociceptive pathway included a 6-mm seed in the periaqueductal grey ($x = 0$, $y = -32$, $z = -10$) and a 2-mm seed in the rostral ventral medulla ($x = 0$, $y = -34$, $z = -50$). (2) A nonlinear transformation of each seed region from standard space to each subject's magnetic resonance imaging space was performed, and the average time series from seeds within each network or pathway were extracted. (3) Dynamic functional connectivity was measured by calculating the dynamic conditional correlation method as described previously.[32,33] (4) The SD of each dynamic conditional correlation across the time series was computed and utilized as the summary metric of dynamic functional connectivity.[33] High dynamic functional connectivity values indicate that the connectivity between seeds (or networks) greatly fluctuates in and out of synchrony, reflecting flexible brain communication between the brain regions.

Statistical Analyses

This is the primary analysis of these data, and all statistical tests were computed to test *a priori* hypotheses. The primary outcome variable of interest for this study was pain relief. No statistical power calculation was conducted before the study, and the sample size was based on the available data. All hypotheses were tested using two-tailed testing procedures. With the exception of one Douleur Neuropathique 4 score from one patient that was missing, there were no

other missing data or outliers excluded from the analysis. Temporal summation of pain was compared between controls and neuropathic pain patients and between Responders and Nonresponders using a Kruskal–Wallis test and Mann–Whitney U *post hoc* pairwise comparisons. The relationship between pretreatment temporal summation of pain and pain relief was determined using a Spearman's correlation. We then determined between-group (controls *vs.* patients) and subgroup (Responders *vs.* Nonresponders) differences in dynamic functional connectivity using a one-way ANOVA (parametric assumptions were met as determined by examination of histograms and tests of normality *via* the Shapiro–Wilk test) and *post hoc* Tukey pairwise comparisons. Furthermore, correlation analyses were conducted to determine the association between dynamic functional connectivity values and the percentage of pain relief. Finally, to determine whether the relationship between temporal summation of pain and pain relief was mediated by dynamic functional connectivity, a mediation analysis was performed using the PROCESS toolbox in SPSS (SPSS Inc., USA).[34,35] The significance of the mediation analyses was evaluated using a bootstrap estimation approach with 1,000 samples. We determined the outcome of our mediation analysis to be significant if the CI does include 0.

Results

Pain and Clinical Characteristics of Patients with Neuropathic Pain

The demographic and clinical characteristics of the patients and corresponding healthy control information are presented in table 1. All patients had a history, signs, and symptoms consistent with the definition of neuropathic pain as "pain arising as a direct consequence of lesion or disease affecting the central and or peripheral somatosensory system" (https://www.iasp-pain.org/GlobalYear/NeuropathicPain; accessed April 5, 2018).[36] Etiologies for neuropathic pain in our study included traumatic injury (n = 23), postherpetic neuralgia (n = 2), vasculitis (n = 1), stroke (n = 1), spinal injury (n = 1), scleroderma (n = 1), or syringomyelia (n = 1). All patients also had features

of sensory gain and or sensory loss (allodynia, hyperalgesia, hypoesthesia) as established by physical examination. Pain was localized to the arm or hand (n = 14), foot or leg (n = 11), abdominal or thoracic wall (n = 4), or on one side of the body (n = 1). The duration of pain ranged from 6 to 240 months (mean, 66 ± 55 months). Approximately 50% of patients (14 of 30) responded to treatment intravenous ketamine infusion (Responders, $61 \pm 35\%$; Nonresponders, $7 \pm 14\%$). There were no significant differences in age ($P = 0.668$) or sex between controls and patients. However, one-way ANOVAs indicated that there were pre-ketamine treatment group Responder *versus* Nonresponder *versus* control differences in anxiety ($F[2,57] = 21.72$, $P < 0.001$), depression ($F[2,57] = 74.35$, $P < 0.001$), pain catastrophizing ($F[2,57] = 13.49$, $P < 0.001$), and resilience ($F[2,57] = 11.73$, $P < 0.001$). Pairwise comparison tests revealed that compared with controls before treatment, Responders had significantly higher anxiety ($P < 0.001$), depression scores ($P < 0.001$), and pain catastrophizing scores ($P = 0.001$) and significantly lower resilience scores ($P = 0.003$). Compared with controls, Nonresponders also had significantly higher anxiety ($P < 0.001$), depression scores ($P < 0.001$), and pain catastrophizing scores ($P < 0.001$) and significantly lower resilience scores ($P < 0.001$). However, the Responders and Nonresponders did not differ in any of the measures assessed. Specifically, there were no significant differences between Responders and Nonresponders for pretreatment measures of clinical pain (Douleur Neuropathique 4, $P = 0.179$; numerical pain rating, $P = 0.059$) or psychiatric or psychologic variables (depression, $P = 0.675$; anxiety, $P = 0.905$; pain catastrophizing, $P = 0.635$; or resilience, $P = 0.585$; descriptive statistics in table 1).

