Incisional Nociceptive Input Impairs Attention-related Behavior and Is Associated with Reduced Neuronal Activity in the Prefrontal Cortex in Rats

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ABSTRACT

Background: Cognitive capacity may be reduced from inflammation, surgery, anesthesia, and pain. In this study, we hypothesized that incision-induced nociceptive input impairs attentional performance and alters neuronal activity in the prefrontal cortex.

Methods: Attentional performance was measured in rats by using the titration variant of the 5-choice serial reaction time to determine the effect of surgical incision and anesthesia in a visual attention task. Neuronal activity (single spike and local field potentials) was measured in the medial prefrontal cortex in animals during the task.

Results: Incision significantly impaired attention postoperatively (area under curve of median cue duration-time 97.2 ± 56.8 [n = 9] *vs.* anesthesia control 25.5 ± 14.5 s-days [n = 9], $P = 0.002$; effect size, $\eta^2 = 0.456$). Morphine (1 mg/kg) reduced impairment after incision (area under curve of median cue duration-time 31.6 ± 36.7 [n = 11] *vs.* saline 110 ± 64.7 s-days [n = 10], $P < 0.001$; $\eta^2 = 0.378$). Incision also decreased cell activity (n = 24; 1.48 ± 0.58 *vs.* control, 2.93 ± 2.02 bursts/min; $P = 0.002$; $\eta^2 = 0.098$) and local field potentials (n = 28; $\eta^2 = 0.111$) in the medial prefrontal cortex.

Conclusions: These results show that acute postoperative nociceptive input from incision reduces attention-related task performance and decreases neuronal activity in the medial prefrontal cortex. Decreased neuronal activity suggests nociceptive input is more than just a distraction because neuronal activity increases during audiovisual distraction with similar behavioral impairment. This suggests that nociceptive input and the medial prefrontal cortex may contribute to attentional impairment and mild cognitive dysfunction postoperatively. In this regard, pain may affect postoperative recovery and return to normal activities through attentional impairment by contributing to lapses in concentration for routine and complex tasks.
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PAIN can impact functional capacity directly or from side effects of drugs to treat pain. Both are clinically relevant problems. Inadequate pain treatment may result in reduced ability to maximally perform simple tasks and affect quality of life and recovery. Moreover, impaired focus or attention may be detrimental for individuals and for people effected by the individual's performance. This has implications after surgery for return to work, school, or even routine activities of daily living that may be dependent on maximal reaction speed and focus, such as slicing vegetables or driving a car.[1,2]

Studies of acute and chronic pain on attention have broadened our understanding of the implications and nuances of pain and its subtle effects on cognitive performance.[1,3–6] Distraction in clinical studies may reduce pain perception by diverting resources from painful stimuli or sensations, particularly less intense pain.[7–9] However, more robust or intense pain may conversely divert resources from other tasks, potentially reducing performance.[1,4,6,9]

Editor's Perspective

What We Already Know about This Topic

- Cognitive capabilities may be impaired in the postoperative period
- Impaired cognition may affect the patient's ability to perform activities of daily living

What This Article Tells Us That Is New

- In a rat model of incisional pain, attention was impaired after injury and improved with an opioid analgesic
- Diminished activity of the medial prefrontal cortex was found and may contribute to pain-induced impaired attention

Attention can readily be measured in a rodent behavioral paradigm, the 5-choice serial reaction time task.[10,11] This has been used to understand attention and distraction and the role of different brain regions and neurotransmitters in visual tasks.[12–14] A novel variant of the 5-choice serial reaction time task was developed using a titration of attentional

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cue duration as a measurement of attentional performance, the titration variant of the 5-choice serial reaction time task.[15–17] The titration variant of the 5-choice serial reaction time task has been used to examine distraction and associated modulation in neuronal activity of the medial prefrontal cortex in the rat.[16] Moreover, acute nociceptive input, specifically acute abdominal nociceptive input, impairs performance in this routine and repetitive task, and this can be reversed with opioid agonists and nonsteroidal antiinflammatory analgesics.[17]

Attention is important for optimal performance of tasks relying on cognitive and executive processes. In rats, executive function relies, in part, on input from medial prefrontal cortex.[12] Regulation of the medial prefrontal cortex contributes to maintaining maximal performance through balancing activity and interactions with other brain regions.[12,14] Hypo- or hyperactivation in medial prefrontal cortex may underlie dysfunctional or disrupted attentional processing.[13] Understanding the relationship of changes in neuronal activity resulting from interventions is valuable for understanding brain-related changes in neuronal activation that may modulate specific behaviors. Many neurotransmitter systems play roles in attentional processing, with cholinergic and noradrenergic input to the medial prefrontal cortex likely contributing to discrimination from interference.[14,18] Neuronal activity in the medial prefrontal cortex is predominantly increased during acute audiovisual distraction.[16,18] Neuronal activity in the medial prefrontal cortex also follows nociceptive input in an intensity- and duration-specific manner.[19] Pain may be just another distraction, or it may disrupt attention in a distinct manner. Examining neuronal activity in the medial prefrontal cortex in animals performing attention-based tasks may permit us to determine the extent to which nociceptive input alters this region in a manner distinct from nonpainful distracting stimuli. In this study we hypothesized that anesthesia and surgical incision would impair attentional performance, that impairment is related to nociceptive input and will be reduced (improved function) with morphine analgesia, and that neuronal activity in the medial prefrontal cortex in the freely behaving rat would be altered in conjunction with the reduced performance from nociceptive input by the titration variant of the 5-choice serial reaction time task.

Materials and Methods

Animals

For the experiments, a total of 46 male Fisher 344 rats (240 to 350 g, Harlan Laboratories, USA) were used for this study. Twenty-two animals were used for behavior alone in the titration variant of the 5-choice serial reaction time task (11 incision and morphine, 10 incision and saline); one animal did not train sufficiently in the titration variant of the 5-choice serial reaction time task and never entered into the study protocol. Twenty-four animals were used for the electrophysiology experiments (nine incision electrophysiology, nine control/anesthesia electrophysiology); six animals did not achieve stable performance in the titration variant of the 5-choice serial reaction time task either before or after electrode placement.

Animal experiments were done in cohorts of a maximum of eight animals with block randomization of half of the animals to treatment or control for each cohort. Animals were kept on a reversed light–dark cycle (dark 05:00 to 17:00) and housed in a temperature- and humidity-controlled room within an Association for Assessment and Accreditation of Laboratory Animal Care–accredited facility, as previously described.[15] Briefly, after a one-week acclimation period with rats housed in pairs and given free access to standard rat chow and water, animals were singly housed and given free access to rat chow until they attained a minimum body weight of 240 g. Animals were then reduced to 90% of their free-feeding weight and given sufficient rat chow thereafter to maintain normal growth and increased weight gain while maintaining 90% of average free-feeding weight for Fisher 344 rats, based on growth curves from the vendor. Animals were given free access to water throughout the experiment except during experimental sessions. All procedures were in accordance with the Guide for the Care and Use of Laboratory Animals as adopted and promulgated by the National Institutes of Health and were approved by the Institutional Animal Care and Use Committee of Wake Forest University Health Sciences (Winston-Salem, NC).

