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CONTRIBUTIONS OF NOCIRESPONSIVE AREA 3A TO NORMAL AND ABNORMAL SOMATOSENSORY PERCEPTION

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Abstract

Traditionally, cytoarchitectonic area 3a of primary somatosensory cortex (SI) has been regarded as a proprioceptive relay to motor cortex. However, neuronal spike train recordings and optical intrinsic signal imaging, obtained from nonhuman sensorimotor cortex, show that neuronal activity in some of cortical columns in area 3a can be readily triggered by C-nociceptor afferent drive. These findings indicate that area 3a is a critical link in cerebral cortical encoding of 2nd/slow pain. Also, area 3a contributes to abnormal pain processing in the presence of activity-dependent reversal of GABA_A receptor-mediated inhibition. Accordingly, abnormal processing within area 3a may contribute mechanistically to generation of clinical pain conditions.

Keywords

C nociception; second pain; pain affect; somatosensory cortex; GABA reversal

Introduction

Somatosensory cortex in the postcentral gyrus of humans and other primates comprises four cytoarchitectonically, connectionally, and physiologically distinct cortical areas – Brodmann areas 3a, 3b, 1, and 2 (Figure 1AB). Each of these areas forms a long strip running along the

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central sulcus from the midline to the lateral fissure. The most anterior of these areas, area 3a, lies in the fundus of the central sulcus, flanked anteriorly by motor cortical area 4 and posteriorly by somatosensory area 3b. Homologs of primate area 3a have been described in carnivores⁸ (Figure 1C) and rodents^{19, 27, 41} (Figure 1D) and phylogenetic relations are discussed by Cooke et al.²⁷

A population of neurons located in posterior part of area 3a receives afferent drive arising in muscle, joint, tendon, and skin mechanoreceptors. This sector of area 3a subserves conscious perception of limb movement and position (muscle sense), and it contributes to skeletomotor control and coordination^{6, 27, 47, 70, 71, 73, 85}. It is not known whether neurons in posterior area 3a also respond to nociceptive input from deep tissues.

This review presents evidence that neurons in an anterior sector of area 3a contribute to cutaneous pain perception. Unless otherwise noted, the reviewed investigations of area 3a neurons have involved optical intrinsic signal (OIS) imaging and/or neurophysiological recordings from the nearly lissencephalic cerebral cortex of squirrel monkeys (Figure 2A). These studies revealed a substantial population of area 3a neurons that is highly responsive to stimulation of unmyelinated (C) nociceptors. The stimulus-evoked firing of area 3a neurons matches characteristics of the human 2nd/slow pain experience¹⁷⁷. The reviewed studies suggest that some human chronic pain disorders might be attributable to neuroplastic adaptation of GABA_A receptor-mediated inhibition resulting in abnormally excessive nociresponsive area 3a neuron activation.

Anatomical and physiological characteristics of area 3a

The cytoarchitecture and intracortical connectivity of anterior and posterior sectors of area 3a in primates are nonuniform^{73, 177}. The internal granular layer (layer IV) is maximal in thickness at the border with area 3b, but it thins and is hard to detect at the border with area 4. Also, large pyramidal neurons in layer V (which resemble the Betz cells of area 4) exclusively occupy the anterior part of area 3a (Figure 2BC). Corticocortical connections extensively interlink the posterior part of area 3a with areas 1 and 2, whereas the anterior region of area 3a is linked with neighboring area 4.

Throughout its mediolateral extent in human cerebral cortex, area 3a is located at or near the fundus of the central sulcus (Figure 1A). The anteroposterior width of human 3a is less than 6mm. Furthermore, the anterior-posterior location of 3a relative to the fundus of the central sulcus varies among individuals⁶⁰. Collectively, these morphological characteristics pose a technical challenge for functional imaging of stimulus-evoked area 3a activity in humans, although suggestive evidence has been reported^{21, 34, 126}.

The receptive fields of area 3a neurons are somatotopically arranged in register with the motor and sensory homunculi in areas 4 and 3b/1, respectively. Neurons in the anterior sector of area 3a are highly responsive to noxious skin heating, as described below. Neurons posterior in area 3a receive input from deep somatic tissue (skeletal muscle, joints, and tendons)^{73, 85}. Both the anterior and posterior sectors of area 3a have been incompletely described in terms of adequate stimuli for activation. For example, anterior 3a has not been mapped for cold or noxious mechanical stimulation, and posterior 3a neurons have not been

tested with painful deep stimuli. Typically, neurophysiological mapping of somatosensation utilizes non-nociceptive search stimulation, and the location of cells sensitive to such stimuli is noted without tests of responsivity to different forms of nociceptive stimulation. For example, a unique sensory system for deep tissues consists of ergoreceptors sensitive to the metabolites produced by skeletal muscle contraction⁹⁹. This system senses muscular fatigue and pain with excessive exertion.