Pretreatment Temporal Summation Is Associated with the Clinical Treatment Effect

The pretreatment temporal summation of pain group scores and individual correlations against pain relief are shown in figure 1A. The group analysis clearly indicates significant differences in pretreatment temporal summation of pain scores between Responders (median [25th, 75th]) = 200

**Table 1.** Pretreatment Psychologic and Pain Measures

|	Healthy Controls (n = 30)	NP (n = 30)	Responders (n = 14)	Nonresponders (n = 16)
Age in yr	42 ± 13	43 ± 14	43 ± 14	43 ± 15
Sex (n)	17 F, 13 M	17 F, 13 M	8 F, 6 M	9 F, 7 M
Douleur Neuropathique 4		7 ± 2	8 ± 2	7 ± 2
Numerical Rating Scale for pain		7 ± 1	7 ± 1	8 ± 1
Depression score	3 ± 2	13 ± 4*	12 ± 4*	13 ± 4†
Anxiety score	3 ± 3	10 ± 5*	10 ± 5*	10 ± 5†
Pain Catastrophizing Scale score	14 ± 9	28 ± 12*	27 ± 13*	29 ± 12†
Resilience score	153 ± 14	125 ± 29*	128 ± 31*	122 ± 28†

All measurements given in mean ± SD.

*Significant difference between healthy controls and Responders, $P < 0.05$. †Significant difference between healthy controls and Nonresponders, $P < 0.05$.
F, female; M, male; NP, neuropathic pain.

A Temporal summation of pain
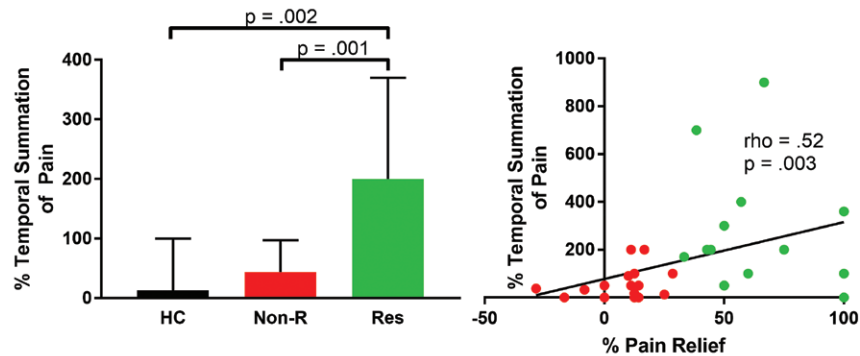
B Dynamic functional connectivity between the default mode network and descending antinociceptive pathway
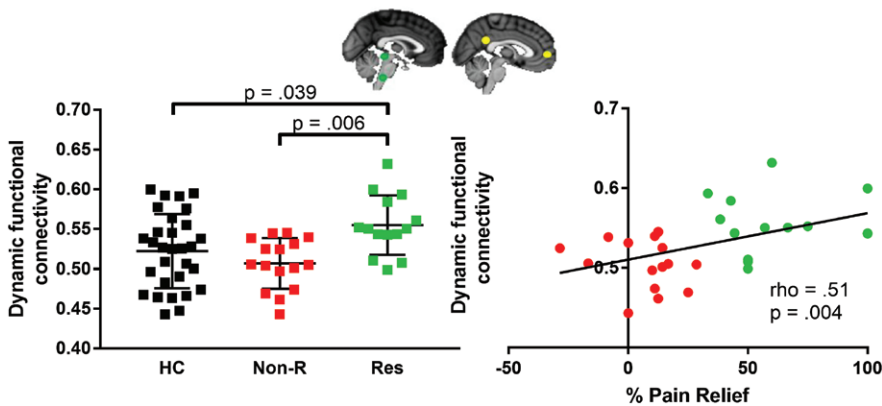
Fig. 1. Pretreatment temporal summation of pain (median [25th, 75th]; (*A*) and mean dynamic functional connectivity (mean ± SD) between the default mode network and the descending antinociceptive pathway (*B*) was significantly enhanced in Responders compared with Nonresponders and controls and significantly predicted percentage of pain relief after ketamine treatment. Significant differences (*$P < 0.05$) are indicated by *horizontal bars* or *P* values. *Black* indicates healthy controls, *red* indicates Nonresponders, and *green* indicates Responders. HC, healthy controls; Non-R, Nonresponders; Res, Responders.