Behavior

All behaviors were conducted in standard operant chambers controlled through a PC-compatible computer and interface with Med-PC IV software (Med Associates Inc., USA), as previously described.[15–17] Briefly, operant chambers with standard stainless-steel grid bar floors were in a sound- and light-attenuating cubicle (Med Associates Inc.). One wall was curved with a bank of five nose poke holes for the rat with light-emitting diodes located in the rear of each and an illuminated food trough with infrared head entry detection located on the opposite wall with a magazine-type pellet dispenser for 45 mg food pellets. A jeweled red lens cap (Allied Electronics Inc., USA) was used for the food trough lamp and a red lens was also used for the house light (Med Associates Inc.). A wide-angle video camera (Genius WideCam F100, KYE Systems Inc., USA) was affixed to the operant chamber top, and all sessions were observed on an external monitor in real time and recorded for later observation. Experiments were conducted during the dark phase of the light–dark cycle. Animals were trained in four phases as described.[15] The final phase consisted of daily 30-min weekday sessions comprised of 100 trials each during which the animal learned to watch the bank of five nose poke holes until an light-emitting diode (the cue) would come on randomly. Responses in the illuminated nose poke hole were reinforced by delivery of two 45-mg chocolate flavored pellets (Bio-Serv

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Inc., USA) into the food trough signaled by illumination of the food trough light. The food trough light was turned off 2 s after head entry into the trough was detected, and the next trial began 5 s later. Incorrect or omitted responses (no response within the cue duration or 5 s, whichever is longer) resulted in no food delivery, no illumination, and turning off the house light. The next trial began 5 s later, as with correct trials. The cue duration was initially set to 30 s and decreased in the next trial after a correct response or increased in the next trial after incorrect or omitted responses, with cue durations being set in discrete increments according to a predetermined array ranging from 30 to 0.1 s.[15] In this manner the animal titrated the cue duration based on the ability to maximally perform in the visual task paradigm. Each trial was signaled by illumination of the house light, followed by a 5-s intertrial interval, during which the animal had to wait for illumination of a light-emitting diode cue at random. Responses during this 5-s interval reset the interval timer to 5 s, such that the animal had to withhold responses until an light-emitting diode cue was provided. The median cue duration was the primary outcome measure of performance in the titration variant of the 5-choice serial reaction time task and was calculated from trials 15 to 100 for each session. Once the median cue duration was stable and titrated to less than 1-s duration for a minimum of five consecutive sessions, the animal was considered fully trained and further surgery involving implantation of electrodes was performed. The measures collected for each trial consisted of the cue duration, latency to correct or incorrect response, and the latency to retrieve food reward. Measures collected and summed across the entire session included the number of total correct, incorrect, and omitted responses, the number of premature and perseverative responses, and the total time required for completion of each session. Premature responses are those that occur between trials but before the light-emitting diode is illuminated, and perseverative responses are multiple repetitive responses in the same nose poke hole during the same trial.

Surgical Implantation of Electrodes

For *in vivo* field potential and spike recording, rats were allowed to free feed for one week after full training in the titration variant of the 5-choice serial reaction time task. Rats were initially anesthetized with pentobarbital sodium 40 mg/kg, intraperitoneal, and maintained with oxygen and isoflurane. Animal breathing, reflexes, and level of anesthesia were monitored throughout surgery. A stereotaxic apparatus was used for implantation of recording electrodes in the medial prefrontal cortex. After sterile prep with betadine and alcohol, the skin was incised and a small burr hole was made at the location identified by the stereotactic coordinates located from the bregma +2 mm anteriorly, 0.8 mm from midline on the right, and electrodes were then placed through the burr hole −3.5 mm from the bone surface, as previously described.[16] After placement, the electrodes were bent at the skull and fixed in dental cement mounted around stainless-steel mounting screws to provide further attachment and stabilization. The posterior attachment screw formed the silver wire reference/ground electrode connection to the electrodes. The wireless electrodes were manufactured with five Teflon-coated 50-μm separate stainless steel insulated electrodes (9 to 10 MOhms) (NB Labs, USA) with the recording and ground electrodes attached to a 10-pin connector (A70010, Omnetics Connector Corp., USA) and implanted with the connector facing upwards.[20] Care was taken to provide a smooth cement surface along the base of the implant so the skin could heal around the implant. After surgery, rats were given an intramuscular injection of 300,000 units/kg penicillin G procaine to prevent infections and placed inside a heated cage to recover for at least 1 h and free fed for one week thereafter or until animals achieved presurgery weight. Animals were then food restricted as described above and began daily sessions of the titration variant of the 5-choice serial reaction time task until the median cue duration stabilized for 5 consecutive days at less than 1 s. Animals were then entered into the study protocol (fig. 1).

Surgical Incision Protocol

The effect of surgical incision or sham with anesthesia on performance in the cue duration titration procedure was determined in all animals. After stable recordings of median cue duration of less than 1 s or after return of the median cue duration to less than 1 s after electrode placement, the animals underwent paw incision under general anesthesia with isoflurane and spontaneous ventilation, as previously described with sterile technique and betadine prep.[21] Sham animals were administered the same concentration of isoflurane anesthesia for the same duration and prepped, but they did not undergo incision. Animals were randomized to treatment. Sutures were removed on day 10 with brief anesthesia, and sham animals had the same brief anesthetic with isoflurane. The average anesthesia time for the incision and sham was 6 min, and the average anesthesia time was 3 min for suture removal. No animal developed wound dehiscence or infection during the study. For the morphine study, animals were randomly assigned to receive 1 mg/kg of morphine or saline subcutaneously daily for 14 days, administered 30 min before the titration variant of the 5-choice serial reaction time task session. Effects on median cue duration were determined daily at baseline and for 14 days after the procedure. Median cue duration, neuronal firing, and local field potential were determined from the same animals. Background electrophysiologic data were determined during sessions in which the animal was placed in the dark operant chamber without the operant paradigm in effect. While the technicians were blinded to treatment, blinding was not possible as the technician could see if an animal had sutures in the paw for the sham and incision groups, but they remained blinded to morphine *versus* saline groups.

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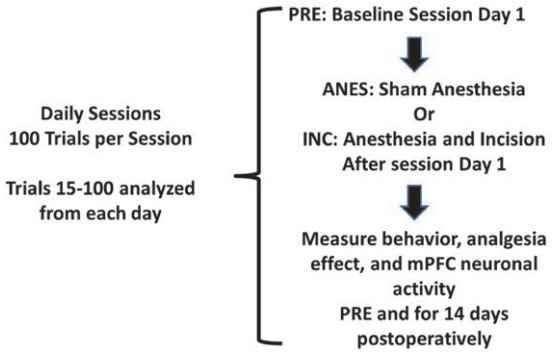

Fig. 1. Study design. The study design for the incision protocol is presented. All animals underwent 100 trial sessions on consecutive days. After the performance was stable with a median cue duration <1 s for a week, the protocol began: session at baseline session day 1 or time 0 (PRE); anesthesia with isoflurane (ANES) in control or incision and anesthesia (INC) after the baseline session on day PRE; testing every day for 14 days postoperation after incision and anesthesia or anesthesia with isoflurane. Median cue durations determined for the 15- to 100-trials period. Single spike data are from the same 15- to 100-trials period, and local field potential data are from a 900-s epoch during the same period.

Neural Recording

A wireless headstage was connected to the implanted electrodes of each animal before each session and used to record, amplify, and digitize electrical activity from each electrode by Neuroware (Triangle Biosystems Inc., USA) acquisition software for recording of extracellular local spike activity and local field potential. Digital online electrophysiologic data are amplified and filtered to only record spike waveforms more than 2.5-times baseline signal/noise with negative and positive threshold and spike template while the analog data are passed through a 1401 CED analog to digital converter (CED Inc., United Kingdom). A low-pass filter was used for local field potential less than 475 Hz, while a high pass filter was used for spikes (300 to 7000 Hz). One of the electrodes was selected as the reference electrode to eliminate muscle activity interference from chewing and licking. This selection is done with the technician blinded to treatment group. Electrode placement in the medial prefrontal cortex was verified in the nine incision animals and nine control animals with brain serial coronal cryosection at the conclusion of all experiments and compared with standard rat brain diagrams.