Area 3a activation in response to noxious skin stimulation

The nociceptive CNS projection path to area 3a in nonhuman primates originates in lamina I of the spinal cord dorsal horn. Spinothalamic neurons in lamina I of the spinal cord dorsal horn receive their main peripheral input from small-diameter afferents^{32, 35, 36, 37}. Spinal lamina I neurons project to neurons in the posterior part of the contralateral thalamic ventral medial nucleus (VMpo). Thalamocortical axons from VMpo terminate in the homolateral area 3a^{31, 32, 33, 36, 43}. It is likely that HPC cells (Heat Pinch Cold cells) in spinal lamina I are the principal source of the C-nociceptive drive that reaches area 3a¹⁷⁰.

Evidence that neurons in primate SI cortex respond selectively to stimulation of cutaneous C-nociceptors has been obtained using optical intrinsic signal imaging^{22, 166, 167}. Skin contact with a probe, maintained at a temperature that evokes a percept of pain for human subjects, triggers an optical response within cytoarchitectonic area 3a in the contralateral SI cortex (Figure 3). Extracellular microelectrode recordings have confirmed the selective response of neurons in this region to nociceptive stimulation of C nociceptors¹⁷⁷ (Figure 2).

The response of nociresponsive area 3a neurons and the 2nd/slow pain responses of human observers to C nociceptor stimulation exhibit striking parallels^{23, 106, 166, 169, 170}: (1) nociresponsive area 3a neuron spike firing and pain ratings increase progressively throughout continuous skin contact and peak multiple seconds after termination of stimulation; (2) area 3a neurons and human subjects exhibit slow temporal summation during repetitive thermal stimulation of C nociceptors at frequencies of 0.3 Hz or greater; (3) responses of area 3a neurons and pain ratings remain elevated for an extended time (hours) subsequent to intracutaneous algogen injection; and (4) pain and area 3a responses to normally innocuous mechanical skin stimulation occur following intradermal algogen injection as well as a multisecond exposure to noxious skin heating (Figure 2E).

In contrast to area 3a, responses of areas 3b/1 nociresponsive neurons are tightly coupled to the temporal profile of stimulation^{25, 80, 81, 82}. Thus, SI neuron populations in areas 3b/1 and in area 3a subserve distinctly different dimensions of pain triggered by environmental stimulation (i.e., fast/discriminative first pain *vs.* slow/nondiscriminative second pain). In addition, neurons in areas 3b and 1 are highly responsive to tactile stimulation, but area 3a neurons respond weakly, if at all, to non-noxious mechanical skin stimuli¹⁷⁷. The anterior sector of area 3a is given over to encoding of C nociception, whereas neurons in areas 3b/1 have innervation from thalamic neurons responsive to stimulation of A-delta nociceptors²⁵.

Influence of area 3a and areas 3b/1 on the spinal cord

The axons of layer 5 pyramidal neurons in area 3a join the pyramidal tract and terminate in the contralateral spinal cord dorsal horn. The corticospinal projections arising in areas 3b, 1,

and 2 terminate in the superficial dorsal horn (laminae I-II), while those arising in areas 3a and 4 terminate in laminae III-V^{16, 20, 90}. Electrical stimulation of areas 3a and 4 has an excitatory effect on wide-dynamic-range (WDR) and high-threshold (HT) nociceptive neurons in the spinal cord dorsal horn of primates,¹⁸⁵ evoking vigorous spike discharges. In contrast, stimulation of areas 3b, 1 and 2 in primates exerts a suppressive effect on dorsal horn neurons.¹⁸⁵ Also, Rojas-Piloni et al.¹⁴⁷ and Moreno-Lopez et al.¹¹⁵ showed that a descending influence arising in rat SI cortex inhibits nociceptive spinal cord dorsal horn neurons. Furthermore, electrical or pharmacological stimulation of rat SI suppresses noxious stimulus-evoked spinal reflexes^{57, 86, 172}.

In rat SI, the dysgranular —transitional zone (TZ) at the interface between lateral agranular motor cortex and granular SI cortex (Figure 1D) is most likely to be a homolog of the nociceptive sector of primate area 3a. TZ neurons are minimally affected by non-noxious somatosensory stimuli but respond to thermnoxious stimuli in a manner closely resembling nociceptive neurons in area 3a of primates (Figure 4). Favorov et al.⁴⁹ and Waters et al.¹⁷³ found that selective inactivation of TZ by cooling or lidocaine injection suppresses the nociceptive flexor withdrawal reflex, suggesting that TZ activation enhances the spinal flexion reflex. To test this possibility, recordings were obtained from nociceptive dorsal horn neurons prior to and after inactivation of the contralateral TZ (Figure 5)⁵⁰. A loss of dorsal horn neuronal responsivity to thermnoxious stimulation followed TZ inactivation.

Enhancement by area 3a (in primates) or TZ (in rats) of spinal nociceptive processing represents a positive-feedback, closed-loop circuit that interlinks nociceptive neurons in area 3a or TZ with nociceptive neurons in the dorsal horn of the spinal cord (Figure 6). By cycling spike discharge activity between nociceptive area 3a/TZ and dorsal horn neurons, such a circuit may amplify nociceptive inputs reaching the dorsal horn to fit ongoing needs. Positive feedback between area 3a/TZ and the superficial dorsal horn could underlie slow temporal summation and the persistence of second pain.