[100, 345]), Nonresponders (44 [9, 92]), and healthy controls (13 [0, 100]), χ^2 (2, N = 60) = 12.51, $P = 0.002$. Follow-up pairwise comparisons indicated that pretreatment temporal summation of pain was significantly higher in responders compared with controls ($U = 87.00$, $P = 0.002$) and compared with Nonresponders ($U = 38.00$, $P = 0.001$) but did not differ between Nonresponders and healthy controls ($U = 206.00$, $P = 0.420$). At the individual patient level, we found a strong correlation between pretreatment temporal summation of pain with the subsequent percentage of pain relief after ketamine treatment (Spearman's $\rho = 0.52$, $P = 0.003$).
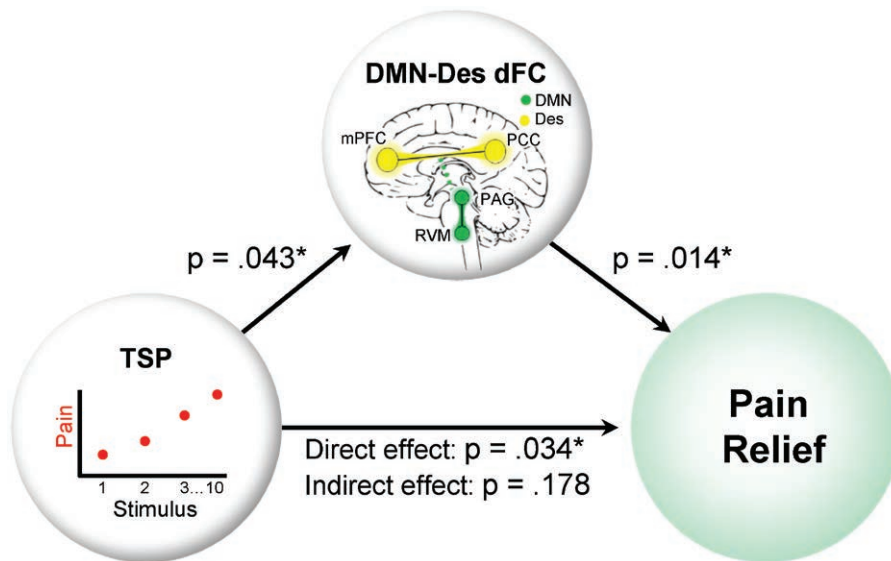
Pretreatment Default Mode Network–descending Antinociceptive Dynamic Functional Connectivity Is Associated with Treatment Effect

The pretreatment dynamic functional connectivity between the default mode network and the descending antinociception pathway is shown in figure 1B at the group level. We identified clear group differences in the default mode network–descending antinociceptive dynamic functional

connectivity between Responders (mean ± SD, 0.55 ± 0.05) compared with Nonresponders (0.51 ± 0.03) and healthy controls (0.52 ± 0.04; $F[2, 57] = 5.4$, $P = 0.007$). Furthermore, pairwise comparisons indicated that pretreatment dynamic functional connectivity was significantly higher in Responders compared with controls ($P = 0.039$) and compared with Nonresponders ($P = 0.006$), but there was no significant difference between Nonresponders and healthy controls ($P = 0.450$). As shown in figure 1B, at the individual level, pretreatment default mode network–descending antinociceptive dynamic functional connectivity was significantly correlated with percentage of pain relief ($\rho = 0.51$, $P = 0.004$).