Neural Activity Analysis

Offline analysis for further spike sorting was used for spike morphology to limit analysis to single-cell depolarizations that were standardized and quality controlled for consistent and reproducible analytics for the primary outcomes of absolute spike count, frequency, and burst count. Secondary analysis included maximum instantaneous frequency, burst-related instantaneous frequency, and spike burst and frequency in bursts. Spike probability was determined during operant sessions for 20 correct and 20 omission trials at baseline and at postoperative day 5 after incision. This included any spike within 1 s of the cue light-emitting diode going on, within 1 s of the cue light-emitting diode going off, within 2 s of the house light going off, or within 2 s of head entry into the food trough as identified in real time by observation of the video for each session. Spike probability for incorrect responses was not assessed as these are infrequent at baseline and become even less frequent after injury, making probability assessment limited. NeuroExplorer version 4 (NEX Technologies, USA) was used for analysis of local field potential and spike characteristics. The term "burst" is a cluster of spikes from a single neuron that differs from other spikes by being more closely spaced in time than neighboring spikes and thus having a higher discharge rate than the surrounding spike trains.[22] Bursts were defined with the Poisson surprise method of Legéndy and Salcman.[23] This method is implemented in NeuroExplorer and was used to quantify bursts between groups. The effects of incision on local field potential were evaluated by use of Fast Fourier Transformation and comparison of the total relative spectral power (in dB or log of the power) over the 1 to 100 Hz range for a 900-s interval at the same time period during each of the daily sessions at baseline and on days 2, 4, 8, and 14 after surgery or control anesthesia during the 15- to 100-trials period. Area under the curve was calculated with the midpoint rectangle Riemann sum for the overall power spectral density-frequency curve; the areas under the curves were compared between treatment groups and over time after treatment at baseline and then for discrete frequency bands delta (1 to 3 Hz), theta (4 to 8 Hz), alpha (9 to 13 Hz), beta (14 to 30 Hz), and low gamma (30 to 50 Hz) between treatment groups and over time after treatment.

Data Analysis

The primary behavioral outcome measure related to attention was the median cue duration that was calculated with Microsoft Excel from the cue durations for trials 15 to 100 for each session. A power analysis was performed *a priori* to detect a difference between incision and sham control for median cue duration, based on previous data using a power of 0.9, an alpha of 0.05, and an estimated effect size of 0.4; 14 repeated measures ANOVA between treatment difference and a correlation between measures of 0.2 and 10 subjects in each group was estimated. The experiment was set up on the basis of this with the expectation that not all animals would train effectively or recover. As outlined in the methods, some animals were not able to participate in the study for inability to adequately train in the titration variant of the 5-choice serial reaction time task initially or after electrode placement (greater after electrode placement), resulting in the sample sizes noted. Effect sizes were subsequently calculated based on the actual subjects in each experiment. Partial eta squared or eta squared (η^2) (partial eta squared is when more than one variable is present) is a measure of effect size and is the

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proportion of the variance accounted for by each of the main effects, interactions, or error in the ANOVA. The effects of incision and morphine on median cue duration were analyzed by two-way mixed ANOVA with one-factor repetition (time). If the interaction term was significant, within-group effects were analyzed by one-way repeated measures ANOVA with the Holms–Sidak method used for correction and pairwise comparisons. The effects of intervention on secondary behavioral outcomes from the titration variant of the 5-choice serial reaction time task were analyzed to test for treatment effects using only one-way ANOVA with no pairwise comparisons. Area under the median cue duration-time curves were calculated with the midpoint rectangle Riemann sum; these areas under the median cue duration-time curves compared with a Student's *t* test for incision and sham/control and with a one-way ANOVA for sham/control, saline incision, and morphine incision groups. Spike, burst, and local field potentials analysis was performed with two-way ANOVA, and within-group analysis was performed if significant by one-way repeated measures ANOVA with pairwise comparisons using the Holms–Sidak method for multiple comparisons. Statistical analysis was performed with Sigmaplot (Systat Software Inc., USA). Data are presented as means (*M*) and SD, except when not normally distributed; then, median and range are presented and noted. Analysis of *P* values were determined by Sigmaplot. Corrections for multiple comparisons were used where appropriate. Where *P* values are reported, these are corrected *P* values. $P < 0.05$ was considered statistically significant.

Results

Behavioral Effects of Incision in the 5-Choice Serial Reaction Time Task Titration Variant

The baseline median cue duration, the measure of attentional performance in the titration variant of the 5-choice serial reaction time task, was 0.6 ± 0.1 s in the sham group and 0.7 ± 0.1 s in the incision group. Paw incision increased the median cue duration, and there was a significant effect of time (F[14,224] = 7.08; $P < 0.001$) and treatment (F[1,224] = 13.31; $P = 0.002$) on the median cue duration as well as an interaction (F[14,224] = 5.92; $P < 0.001$) (fig. 2A). The median cue duration in the sham group with anesthesia alone was not different over time (F[8,14] = 0.771; $P = 0.70$) (fig. 2A). The cumulative effect of incision (97.2 ± 56.8 s-days) on performance in the titration variant of the 5-choice serial reaction time task was a four-fold increase in area under the median cue duration-days curve compared to the anesthesia control (25.5 ± 14.5 s-days), representing a significant impairment in performance (t[16] = 3.67; $P = 0.002$). Response data during the titration variant of the 5-choice serial reaction time task are shown in figure 2B. Paw incision decreased correct responses compared to anesthesia only (F[1,268] = 20.36; $P < 0.001$) and increased the number of omission responses (F[1,168] = 11.74; $P < 0.001$), while incorrect responses were not significantly different

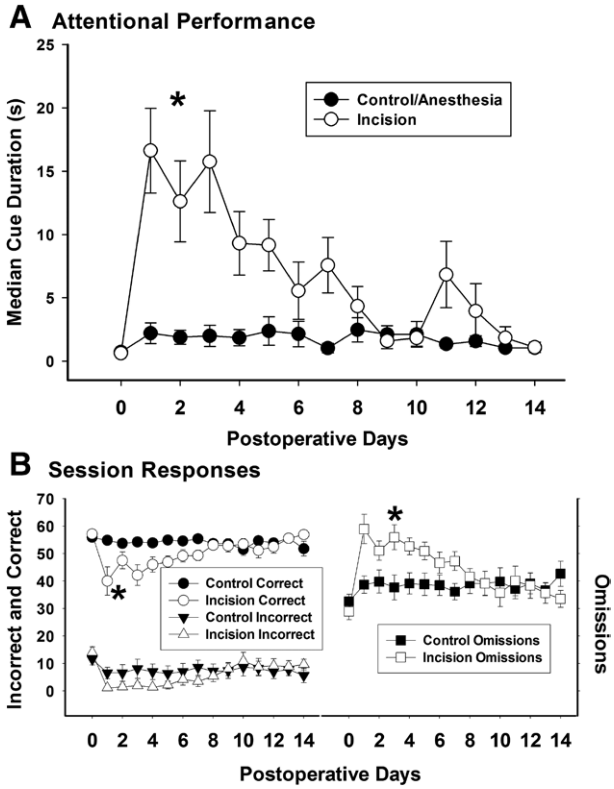

Fig. 2. Effect of incision median cue duration and session data. (*A*) Attentional performance was assessed with median cue duration from trials 15 to 100, at baseline and for 14 days postoperation, from 18 animals (9 control and 9 incision animals). There was a significant increase in median cue duration after incision compared to control. (*B*) Along with the increase in median cue duration, there was a significant increase in omissions and a significant decrease in correct responses. No difference in incorrect responses was present. *One-way repeated measures ANOVA between groups.