In addition to the excitatory descending projections that arise in area 3a, the connectional diagram in Figure 6 includes the well-documented inhibitory projections from sectors of SI driven by A β mechanoreceptive afferent drive (areas 3b/1). Considered collectively, these cortical areas are components of a dynamical system, contributing to nociception, to non-noxious somatosensation and to motor control.

GABAergic interactions between area 3a and areas 3b/1

Vibrating a skin site with a probe pre-heated to a noxious temperature simultaneously activates areas 3b/1 (input from A β afferents sensitive to vibration) and area 3a (input from C nociceptors). The combination of heat and mechanical stimulation significantly reduces neuronal responses to low intensity vibration in areas 3b/1, relative to exactly the same vibrations without heat^{166, 167, 177, 178} (Figure 3). Suppression is mediated via GABA release from inhibitory neurons in areas 3b/1 which are activated by axon collaterals of neurons in area 3a. This finding is compatible with the degradation of human tactile sensitivity and discrimination that accompanies C-nociceptor afferent drive (for review, see Moseley et al.¹¹⁸).

Interactions between A β and C-nociceptor afferent drives at the level of SI cortex can change from suppressive to facilitatory following intracutaneous algogen injection (such as capsaicin, formalin, or alpha-beta-methylene ATP). These agents trigger a vigorous and prolonged activation of C-nociceptors^{17, 178}. Subsequent to algogen injection, contact of skin in the vicinity of the injection site evokes more and longer spike firing in area 3a than prior to injection (Figure 2D). Post-injection responses of area 3a neurons to previously ineffective mechanical skin stimulation (Figure 7) replicate, in time course and intensity, the tactile allodynia experienced by normal human subjects in response to gentle tactile stimulation following such an injection^{123, 177, 178}.

Increased responsivity of area 3a neurons to A β afferent drive following an algogen injection suggests that intracortical input from areas 3b/1 changes from inhibitory to excitatory¹⁷⁸. Relevant to these findings are observations that GABA action via GABA_A receptors is activity-dependent^{91, 145}. The GABA_A receptor-mediated postsynaptic potential is hyperpolarizing/inhibitory when the recent history of local neuronal activity is near background, but when neuronal activity is highly elevated it converts to depolarization/excitation. Such a change is a result of a progressive increase in [Cl⁻]_i that typically accompanies spike firing in a network^{63, 69, 105, 116, 159, 171, 181}, due to limited capacity of KCC2-mediated outward transport of Cl⁻^{17, 26, 143}. When neuronal [Cl⁻]_i is sufficiently elevated, the transmembrane ionic current through GABA_A receptor-regulated membrane channels changes direction and becomes depolarizing/excitatory^{77, 87, 158, 181}.

Lee et al.⁹¹ demonstrated the effect of local neural activity on GABAergic synaptic transmission in a rat sensorimotor slice preparation. A cortical column was activated using a bipolar electrode placed at the Layer VI-white matter junction (Figure 8). Then, puffs of GABA were released in close vicinity to whole-cell patch clamp-recordings of pyramidal neurons. The GABA puffs depolarized or hyperpolarized the recorded neurons, depending on activation of the cortical column. A train of 20Hz electrical pulses, delivered at the Layer VI-white matter junction over 1sec, was sufficient to convert GABA puffs from being hyperpolarizing to becoming depolarizing for up to 15sec. Furthermore, subsequent to white matter conditioning stimulation, neurons in the activated cortical column exhibited a substantial elevation of [Cl⁻]_i. The [Cl⁻]_i elevation is the result of GABA binding to GABA_A receptors, because the same neurons exhibit little or no increase in [Cl⁻]_i when stimulation is delivered in the presence of gabazine, a potent and selective GABA_A receptor antagonist.

Activity-driven conversion raises the possibility that tactile allodynia is explicable in terms of a depolarizing influence conveyed by GABAergic interneurons to nociresponsive neurons within area 3a, via corticocortical connections from area 3b/1 neurons responsive to gentle mechanical skin stimulation. Thus, some chronic pain disorders may result from neuroplastic adaptation that increases area 3a neuron activation^{58, 133}. The therapeutic implications of this explanation are potentially substantial. Agents and approaches that selectively reduce/eliminate the depolarizing influence of GABA on nociresponsive area 3a neurons would secondarily reduce or eliminate tactile allodynia.

Activity-dependent reversal of GABA modulation is relevant to reports that exposure of a skin region to high-frequency electrical skin stimulation (HFS), which activates peptidergic

C-nociceptive afferents, is followed by secondary mechanical hyperalgesia^{83, 168}. Cerebral cortical event-related potentials and perceptual responses to C-nociceptor afferent drive are enhanced. Also, pain is evoked by gentle tactile stimulation of skin regions adjacent to the stimulated skin region.