Relationship between Temporal Summation of Pain and Pain Relief Is Mediated by Default Mode Network–descending Antinociceptive Dynamic Functional Connectivity

We used a mediation analysis to test the hypothesis that the dynamic engagement of the descending antinociceptive

Fig. 2. The relationship between temporal summation of pain (TSP) and pain relief is mediated by default mode network–descending antinociceptive pathway dynamic functional connectivity (DMN-Des dFC). These variables were entered as predictors into a model with pain relief as the outcome variable. The direct path and indirect effect are shown. *$P < 0.05$. mPFC, medial prefrontal cortex; PAG, periaqueductal grey; PCC, posterior cingulate cortex; RVM, rostral ventral medulla.

system mediates the relationship between pretreatment pain facilitation and pain relief. The outcome of this mediation analysis is shown in figure 2. The analysis indicated that pain relief was significantly predicted by temporal summation of pain ($P = 0.035$) and also by the dynamic functional connectivity between the default mode network and descending antinociception pathway ($P = 0.014$). Furthermore, temporal summation of pain was significantly related to the dynamic functional connectivity between the default mode network and descending antinociception pathway dynamic functional connectivity ($P = 0.043$). However, when both temporal summation of pain and the dynamic engagement of the descending antinociceptive system variables were included in the model, temporal summation of pain was no longer a significant predictor of pain relief ($P = 0.178$). A bootstrap estimation, in which our data were compared with an empirically derived distribution generated based on resampling, indicated a significant full mediation (95% CI from bootstrap analysis, 0.005 to 0.065).

Discussion

This study provides novel insight into brain and behavioral factors that are prognostic indicators of the effect of ketamine infusion for the treatment of neuropathic pain. Our key findings were that (1) the effect of ketamine for pain relief in patients with refractory neuropathic pain was associated with pretreatment temporal summation of pain and by pretreatment engagement of the descending antinociceptive pathway, as measured by default mode network–descending antinociceptive pathway dynamic functional connectivity, and (2) the dynamic engagement of the descending antinociceptive system significantly mediates the relationship

between pretreatment pain facilitation and pain relief. By understanding factors that promote or constrain responsiveness to ketamine treatment, we can better develop and target therapeutic approaches with the purpose of alleviating pain in patients with neuropathic pain.

Approximately 50% of patients in our study had a reduction in numerical rating scale pain scores of 30% or greater at 1 month after intravenous ketamine infusion. This rate of response is consistent with previous findings and suggests that in some patients, neuropathic pain is related to NMDA receptor–independent mechanisms.[37] Furthermore, patients who were in the Responder and Nonresponder subgroups did not differ on clinical pain or psychologic measures in the pretreatment phase or on pretreatment clinical pain measures. This again suggests that patients with neuropathic pain can have identical pain characteristics and psychologic profiles and yet have completely different underlying pain mechanisms (*i.e.*, central sensitization, changes in descending antinociceptive activity),[38] which may account for why some patients respond or do not respond to treatment with ketamine. Thus, the first part of our study was to examine whether we could use quantitative sensory tests to probe underlying pain mechanisms associated with NMDA-related central sensitization[11] and determine who would respond to ketamine.

Our main psychophysical finding is that pretreatment temporal summation of pain measured in neuropathic pain patients is associated with the clinical effect of intravenous ketamine. Temporal summation of pain is a sensory phenomenon that is known to reflect NMDA-mediated enhancement of nociceptive signaling.[10,11] Thus, our results support our hypothesis that patients who have enhanced temporal summation of pain benefit from treatment with an NMDA antagonist. This study builds on previous work using

quantitative sensory testing to profile individual patient pain modulation patterns and predict treatment outcomes. For example, Yarnitsky *et al.*[39] have demonstrated that patients with painful diabetic neuropathy who have lower pain inhibitory capacity, as assessed by less efficient conditioned pain modulation, are most likely to benefit from treatment with duloxetine. Because duloxetine is a serotonin-noradrenalin reuptake inhibitory that acts to enhance the pain inhibitory system and not sensitization, it is unsurprising that pretreatment temporal summation of pain did not predict the efficacy of duloxetine.[39] This provides further evidence that quantitative sensory tests such as temporal summation of pain and conditioned pain modulation reflect distinct underlying pain mechanisms. These measures therefore can provide some indication of dysfunctional mechanisms of pain modulation in patients, which could subsequently guide targeted therapeutic approaches according to this dysfunction.[40,41]