between groups (F[1,268] = 2.85; $P = 0.093$) (fig. 2B). There was also a decrease in premature responses in the incision group compared to the control group (F[1,268] = 15.88; $P < 0.001$). Representative plots of cue duration over trials are presented for a control animal and an incision animal for sessions at baseline and after incision or anesthesia only (fig. 3). The overall average latency to correct response was higher in the incision group (3.5 ± 2.6 s) than in the control group (2.1 ± 1.3 s) (F[1,268] = 35.66; $P < 0.001$), and the overall average latency to reward was higher in the incision group (7.4 ± 2.7 s) than in the control group (2.4 ± 1.5 s; F[1,268] = 7.91; $P = 0.005$). The average latency to incorrect responses was no different between the incision group (2.8 ± 3.3 s) and the control group (2.3 ± 2.0 s; F[1,208] = 1.95; $P = 0.164$). However, while all animals had incorrect responses in all baseline sessions, there were more sessions with no incorrect responses in the incision group (36 out of 126) than sessions with no incorrect responses in the control group (19 out of 126; X^2[1, N = 252] = 6.72; $P = 0.009$). The overall average

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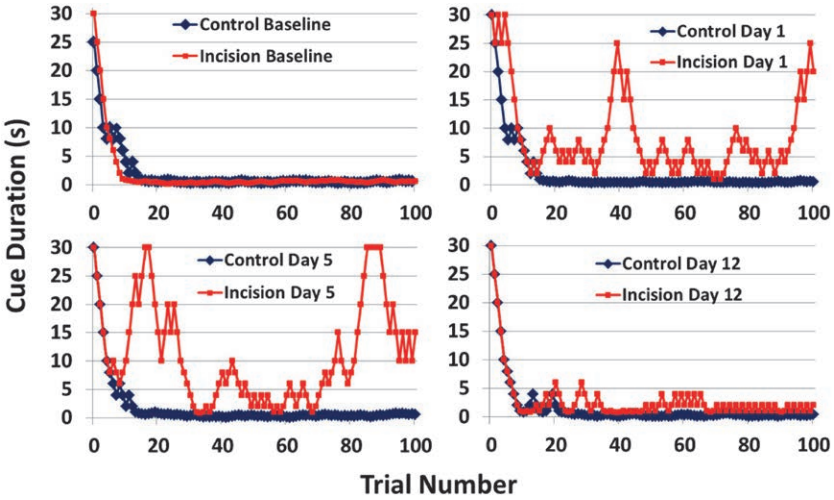

Fig. 3. Representative examples of the effects of incision in the titration variant of the 5-choice serial reaction time task. The *blue* is from a control/anesthesia-only animal and the *red* is an animal that underwent anesthesia and incision. At baseline the behavior over the 100 trials is similar. On postoperative day 1 and 5, the inability of the animal to maintain performance after incision can readily be seen in the persistent increase in cue duration and inability to maintain performance, with a lower cue duration than the control animal. By day 12, there is still some reduced performance in the animal after incision, but it is very similar to the control and close to baseline performance.

rate of completion of trials within the sessions went down in the incision group (M 3.7 SD 0.7 trials/min) compared to the control group (4.4 ± 0.2 trials/min; t[28] = –3.62; $P = 0.001$).

Behavioral Effects of Morphine on Performance in the Titration Variant of the 5-Choice Serial Reaction Time Task after Incision

The baseline median cue duration was 0.5 ± 0.1 s in the incision plus saline group and 0.5 ± 0.1 s in the incision plus morphine group. A single dose of 1 mg/kg of morphine was used to verify the role of pain from the incision in reducing performance in the titration variant of the 5-choice serial reaction time task, although a full dose response has been demonstrated with a different model of pain.[17] This dose is an intermediate dose in efficacy for pain treatment in the rat and has no effect in normal animals in this task.[17] Median cue duration increased significantly over time compared to baseline in both the incision plus saline group (F[14,149] = 2.48; $P = 0.004$) and in the incision plus morphine group (F[14,164] = 2.27; $P = 0.008$). However, morphine significantly attenuated the increase in median cue duration after incision compared to saline (F[1,314] = 10.99; $P = 0.004$; fig. 4A). There was a cumulative effect of morphine on performance in the titration variant of the 5-choice serial reaction time task (F[2,28] = 11.51; $P < 0.001$), and this effect is represented by a four-fold decrease in area under the median cue duration-days curve (31.6 ± 36.7 s-days) compared to the incision plus saline control (110.0 ± 64.7 s-days; t[20] = 4.07; $P < 0.001$; fig. 4B). The morphine effect was also compared to the control anesthesia group (25.5 ± 14.5 s-days) and no difference in area under curve was noted between the control/anesthesia group and the incision plus morphine group (t[18] = 0.30; $P = 0.77$). Representative plots of cue duration over trials are presented for sessions with an incision plus saline and an incision plus morphine animal at baseline and after incision (fig. 5).

There was an overall effect of morphine on correct responses after incision with an increase in correct responses (F[1,313] = 43.45; $P < 0.001$) in the morphine group (53.9 ± 9.7) compared to the saline group (44.8 ± 14.5), and an overall effect of morphine (34.1 ± 11.6) decreasing omissions compared to the saline group (41.0 ± 9.2) after incision (F[1,313] = 34.66; $P < 0.001$). Morphine also increased incorrect responses (9.6 ± 8.8) compared to saline (4.2 ± 7.6) after incision (F[1,313] = 34.17; $P < 0.001$). The overall average latency to correct responses was lower in the morphine group (1.9 ± 1.7 s) compared to the saline group after incision (4.3 ± 3.4 s; F[1,313] = 67.55; $P < 0.001$) and the overall average latency to reward was lower in the morphine group (1.9 ± 0.7 s) compared to the saline group after incision (3.1 ± 2.2 s; F[1,313] = 44.51; $P < 0.001$). The overall average latency to incorrect responses was shorter in the morphine group (1.9 ± 1.9 s) compared to the saline group (3.6 ± 4.1 s) after incision (F[1,246] = 20.49; $P < 0.001$). There were fewer sessions with no incorrect responses in the morphine group (16 out of 149) compared to sessions with no incorrect responses in the saline groups (50 out of 100) after incision, reversing the effect seen from the incision (X^2[1, N = 325] = 29.21; $P < 0.001$). The overall average rate of completion of trials within the sessions was not different between the morphine (5.7 ± 7.4 trials/min) and the saline groups (5.6 ± 12.5 trials/min) after incision (F[1,313] = 0.003; $P = 0.96$).