Development of clinical pain conditions

Chronic postoperative pain.—Following a number of surgical procedures, chronic pain develops over days to years for some individuals but not others. Mild to severe chronic pain is not necessarily associated with evidence of nerve injury (neuropathic pain). However, inflammation is an inevitable consequence of tissue injury, with or without nerve injury, that can determine whether pain recovers over time. C nociceptor discharge in response to inflammatory injury is associated with many forms of chronic pain^{88, 153}. Accordingly, in search of mechanisms for chronic pain, it should be instructive to consider neuroplastic adaptations that affect the cortical recipients of C nociception, such as area 3a.

Postoperative pain is present and lasts approximately one week for all individuals, and its intensity is an important risk factor for development of chronic pain^{74, 139, 140}, as is the presence of pain preoperatively^{1, 46, 59, 79, 124, 129, 175, 179, 183, 184}. Furthermore, aggressive analgesic medication soon after surgery can reduce the incidence of chronic pain development^{18, 75, 117, 151, 165}. Thus, if a high/abnormal level of nociresponsive area 3a neuronal activation is maintained over days, conversion of the synaptic action of GABA could contribute to development of chronic postoperative pain. If sufficiently strong, C-nociceptor activation by tissue injury with nerve trauma and/or inflammation could convert GABAergic synapses in area 3a from inhibitory to excitatory. As a result, myelinated non-nociceptive skin mechanoreceptor input, which normally inhibits nociresponsive area 3a neurons, would excite them, resulting in allodynia.

The role of glia in development of pain.—Astrocytes contribute to GABA-mediated regulation of the excitability of individual CNS neurons as well as large CNS networks^{120, 135, 154}. For example, Heja et al.⁶⁷ found that neural activity is accompanied by uptake of extracellular glutamate by astrocytes. In turn, a glutamate-mediated inhibition of the GABA transporter triggers an astrocytic release of GABA. This constitutes a neuroprotective mechanism by which astrocytes offer tunable negative feedback to the CNS network in which they reside⁶⁷. While this sequence of astrocytic mechanisms normally results in neuronal inhibition, activity-driven conversion of GABA's synaptic action from hyperpolarizing/inhibitory to depolarizing/excitatory can occur. Subsequent to prolonged exposure of nociresponsive area 3a neurons to vigorous C-nociceptor afferent drive, astrocytic release of GABA would promote, rather than hinder, development of hyperactivity, contributing to emergence of hyperalgesia, tactile allodynia, and spontaneous 2nd/slow/burning pain.

Microglia contribute to the sign (inhibitory vs. excitatory) of GABA's action on CNS neurons²⁸. In particular, microglial activation is accompanied by release of brain-derived neurotrophic factor (BDNF). BDNF, in turn, can result in abnormal accumulation of chloride (a —chloride-opathyll) via downregulation of neuronal KCC2 transport, raising the

equilibrium potential of GABA_A receptor-regulated ion channels. GABA-mediated synaptic transmission becomes less hyperpolarizing/inhibitory and ultimately depolarizing/excitatory.

Phantom limb pain.—Many individuals (50–85%¹⁷⁴) who suffer loss of a limb develop phantom limb pain (PLP). PLP can be associated with reorganization of SI^{54, 55, 61}. Loss of a limb deprives SI of a portion of its peripheral input but does not silence it^{130, 131, 132, 152}, because the deafferented SI region is still connected with the thalamus and other SI regions^{13, 128, 146}. Over time, the deafferented SI region undergoes internal reorganization, increasing excitatory synaptic transmission, decreasing inhibitory transmission, unmasking latent excitatory synapses and creating new input by extensive axonal sprouting^{56, 76, 96}. These changes result in enhanced excitability of the deafferented SI cortex, as demonstrated in patients with PLP by Larbig et al.⁸⁹ and Karl et al.⁷⁸. Also, the deafferented cortex gradually becomes responsive to stimulation of previously ineffective body regions^{98, 130, 131, 132}.

Nonhuman animal models of this neuropathy have revealed microglial activation in spinal segments ipsilateral and somatotopically related to an injured/transected nerve²⁸. The microglial activation has been shown to spread progressively (become multifocal)^{9, 150}, presumably by chemical signals conveyed via axonal transport. If microglial activation were to extend to area 3a, then it could lead to development of chloride-opathy in deafferented nociresponsive neurons. The result would be a loss of GABA_A receptor-mediated inhibition and possibly emergence of GABA_A receptor-mediated excitation.

SI post-amputation reorganization can be viewed as a homeostatic response of deafferented cortex to a decreased dynamic range of activity. The excitatory/inhibitory balance of SI is altered, increasing activity. However, such a —“fix” produces abnormal and perceptually misleading responses to newly developed inputs. For example, as result of arm amputation, an SI neuron with a receptive field on the hand might become responsive to tactile stimulation of the lips¹⁴¹ while retaining the perceptual meaning of —“hand”⁴⁰. As an fMRI study of Makin et al.¹⁰³ suggests, the activity of deafferented neurons with new input from normally innervated neurons is experienced as kinetic, kinesthetic and exteroceptive phantom sensations, including phantom limb pain (PLP).