The development of predictive measures of the effect of ketamine has a practical importance because the treatment is not currently widely available because it requires significant resources for drug administration, titration, and patient monitoring. The treatment could become more widely available if overall costs could be reduced by treating only those patients most likely to respond. Personalized pain medicine has the potential to substantially reduce healthcare-related costs that result from series of unsuccessful therapies and may improve disease management, enabling faster return to normal daily functioning. However, measures used for treatment prognostics must be standardized, reliable, and easily adaptable for clinical assessment purposes. Although quantitative sensory testing has been extensively used in clinical research, it is not largely used in clinical practice.[39] However, a lot of work is currently underway, building a repertoire of evidence toward the clinical feasibility and use of these measures.[42] The results of the current study provide the foundation for future studies to continue to examine the clinical utility of temporal summation of pain to predict treatment response in individual patients with neuropathic pain.

The second part of our study used neuroimaging to identify abnormalities in brain function that provide insight into the mechanisms underlying dysfunctional pain modulation and neuropathic pain. Our analysis of dynamic functional connectivity between the default mode network and descending antinociceptive pathway identified clear group differences between Responders compared with Nonresponders and healthy controls. Specifically, pretreatment dynamic functional connectivity was significantly higher in Responders compared with controls and compared with Nonresponders, but there was no significant difference between Nonresponders and healthy controls. Previous work has demonstrated that fluctuations in connectivity (*i.e.*, as measured by dynamic functional connectivity) between the default mode network–descending antinociceptive pathway reflects an individual's capability to orient attention away

from pain.[18] Thus, greater pretreatment dynamics between these regions may reflect a greater capacity of patients with neuropathic pain to decouple attention and perception. Furthermore, at the individual level, pretreatment default mode network–descending antinociceptive pathway dynamic functional connectivity was significantly correlated with the magnitude of pain relief. Cognitive modulations of pain, such as manipulation of attention, are believed to involve endogenous analgesic activity within the descending antinociceptive system.[43] Thus, our findings may reflect an adaptive mechanism by which neuropathic pain patients with high pretreatment default mode network–descending antinociceptive pathway dynamic functional connectivity have high attention–perception decoupling yet fail to adequately modulate their chronic pain. In support of this, previous work in patients with chronic lower back pain has demonstrated that default mode network–descending antinociceptive pathway functional connectivity is associated with the ability to modulate pain.[44] Thus, we propose that the capacity to engage these brain systems predicts treatment effect of ketamine infusions in patients with neuropathic pain.

Finally, we used a mediation analysis to test the hypothesis that the dynamic engagement of the descending antinociceptive system mediates the relationship between pretreatment pain facilitation and pain relief. We found a significant mediation indicating that dynamics within the default mode network–descending antinociceptive pathway systems plays an important mechanistic role linking temporal summation of pain and pain relief. Default mode network–descending antinociceptive pathway dynamic functional connectivity has been linked to the ability to let the mind wander away from pain, a cognitive modulation that likely involves engaging endogenous antinociceptive processes.[18] Therefore, patients with high pain facilitation who also activate/engage the descending antinociceptive system, perhaps indicative of low intrinsic attention to pain, will experience the greatest pain relief with ketamine treatment. Previous studies have demonstrated that in healthy controls, ketamine suppresses temporal summation of pain[11] and also alters resting-state brain networks, including cross-network connectivity with the default mode network.[45] Furthermore, although temporal summation of pain paradigms may evoke enhancement of the dorsal horn signal trafficking (wind-up) through the ascending nociceptive pathway, it is also known that wind-up engages endogenous inhibitory mechanisms.[46] It is the dynamic balance between excitatory and inhibitory mechanisms that determines the level of neuron excitability and spinal pain transmission.[46,47] We have demonstrated that variability in temporal summation of pain scores reflects intersubject variability in the balance of functional connectivity between the ascending nociceptive and descending modulatory pathways.[16] Therefore, we propose that treatment response to ketamine also depends on an individual's capacity to modulate pain *via* their antinociceptive pathways. In addition to their predictive value, future studies are required to determine how