Single Spike Activity in the Medial Prefrontal Cortex from Incision during 5-Choice Serial Reaction Time Task Titration Variant

Neuronal spike analysis was performed from 24 distinct neuronal spikes isolated from 45 electrodes in 9 animals in the

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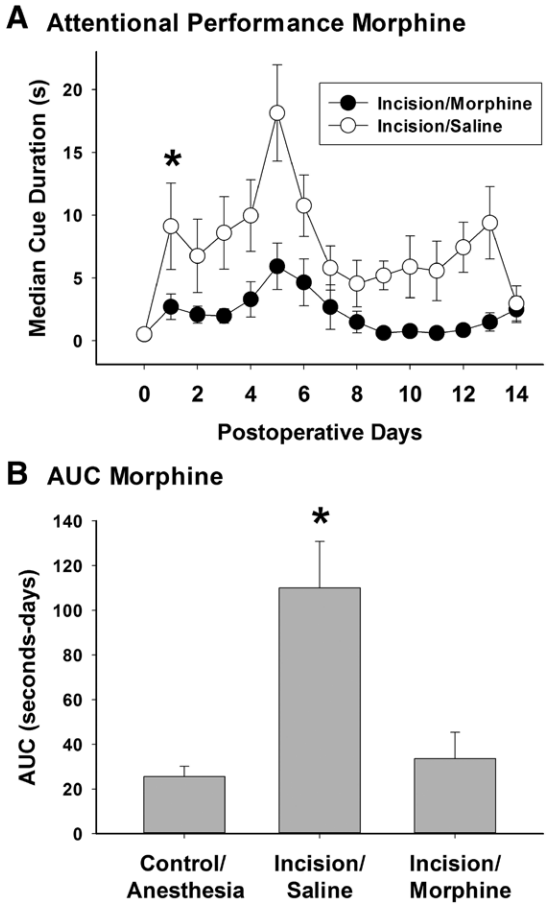

Fig. 4. Effect of morphine or saline on performance in the titration variant of the 5-choice serial reaction time task after incision. (*A*) Median cue duration was increased over time in both the incision plus saline (n = 10 animals) and the incision plus morphine (n = 11 animals) groups, with a significant difference between the two groups. *One-way repeated measures ANOVA between groups. (*B*) For the area under the median cue duration-time curve, the incision plus saline group is significantly different from both the control/anesthesia (n = 9 animals) group and the incision plus morphine group, but no difference was seen between the control/anesthesia group and the incision plus morphine groups. *One-way ANOVA between groups with pairwise comparisons using Holm–Sidak method.

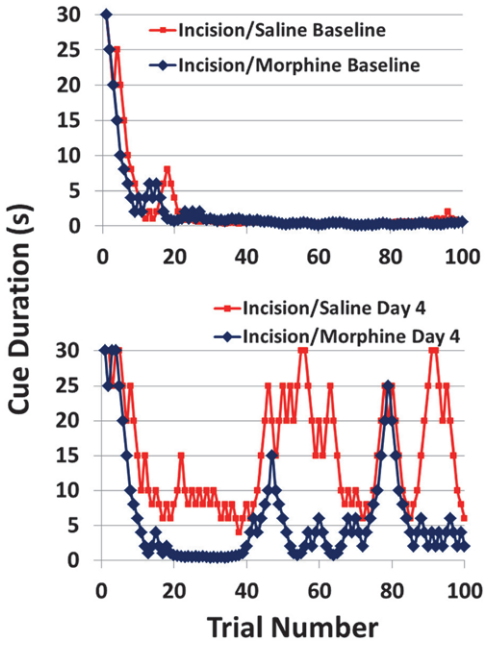

Fig. 5. Representative examples of the effects of morphine on incision in the titration variant of the 5-choice serial reaction time task. The *blue* is from a morphine plus incision animal, and the *red* is an incision plus saline animal. At baseline, the behavior over the 100 trials is similar. On postoperative day 4, the effect of morphine to improve performance improvement and reduce the overall cue duration after incision can readily be seen when compared to the more impaired performance and more consistently higher cue duration over the trials in the session in the incision plus saline animal.

incision group and 28 distinct neurons from 45 electrodes in 9 animals in the control sham group. Spike frequency during background sessions (dark chamber, no titration variant of the 5-choice serial reaction time task) was found to be 0.38 ± 0.14 spikes/s and burst rate 1.43 ± 0.48 burst/min; these were increased to 0.68 ± 0.48 spikes/s and 2.93 ± 2.02 burst/min during the titration variant of the 5-choice serial reaction time task procedure (spike frequency F[2,77] = 5.50, P = 0.006; burst rate F[2,77] = 9.22, P < 0.001). No difference was found between baseline control and incision group spike frequency and burst rate (incision, 0.71 ± 0.56 spikes/s; control, 0.66 ± 0.40 spikes/s; incision, 2.93 ± 2.02 burst/min; control, 2.68 ± 1.32 burst/min) (spike frequency, t[52] = 0.391; P = 0.64; burst rate, t[52] = 0.54; P = 0.594). There was an overall interaction effect of treatment and time on spike rate or spike frequency (F[7,350] = 4.66; P < 0.001), with significant differences from postoperative day 1 through postoperative day 7 noted by using the Holms–Sidak method for pairwise multiple comparisons (fig. 6A). Within-group comparisons revealed that there was no overall effect of sham surgery on spike rate (F[7,216] = 1.03; P = 0.412), but there was a reduction in spike frequency over time in the incision group (F[7,184] = 4.214; P < 0.001). Spike probability was a secondary outcome and only determined at baseline and on postoperative day 5 after incision or sham (table 1). Spike probability was higher when the light-emitting diode turned on and off for the correct responses, but there was no difference between spike probability with the light-emitting diode on and off during omissions. However, after incision the light off increased the spike probability for correct responses, but for incision there was a decrease in spike probability with light off with omissions. Behavior at baseline and postoperative day 5 is presented for comparison in table 2.

Burst rate was determined for each session. There was an overall interaction between treatment and time on burst rate (F[7,350] = 5.99; P < 0.001), with significant differences from postoperative day 1 through postoperative

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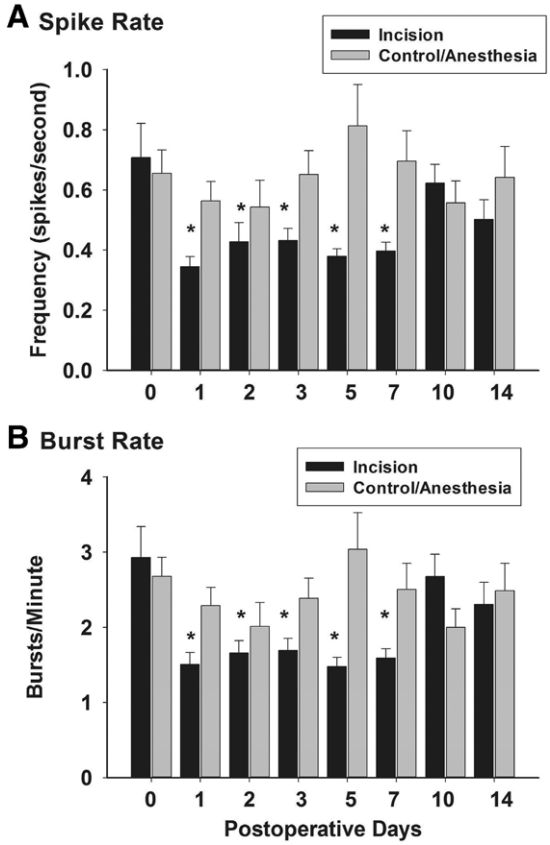

Fig. 6. Effects of incision on neuronal action potential spike and burst rates. Spikes and burst were determined from a total of 18 animals (n = 9 control and n = 9 incision animals). A total of 24 distinct neuronal spikes were isolated from 45 electrodes in the incision animals and 28 distinct neurons in the control animals. (*A*) There was no difference in spike rate between the incision and the control/anesthesia group at baseline. There was no difference in spike rate over time after sham anesthesia in the control. Spike rate was reduced significantly after incision on day 1 and remained so through day 7. Thereafter, no difference was noted. (*B*) There was also no difference in burst rate between the incision and the control/anesthesia group at baseline. There was also no difference in burst rate over time after sham anesthesia in the control. Burst rate was reduced significantly after incision on day 1 and remained so through day 7. Thereafter, no difference was noted. Characteristics of spike in bursts are presented in table 3 for baseline and postoperative day 5 only. *One-way repeated measures ANOVA between groups, with pairwise comparisons using the Holm–Sidak method.

day 7 noted by using the Holms–Sidak method for pairwise multiple comparisons (fig. 6B). Within-group comparisons revealed that there was no overall effect of sham on spike rate ($F[7,216] = 1.16$; $P = 0.327$), but there was a reduction in spike frequency over time in the incision group ($F[7,184] = 5.49$; $P < 0.001$). Characteristics of spikes in bursts were secondary outcome measures and only analyzed at baseline and on postoperative day 5 after incision or sham (table 3).