Evidence that neural activity in reorganized SI can evoke PLP is provided by neurosurgeons who have attempted to treat severe cases of PLP by performing postcentral topectomy, in which the partially deafferented SI region is surgically ablated^{48, 66, 68, 97, 161, 182}. Prior to topectomy, locations on the crown of the postcentral gyrus (mostly Brodmann area 1) were electrically stimulated. In most of the patients, such stimulation of the deafferented SI region evoked pain sensations resembling in quality the patient’s PLP. Stimulation of the same regions in subjects with intact limbs does not evoke pain^{107, 134}. Also, in individuals with limb loss, stimulation of postcentral sites outside the deafferented zone does not evoke pain sensations. A possible explanation for PLP in response to post-amputation electrical stimulation of the deafferented SI is that the overall physiological effect of projections sent by the deafferented regions in areas 3b/1 to the homotopic deafferented regions in area 3a becomes converted from normally inhibitory to excitatory as a result of SI reorganization.

Another source of activity in the deafferented portion of nociresponsive area 3a can be expected from the spinal dorsal horn. Peripheral nerve transection results in degeneration of C-fiber primary afferents terminating in the superficial dorsal horn, leading to synaptic reafferentation of dorsal horn laminae I-II neurons^{14, 122}. Reafferentation of laminae I-II neurons from skin regions with intact afferentation can trigger activity in the CNS projection path that links lamina I neurons with nociresponsive neurons in the contralateral area 3a.

Migraine pain.—Considerable research has linked cortical spreading depression (CSD) to migraine headaches. CSD triggers meningeal nociceptors with input to the trigeminovascular projection path, to multiple targets^{12, 45, 94, 125, 136}, including area 3a. A resulting cortical hyperactivity/hyper-responsivity of migraineurs is revealed by failure of cortical evoked potential responses to somatosensory, visual, or auditory stimulation to exhibit habituation^{2, 29, 160}. Failure of habituation to repetitive stimulation, similar to such failure in neurons in areas 3a, 3b, and 1 following intradermal injection of capsaicin^{177, 178}, reveals central sensitization.

While there is agreement that cortical excitability is dysfunctional in migraineurs, the underlying molecular and cellular mechanisms are inadequately understood¹³⁶. GABA has figured prominently in theories of migraine pathogenesis, but cortical levels are not significantly different in migraineurs *vs.* control subjects^{10, 95}. An alternative explanation is that dysfunctional regulation of cerebral cortical excitability results, in part, from depolarizing/excitatory influences of GABA released in area 3a by local inhibitory neurons^{177, 178}. If this explanation is confirmed, susceptibility to migraine might be viewed as attributable to specific variants of GABA genes responsible for depolarization/excitation^{52, 144, 148}.

If migraine pain is associated with hyperactivity/hyper-responsivity of nociresponsive neurons in area 3a, the sensitivity of area 3b/1 neurons would be altered, depending on the recent intensity of abnormal activity in area 3a. As a result, tactile perceptual function on the contralateral face and forelimb could be impaired. To test this hypothesis, Nguyen et al.¹²¹ compared tactile discriminative abilities of normal subjects *vs.* migraineurs. Using precisely controlled mechanical stimulation to the glabrous skin of the hand, Nguyen et al.¹²¹ found significant impairment of migraineurs' abilities to: (1) discriminate vibrotactile skin stimulation on the basis of stimulus amplitude; (2) identify the temporal order of two brief tactile contacts ("taps"), and 3) distinguish two successive vibrotactile stimuli on the basis of their duration.

Treatment of clinical pain conditions

Cerebral cortical lesions.—In the mid-20th century, surgical ablations of SI cortex were used as a therapeutic means of treating patients suffering from severe chronic pain of central origin. For example, Lewin and Phillips⁹⁷ reported that 3 patients with severe spontaneous pain experienced relief following surgical removal of the postcentral region where electrical stimulation evoked comparable pain. A review of the postcentral topectomy literature^{44, 48, 64, 65, 66, 68, 92, 93, 97, 161, 163, 176, 182} reveals that 15 out of 25 (60%) post-central ablations obtained permanent relief of pain; 6/25 provided temporary relief; and 4/25

were completely ineffective. A parsimonious interpretation of these reports is that permanent loss of pain was achieved when both area 3a and areas 3b/1 were removed. Given that the arm region of area 3a lies deep in the central sulcus, whereas the face and leg representations are closer to the crown, the arm region of area 3a was more likely to be spared. Attempts at treating facial or leg pain were most effective (permanent pain loss in 9 out of 12 attempts, or 75%), while the success rate for arm pain was 6/13 (46%).

Kleist⁸⁴, Russell¹⁴⁹, and Marshall¹⁰⁴ observed a loss of pain sensibility in soldiers with shrapnel or bullet injuries of the postcentral gyrus. In some individuals the pain loss was temporary, but in others it was permanent. The cases with permanent loss suggest that (1) functional integrity of cortex located at or near the fundus of the central sulcus (area 3a) is necessary for an individual to be able to perceive pain; and (2) once this region is destroyed, its contribution to pain perception cannot be compensated for by other CNS regions. Importantly, the damage in cases with pain loss was confined to SI and did not involve anterior cingulate cortex, SII, or the insula.