Pre-treatment facilitatory and inhibitory capacity predict treatment outcome
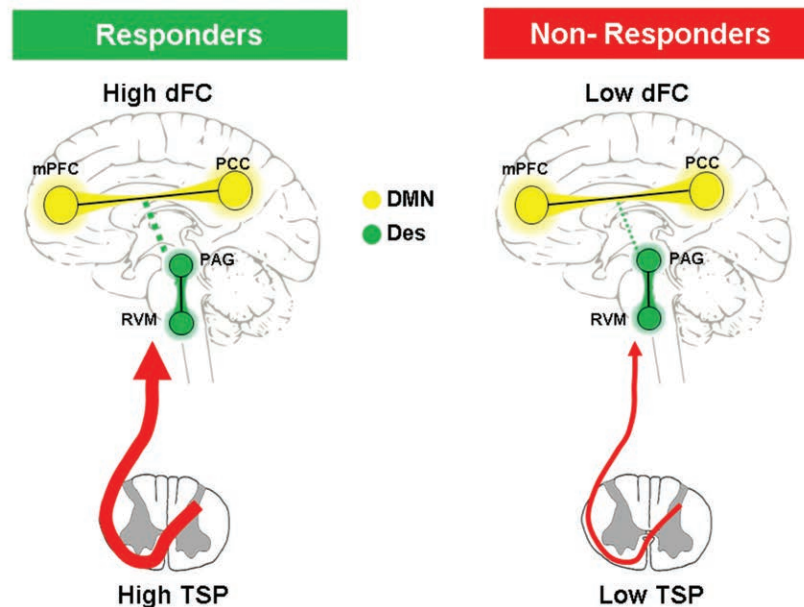
Fig. 3. Summary figure depicts the main findings that patients who had enhanced levels of temporal summation of pain (TSP) and who had greater default mode network–descending antinociceptive pathway dynamic functional connectivity (DMN-DeS dFC) were more likely to respond to treatment with ketamine. mPFC, medial prefrontal cortex; PAG, periaqueductal grey; PCC, posterior cingulate cortex; RVM, rostral ventral medulla.

ketamine changes these brain and behavioral measures post-treatment in patients with neuropathic pain.

Although numerous laboratory studies have used heat pain temporal summation of pain paradigms and demonstrated changes in central sensitivity in chronic pain patients, the clinical utility of these measures is still limited by the lack of standardized protocols and interpretation. Similarly, although functional magnetic resonance imaging measures have provided great insights into the mechanisms underlying pain perception in humans, these measures require complex statistical analyses to derive that are not readily implemented. The sample size of our study does not allow us to make definitive conclusions regarding the impact of higher intensity of neuropathic pain or depression on the likelihood of analgesic benefit. The small sample size also limited our ability to explore relationships between analgesic response to ketamine and the etiology of neuropathic pain. The results of this study may also not be applicable to patients with pain in whom neuropathic mechanisms are contributory but not the major cause of ongoing pain (*e.g.*, low back pain and osteoarthritis). Furthermore, the new consensus guidelines describe that the optimal dosage of ketamine varies by patient.[48,49] However, there is evidence that higher dosages of ketamine, over longer periods of time, may be effective for chronic pain management.[48]

Altogether, our findings demonstrate that enhanced temporal summation of pain and the dynamic engagement of the descending antinociceptive system are important predictive markers (at the subgroup level and in individuals) of the effect of ketamine treatment and point to mechanisms by which ketamine can relieve refractory neuropathic pain (fig. 3). This study

is an important step toward a personalized approach to pain therapy based on individual brain and personality characteristics. Development of a prediction tool using this model could also optimize use of other expensive and resource-intensive therapies to treat neuropathic pain (*e.g.*, spinal cord stimulation).

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