Local Field Potentials Activity Changes in the Medial Prefrontal Cortex from Incision during the Titration Variant of the 5-Choice Serial Reaction Time Task

Local field potentials were analyzed from 21 distinct neurons isolated from 45 electrodes in 9 animals in the incision group and 28 distinct neurons from 45 electrodes in 9 animals in the control sham group. One electrode was used as a ground to reduce noise from areas outside of the location of the electrodes. The local field potentials were analyzed to compare area under curve for the power spectral density- (in dB or log of the power) frequency curve from 0 to 100 Hz from baseline after incision or in sham control. There was an overall interaction effect of treatment and time on local field potentials ($F[4,235] = 2.44$; $P = 0.048$; fig. 7A). Within-group comparisons showed the time effect was only present for the incision group ($F[4,100] = 5.812$; $P < 0.001$) with a reduction in local field potential area under curve of the power spectral density-frequency curve that was apparent at postoperative day 2 and remained through postoperative day 14 by the Holms–Sidak method. This time-dependent effect was present at each of the frequencies (delta, 1 to 3 Hz; theta, 4 to 8 Hz; alpha, 9 to 13 Hz; beta, 14 to 30 Hz; low gamma, 30 to 50 Hz; fig. 7B). There was no difference in local field potential over time after sham anesthesia ($F[4,135] = 0.487$; $P = 0.745$). A diagram for the location of all electrodes in the brain is presented in figure 8.

Discussion

These data establish that impaired attentional performance results from incision and that nociceptive input plays a role because morphine attenuates this impairment. The functional impact of paw incision is readily assessed longitudinally until resolution with the titration variant of the 5-choice serial reaction time task. This study corroborates the effect of nociceptive input on attentional performance and extends these findings by suggesting a role for the medial prefrontal cortex neuronal activity in the effect of incisional nociceptive input as measured by the increased median cue duration, with associated changes in individual spike activity and local field potential power.[17] These changes in neuronal activity after incision are distinct from changes induced by audiovisual distraction and suggest that interference from pain is not due to competing distracting stimuli.[16,24]

Attentional deficits from pain are reported.[17,24–29] Interestingly, nerve injury did not induce deficits until 2 weeks after injury and were most marked months later. While chronic pain and acute postoperative pain may be different, one would anticipate acute postoperative nerve injury would cause disruption early. Alternatively, the standard 5-choice serial reaction time task may be less sensitive at detecting impairment. Enhanced sensitivity of the titration variant of the 5-choice serial reaction time task to detect impairment may be from cue titration to performance capability instead of measuring success rates in a paradigm with fixed difficulty.[15–17] The titration method results in cue changes until reaching the limits of performance capability. Thus, the

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Table 1. Behavior-related Spike Probability

	Nose Poke Light			
	Spike Probability, Pre	Spike Probability, Post	Spike Probability, House Light Off	Spike Probability, Feed Reward
Correct	0.31 ± 0.11	0.42 ± 0.16	NA	0.51 ± 0.26
Omission	0.16 ± 0.09*	0.16 ± 0.10*	0.24 ± 0.16	NA
Correct postoperative day 5	0.29 ± 0.17	0.59 ± 0.02†	NA	0.39 ± 0.28
Omission postoperative day 5	0.18 ± 0.11	0.04 ± 0.04*,‡	0.19 ± 0.12	NA

Spike probability is shown for the visual cue (Nose Poke Light) both before (Pre, any spike within 1 s of cue light going on) and after (Post, any spike within 2 s of cue light going off). Spike probability is shown for spikes within 1 sec after house light goes off after omission trials or for spikes within 2 s of food trough head entry. Data were collected over 20 trials for each animal (n = 11). Incorrect responses are too few to adequately evaluate. Data were analyzed with a paired Student's *t* test, and $P < 0.05$ was considered significant.

*Different from correct.†Different from light on pre. ‡Different from baseline.

Table 2. Characteristics of Spikes in Bursts in Incision Group after Surgery

	Baseline	Postoperative Day 5	Statistics
Burst number, total	62.8 ± 45.7	39.2 ± 13.4	T(23) = 2.442, $P = 0.023$
Burst rate, no./min	2.93 ± 2.02	1.48 ± 0.58	T(23) = 3.364, $P = 0.003$
Spikes in bursts, %	57.6 ± 9.9	62.2 ± 8.4	T(23) = –1.762, $P = 0.091$
Mean frequency, Hz	74 ± 36	70 ± 25	T(23) = 0.493, $P = 0.627$
Mean burst duration, s	0.95 ± 0.81	1.46 ± 1.11	T(23) = –2.654, $P = 0.014$
Mean spikes in bursts, no.	8.3 ± 1.8	10.1 ± 3.4	T(23) = –2.300, $P = 0.031$
Mean peak frequency, Hz	401 ± 88	406 ± 57	T(23) = –0.384, $P = 0.704$
Mean interburst interval, s	27.4 ± 14.9	46.2 ± 19.8	T(23) = –4.648, $P < 0.001$

Baseline session and postoperative day 5 session in incision group. Significance was tested with the paired Student's *t* test, and statistical data shown for the analysis. $P < 0.05$ is considered significant.

Table 3. Behavior for Baseline, Spike Probability, and Burst Characteristics on Postoperative Day 5

	Baseline	Postoperative Day 5	Overall Statistics
Median cue duration, s	0.6 ± 0.3	9.2 ± 6.1	T(11) = 4.274; $P = 0.003$
Correct, total	57.1 ± 3.2	46.9 ± 6.5	T(11) = 5.145; $P = 0.063$
Incorrect, total	9.2 ± 6.1	0.6 ± 0.3	T(11) = 4.274; $P = 0.003$
Omissions, total	28.9 ± 8.8	50.9 ± 9.6	T(11) = 7.645; $P < 0.001$
Premature, total	8.3 ± 5.7	1 ± 1.6	T(11) = 4.158; $P = 0.003$
Perseverative, total	3.7 ± 3.3	2.9 ± 2.9	T(11) = 0.428; $P = 0.68$

titration variant seems positioned to detect small decrements in capability on the basis of maximal performance in a given animal through enhanced sensitivity to both disruption and reversal with analgesics.[24,29] The abilities of the titration variant to detect individual differences within sessions and individual differences in response to surgery are unique and powerful. This may partially explain some of the differences in responses to incision in study cohorts between the incision group in the sham initial experiment and the incision group in the morphine experiment.