In contrast to SI lesions involving area 3a, traumatic damage restricted to the crown of the postcentral gyrus resulted in hyperesthesia and allodynia. Similarly, Feinstein et al.⁵¹ investigated a patient with herpes simplex encephalitis resulting in bilateral loss of the insula, ACC, amygdala, and part of SII, but leaving SI intact/functional in both hemispheres. Despite a loss of cerebral cortical structures believed to subserve emotional experiences associated with pain, this patient's affect was amplified (as measured by self-report, facial expression, vocalization, withdrawal reactions, and autonomic responses).

Additional insight into the contribution of cerebral cortex to human pain perception comes from Ploner et al.¹³⁷, who described stimulus-evoked perceptual experiences of a patient with an ischemic lesion that selectively involved SI and SII on the right. According to magnetic resonance imaging (MRI), the lesion did not extend to the fundus of the central sulcus (sparing area 3a). In response to nociceptive laser stimulation of the left hand, this patient experienced an "unpleasant" feeling after 1.4sec. He could neither describe the feeling qualitatively nor localize it more accurately than "somewhere between fingertips and shoulder." This patient lacked the discriminative component of conscious pain perception, but an affective component was preserved. Thus, nociresponsive area 3a activation contributes to affective/emotional experiences that accompany painful stimulation, and interactions with areas 3b/1 may be required for pain localization and intensity discrimination (for review of cortical lesions in humans and their relevance to pain, see Ploner and Schnitzler¹³⁸).

Transcranial stimulation.—Treatment of clinical pain with transcranial stimulation is most effective when it targets the posterior hand-face region of the "primary motor cortex", where area 3a is uniquely accessible for stimulation. At no other location on the dorsal surface of the skull has stimulation been shown to provide effective pain relief (for discussion of cerebral cortical stimulation therapies for headache pain, see^{39, 42, 102, 113, 127}). While low frequency (1Hz) repetitive transcranial magnetic stimulation (rTMS) over area 4, and presumably area 3a, increases cortical facilitation and decreases inhibition, high frequency (10 Hz) has the opposite long lasting effect, decreasing cortical facilitation and

increasing inhibition¹¹, thereby reducing neural activity in the targeted regions. Such ability of high frequency rTMS to depress the face region of nociresponsive area 3a might underlie its demonstrated effectiveness in reducing the frequency of migraine attacks³⁰.

Vestibular stimulation.—Vestibular stimulation (either caloric or galvanic) can reduce multiple varieties of pathological pain, including phantom limb pain, spinal cord injury pain, complex regional pain syndrome, and central poststroke pain^{108, 109, 110, 142}. High-resolution human cortical imaging methods demonstrate that the afferent drive that arises in the vestibular apparatus of the inner ear is processed in a manner distinctly unlike visual, somatosensory, or auditory afferent drive^{101, 186}. Vestibular afferent drive accesses at least ten different regions in human cerebral cortex, all of which exhibit multisensory integration. Because no cerebral cortical region is devoted exclusively to the processing of vestibular input¹⁰¹, vestibular afferent drive is viewed as modulating the cortical processing of other sensory modalities. Consistent with this perspective, vestibular stimulation lowers the detection threshold for light touch but elevates the heat pain threshold⁵³. The pain-reducing effect of vestibular stimulation could be attributed to suppression of anterior cingulate cortical activity. Another possibility is that nociresponsive responses in a region within area 3a that receives vestibular afferent drive are suppressed (area 3av^{3, 27, 62, 71, 72, 100}). Vestibular stimulation reduces post-stroke tactile allodynia and reduces magnetoencephalography (MEG) activation of a “posterior location in primary motor cortex”¹¹⁰, which might actually correspond to nociresponsive anterior sector of area 3a.

Clinical pain and the actions of topiramate.—Mechanisms of action of analgesic agents are often unknown. For example, topiramate can reduce migraine or neuropathic pain, but sites of action in the CNS are unknown. At therapeutically relevant concentrations, topiramate alters neuronal activity via multiple actions: (1) voltage-gated Na⁺ channel block; (2) enhancement of GABA's action on GABA_A receptors; (3) blockade of glutamate-mediated kainate/AMPA receptor activation; (4) inhibition of voltage-gated Ca⁺⁺ channels; and (5) carbonic anhydrase inhibition (for review, see^{4, 5, 7, 15, 24, 38, 45, 114, 119, 156, 162}).

How would each of topiramate's mechanisms impact hyperactive/hyper-responsive area 3a neurons? First, topiramate's inhibition of carbonic anhydrase would lead to decreased intraneuronal [HCO₃⁻]_i and a decreased depolarizing/excitatory outward-directed HCO₃⁻ current in response to GABA binding when area 3a neurons are highly active. Second, topiramate's enhancement of the action of GABA release from local interneurons would result (due to lowering of [HCO₃⁻]_i) in an increased hyperpolarizing/inhibitory transmembrane Cl⁻ current. Third and fourth, area 3a neuronal excitability/responsivity would decrease due to topiramate's block of Ca⁺⁺ channels and voltage-gated Na⁺ channels. And fifth, area 3a neuron responsivity/activity would decrease due to suppression of glutamate-mediated excitatory synaptic transmission. Thus, the five actions of topiramate would collectively suppress/normalize area 3a activity and, as a consequence, reduce migraine or phantom limb pain.