Time and ability to respond to cue change likely reflect either a delay in processing speed or a decision to move more slowly. Based on video observation, slower or less movement seems unlikely, although not specifically measured. Additionally, incision did not impair total distance traveled in open-field analysis previously.[30] The decreased performance seems to be the "decision" to omit or the inability to process the cue, resulting in increased cue duration reflected in more omissions and less correct responses. Motivation could be a factor; while motivation was not measured directly, it has been suggested that disruption in attentional tasks from pain is related to decreased processing speed and not decreased motivation.[25]

Measuring medial prefrontal cortex neuronal activity in behaving animals during these tasks allows further validation of its role in attentional performance and nociceptive processing. Attention-related burst firing of individual neurons occurs in prefrontal cortex.[31] In this study spike frequency and bursting decreased with nociception generated by incision. The character of the bursts also changed, with increased burst duration, increased spikes within a burst, and increased interburst interval after injury. Neuronal bursts may globally increase neurotransmitter release and information processing, whereas reduced burst activity

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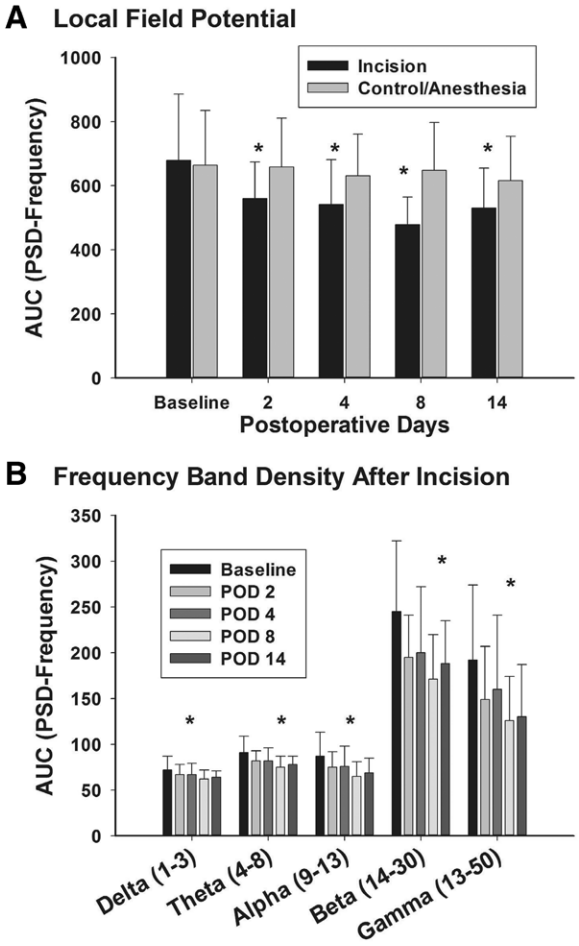

Fig. 7. Effects of incision on local field potentials. The power spectral density is the log of the frequency domain of the local field potentials in the medial prefrontal cortex and was determined from 21 electrodes (n = 9 animals for control) for control and 28 electrodes for incision (n = 9 incision animals) over a 900-s epoch during trials 15 through 100. (*A*) There was no difference in baseline local field potential between control and incision groups. There was no difference in local field potential over time after sham anesthesia in the control. After incision, there was a significant decrease in local field potential that persisted through day 14, at which point the behavior had returned to normal. *One-way repeated measures ANOVA between groups, with pairwise comparisons using the Holm–Sidak method. (*B*) The local field potentials were further broken down into specific frequency bands to determine if any one band had a different behavior. No frequency band was different from the overall effect on local field potential because a time-dependent effect was present at all of the frequencies (delta, 1 to 3 Hz; theta, 4 to 8 Hz; alpha, 9 to 13 Hz; beta, 14 to 30 Hz; low gamma, 30 to 50 Hz). *One-way repeated measures ANOVA over time at each frequency band revealed a similar significant effect at each frequency for the incision group for all times.

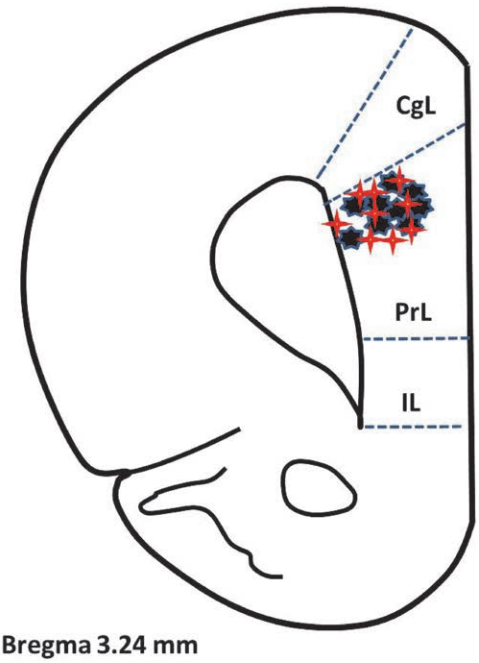

Fig. 8. Location of the electrodes in the prelimbic area of the medial prefrontal cortex at the conclusion of the experiments. There were five electrodes placed in each animal, but the location of each was in close proximity to the other for each animal (N = 18), and the five are represented by a single *red star* (control) or *black star* (incision).

may attenuate the signal transmission efficiency.[32,33] Thus, after injury, signaling may be dampened as a result of ongoing nociceptive input. Interestingly, increased bursts seen with distraction and decreased bursts with nociceptive input both are associated with reduced performance in the titration variant of the 5-choice serial reaction time task and other behaviors.[13,15,17] This may be why nociceptive input appears to be different than distraction from the perspective of neuronal activity in the medial prefrontal cortex despite the similar behavior. Such findings are consistent with both hyperactivity and hypoactivity of the medial prefrontal cortex, producing disruption in the classical 5-choice task.

Nociceptive input may have a dual effect on prefrontal cortex activity. The immediate response to nociceptive input is intensity-dependent increased activity.[19] However, nociceptive activation also induces medial prefrontal cortex deactivation that may be modulated by dopamine from amygdala.[34,35] This is consistent with reduced activity of total spike frequency and medial prefrontal cortex bursts in our freely moving animals during the task. The decreased activity may result from increased γ-aminobutyric acid–mediated tone.[35] Increased synaptic activity might result in an increase in local field potential from activation of inhibitory neurons and release of γ-aminobutyric acid in large quantities. This was likely not the case as local field potential was also reduced. These relationships were previously studied during anesthesia, so the awake or behaving state could affect these relationships. Differences in immediate and delayed nociceptive input could be from a feed-forward circuit; while acute pain from surgery may activate

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medial prefrontal cortex, the longer-term nociceptive input likely increases activity elsewhere to reduce medial prefrontal cortex output. Initial pain activation of medial prefrontal cortex would result in heightened attention, awareness, and focus. Persistent nociceptive input to the brain, likely through amygdala activation, produces a predominance of inhibitory input to the medial prefrontal cortex to reduce activity and impair attentional performance.[36] Neuronal activity was measured in the prelimbic prefrontal cortex; studies suggest that noxious input increases activity in prelimbic prefrontal cortex alone, but increased activity in infralimbic prefrontal cortex may reduce or inhibit activity of pyramidal cells in the prelimbic area.[37] Thus, the reduction in bursts and spike frequency in the prelimbic prefrontal cortex seen as a result of incision could also be related to increased activity in infralimbic-modulating prelimbic prefrontal cortex. This increased activity in the infralimbic prefrontal cortex may be a compensatory mechanism to nociceptive input, persisting beyond the immediate first pain response and permitting the animal to function by reducing the effect of the negative consequence of increased activity within the nociceptive circuit.[38] This may be the very modulation that permits the animal to function, although with reduced maximal performance, with persistent and ongoing nociceptive input while the surgical injury is healing. Reduced cholinergic input to prefrontal cortex from nociceptive input could also reduce activity in prefrontal cortex since cholinergic input is considered an amplification mechanism for local glutamatergic circuits necessary for cue detection.[26] It is possible that opioids may partially release this modulation to improve performance. Regardless of the etiology of reduced prefrontal cortex activity, prefrontal cortex is affected by pain, as demonstrated by structural changes from pain as early as one week after injury.[27] Further studies to understand opioid and nonopioid analgesics in improving attentional performance and altering neural responses in the face of nociceptive input will be valuable to understand the implications for when these pharmacologic interventions may improve attentional function or lead to decrements in cognitive and executive function.

Composite electrical local field potential signals were measured, which have contributions from multiple neuronal and nonneuronal processes.[39] The medial prefrontal cortex local field potential activity likely plays a role in memory and attentional processes and contains synaptic-processing information from many sources distinct from information obtained from spiking activity.[40] In our study we limited local field potential activity to truly "local" electrical activity to reduce interference from distant sources, particularly motor noise.[41] This was done by using a local electrode as reference instead of the wire on the skull. This reduces nonneural and nonlocal contamination from the reference electrode and movement. Gamma oscillations have been largely attributed to volume-conducted noise, and the local reference reduces gamma power immensely, such that in our studies the high gamma (50 to 100 Hz) is so low that interpretation is not meaningful.[41] Separation of local field potential into distinct bands is supported by associations of band-limited power signals with certain behavioral states or sensory inputs.[39] Theta bands in particular are thought to be associated with learning and attention.[40] In our study, all frequency bands were decreased in response to incision and remained so throughout the course of the study. Further studies involving event-related changes will be valuable, particularly for understanding theta oscillations in the prefrontal cortex with respect to correct and incorrect responses and future response successes as a dynamic learning process altered from nociceptive input. Likely the specific signal correlations will emerge with this more granular approach and lead to greater understanding of the role of nociceptive input, leading to altered processing in prefrontal cortex. Further understanding will also come from defining the relationship between frequency band–specific oscillations and spike probability as a function of the event outcome. This should include understanding the firing patterns and abnormalities in firing and synchrony of neural activity that underlies specific behavioral changes. Additionally, one limitation of our study was recording only on the right side (opposite the injury). Considering the role of both sides, their interaction and the laterality may be important to understand the impaired attention.

Pain may alter attention by increasing attentional load, disrupting information processing, and altering input. The association of nociceptive input with the reduced prelimbic-medial prefrontal cortex synaptic activity measured by decreased local field potential power or reduced spike and burst activity may underlie the inability to maintain attention and perform maximally. These effects of incision extend beyond the day of anesthesia and surgery and may reduce attentional performance for days after a small procedure. Future improvement in understanding the effects of pain and therapeutic interventions will come from resolving changes occurring during specific actions in the titration variant of the 5-choice serial reaction time task and will involve event-related spike and potential analysis. Further study is warranted as recovery time ramifications exist from the standpoint of return to optimal functioning in daily activities. This is particularly salient for the return of patients to activities with higher risks, requiring maximal attention and optimum performance for the greatest safety for the patient and those effected by their performance.

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Competing Interests

The authors declare no competing interests.

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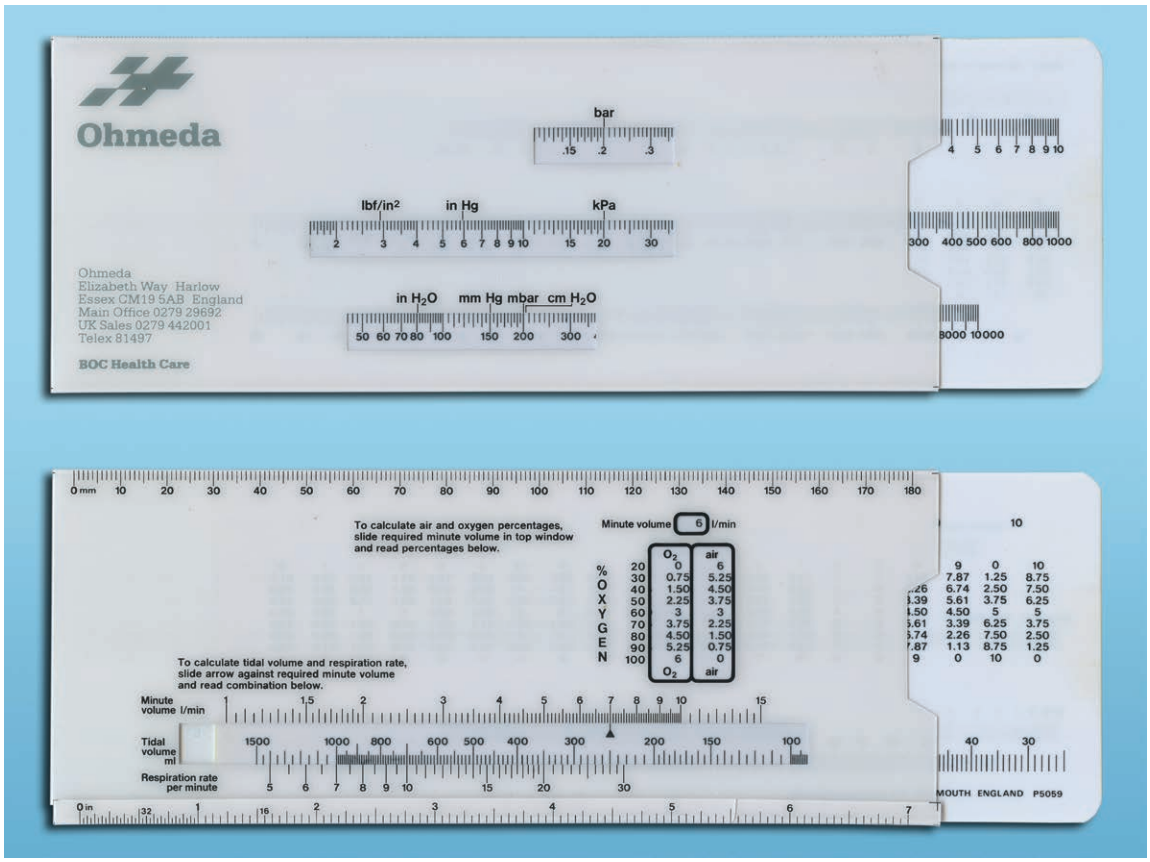
ANESTHESIOLOGY REFLECTIONS FROM THE WOOD LIBRARY-MUSEUM

Ohmeda Slide Rule for Pressures and Volumes



For decades, clinicians have appreciated shortcuts for calculating numbers and for converting units of measure. In both surgical and critical care suites, some "seasoned" anesthesiologists and intensivists appreciated using handy slide rules for a host of patient- and apparatus-related tasks. Assisted by this Ohmeda slide rule (*upper image*), one learned that 150 mmHg equals 20 kPa. On the back (*lower image*), a tidal volume of 700 ml at a respiratory rate of 10 per min was slide rule–calculated as having a 7 l/min minute volume. The Cleveland-based company founded in 1910 as "Ohio Chemical" shifted its corporate headquarters to Madison, Wisconsin, in 1946. Yet, starting in 1967, the firm still called itself Ohio Medical Products. By 1984 the Wisconsin-based company finally shelved the name "Ohio" and rebranded itself as "Ohmeda." And by then, calculators, computers, and digitization had combined to make handheld slide rules, like this one, largely obsolete. (Copyright © the American Society of Anesthesiologists' Wood Library-Museum of Anesthesiology.)

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