Conclusions

The need for research focused on identification of the CNS pain mechanisms that underlie chronic pain is widely acknowledged. According to Sessle¹⁵⁵, “Chronic pain is present in epidemic proportions in most countries, is often unrelieved, and has a huge socioeconomic impact. It is a problem that faces all healthcare professional fields.”

Experimental and clinical observations suggest that the activity of neurons in cytoarchitectonic area 3a of the cerebral cortex is driven by input from unmyelinated nociceptors that are implicated in many pain conditions. Thus, hyperactivity/hyper-responsivity of nociresponsive area 3a neurons likely contributes to human pathological pain. Furthermore, abnormal pain experienced by individuals may depend upon loss of GABA-mediated and normally inhibitory/hyperpolarizing influences. Therefore, restoration of hyperpolarizing influences of GABA on nociresponsive area 3a neurons has the potential to attenuate many forms of clinical pain and minimize tactile allodynia, hyperalgesia, and deficits in tactile perceptual discriminative capacity that are exhibited by individuals with these disorders.

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HIGHLIGHTS

- Anterior subdivision of area 3a subserves nociception and generation of 2nd/slow pain
- Under extreme conditions area 3a can partially lose inhibition and become hyperactive
- Abnormal hyperactivity of nociceptive area 3a likely promotes some pain disorders
- Such disorders can be alleviated by permanent or temporary inactivation of area 3a
- Alternatively, hyperactive 3a might be treated by restoring its inhibitory mechanisms

PERSPECTIVE

Optical imaging and neurophysiological mapping of area 3a of primary somatosensory cortex (SI) has revealed substantial driving from unmyelinated cutaneous nociceptors, complementing input to areas 3b and 1 of SI from myelinated nociceptors and non-nociceptors. These and related findings force a reconsideration of mechanisms for SI processing of pain.

FIGURE 1. Location of area 3a in different mammalian species.

Shown are the surface views of the cerebral cortex and representative sections. Section locations are indicated on the views by dashed lines. CS – central sulcus. **A:** human cortex view and coronal section. **B:** macaque cortex view and sagittal section. **C:** cat cortex view and sagittal section. **D:** surface view of the rat sensorimotor cortex and its location on the cerebral hemisphere. In rat SI, the dysgranular zone (DZ) and the transitional zone (tz) are proposed to be homologs of area 3a in nonrodent mammals^{19, 27, 41, 157, 180}, whereas the granular zone (GZ) is a homolog of area 3b and the lateral agranular cortex (AGI) is the primary motor cortex. Portions of Figure 1 have been reproduced with permission. (Adapted from: human⁶⁰; macaque¹¹²; cat¹¹¹; rat¹⁹)

FIGURE 2. An exemplary nociresponsive area 3a neuron.

A: Photograph of the surface of squirrel monkey right hemisphere. Dots anterior to the central sulcus (CS) mark locations of microelectrode penetrations that sampled the spike firing of area 3a neurons responsive to noxious stimulation of the contralateral hand (lateral group of dots) or foot (medial dots). LF – lateral fissure. **B:** Photomicrograph of a Nissl-stained parasagittal section showing an electrolytic lesion (indicated by open arrow) at the site where spike firing activity of an individual nociresponsive area 3a neuron was recorded. Filled arrows identify the 3b/3a and 3a/4 boundaries. Note progressive thinning of layer IV, which starts at the 3b/3a border, and ends at the 3a/4 border, as well as the presence of large pyramidal cells in layer V in the anterior third of area 3a (marked with a horizontal two-headed arrow)—the locus where this exemplary neuron was recorded. **C:** Higher-power image showing cytoarchitectural details in the vicinity of the electrolytic lesion. Tic marks on the left (posterior) and right (anterior) edges indicate boundaries between layers III, IV, and V. **D:** Spike firing response of this area 3a neuron to intradermal injection of α,β methylene ATP (a potent algogen) at a site within its receptive field. Arrow – time of injection. Note prominent elevation of spike firing which persisted for ~13s and then transitioned to an irregular, and prolonged elevation of mean firing rate (MFR). **E:** Superimposed PST histograms showing the same neuron's spike firing response to nonnoxious (25°C) skin indentation before and after intracutaneous injection of α,β

methylene ATP. Note the strengthening of this neuron's response to mechanical stimulation that occurred subsequent to algogen injection. (Reproduced with permission¹⁷⁷)

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Figure 3. Optical intrinsic signal imaging response of SI cortex to thermoneutral vs. thermonoxious vibrotactile stimulation.

A: Dorsal surface of SI cortex of a squirrel monkey with the location of responses to stimulation (red spot). **B:** Site on contralateral digit 1 exposed to 5s vibrotactile stimulation delivered via a temperature-controlled contactor. **C:** Averaged SI activity pattern evoked by a neutral contactor temperature of 38°C. Green rectangles indicate regions of interest in areas 3a, 3b, and 1. Note the prominent response in areas 3b and 1. **D:** Averaged SI activity pattern evoked at a noxious contactor temperature of 47.5°C. Note that raising the contactor temperature led to emergence of a response in area 3a, while significantly reducing the response in area 3b and completely abolishing it in area 1.

FIGURE 4. Exemplary recordings from rat transitional zone, TZ.

A: Cytochrome oxidase-stained tangential section of a rat's somatosensory cortex. PMBSF – posterior medial barrel subfield representation of mystacial vibrissae. FBS – forelimb barrel subfield. HBS – hindlimb barrel subfield. The arrow points at an electrolytic lesion made in a microelectrode penetration in TZ. **B:** A representative examples of raw neuroelectrical activity recorded at the TZ site before, during, and after submerging the contralateral forepaw in either noxious 50°C or non-noxious 45°C water (the stimulus period is marked by the black bar). The 50°C bath evoked vigorous spike discharging activity, with a 2-sec delay after forepaw submersion and also around the time of forepaw extraction and for 3 sec thereafter. In contrast, the 45°C water bath did not evoke any response. **C:** An example of a single-unit TZ recording from another rat showing the buildup of response after submerging the contralateral forepaw in the heated water bath, but not after submersion in the warm water bath. Note the delayed and long post stimulus firing in response to thermonoxious stimulation.

Figure 5. Exemplary neuroelectric activity recorded in superficial dorsal horn of the spinal cord before, during (red bar), and after submerging the ipsilateral hindpaw in a heated water bath before and after ablation of contralateral TZ.

Left: Representative examples of raw neuroelectric activity recorded in the superficial dorsal horn in response to 50°C thermnoxious vs. 41°C thermoneutral stimulation. **Center:** Cytochrome oxidase-stained tangential section of the contralateral sensorimotor cortex showing the site and extent of TZ ablation by cauterization. **Right:** Representative responses to thermnoxious vs. thermoneutral stimulation, recorded at the same dorsal horn site 30min after the contralateral TZ ablation.

Figure 6. Diagram of circuitry linking somatosensory cortex with dorsal horn region that processes C-nociceptor afferent drive.

Figure 7: Optical intrinsic signal imaging of SI responses to non-noxious vibrotactile stimulation before and after the intradermal injection of the algescic chemical formalin.

A: Dorsal surface of SI cortex of a squirrel monkey. **B:** Site on contralateral hand exposed to 5s vibrotactile stimulation at the neutral contactor temperature of 25°C and the location of formalin injection. **C:** Averaged SI activity pattern evoked before formalin injection. **D:** Averaged SI activity pattern evoked 50–60min after injecting 5% formalin at a skin site located 3cm from the stimulated site. Note that before the formalin injection, non-noxious flutter stimulation evoked a local response at the border between areas 3b and 1. However, 1hr after the injection the flutter stimulus activated a much larger SI territory in the vicinity of the border between areas 3b and 1, as well as in area 3a.

Figure 8. Depolarizing effect of GABA in actively driven cortical columns.

A: Experimental design. A bipolar electrode (E-labeled black circle) placed at the layer VI-white matter junction was used to activate a cortical column-shaped region (delineated by enclosed rectangle) in a rat sensorimotor slice preparation. A series of 20 2mA electrical pulses at 20Hz was delivered. A pyramidal cell (shown as a triangle) was isolated with a whole-cell patch clamp recording electrode in the upper layers, radially aligned with the stimulating electrode. The tip of a GABA-containing micropipette was placed in close proximity to the recorded neuron. GABA was repeatedly pressure-ejected from the micropipette following electrical stimulation of the column. **B:** Representative example of an optical intrinsic signal imaging response to 20Hz electrical stimulation, revealing activation of a column-shaped cortical region. **C:** GABA's effect on an exemplary pyramidal neuron before and after 20 Hz electrical stimulation of the host cortical column. The top trace shows that GABA puff applications before such —conditioning stimulation hyperpolarized the neuron's membrane potential (P-labeled dots below the trace indicate time of each GABA puff release). The bottom trace shows that for 20 seconds after 1 second activation of the

column by 20Hz conditioning electrical stimulation, GABA puff applications prominently depolarized, rather than hyperpolarized, the neuron's membrane potential (C-labeled filled box indicates the duration of electrical stimulation). **D:** Responses of 16 upper-layer pyramidal neurons to a train of GABA puffs. Amplitude of the response of each neuron to GABA is plotted as a function of time of each puff in series delivered before or after 20Hz conditioning electrical stimulation. The plot shows that for 15sec subsequent to the conditioning electrical stimulation of the column, GABA puffs produce prominent neuronal depolarization, whereas prior to such conditioning stimulation GABA puffs produced neuronal hyperpolarization. (Reproduced from⁹¹)

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