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Basic Section

Pain perception in a man with total corpus callosum transection

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Summary While classical and current theories of pain emphasize the critical role of central neural pathways that represent the contralateral body surface and cross within the spinal cord, the role of neural input representing the ipsilateral body surface is uncertain. In the present experiments with a complete corpus callosum-sectioned patient, both tactile and low intensity noxious stimuli (43–47°C) ipsilateral to the responding cerebral hemisphere were poorly perceived and/or rated low on verbal and visual analogue scales (VAS). Surprisingly, however, high intensity noxious thermal stimuli (49–51°C) were rated on verbal or visual analogue scales as very intense and unpleasant, thereby reflecting both sensory-discriminative and motivational-affective dimensions of pain. Thus, the pathways and mechanisms subserving this ipsilateral input have high thresholds for activation, but once activated are sufficient to evoke all of the critical dimensions of the experience of pain.

Key words: Pain perception; Corpus callosum transection; Verbal scales; Visual analogue scales

Introduction

Despite the crossed nature of much of the sensory input to the brain, the two cerebral hemispheres share their sensory information via a massive interhemispheric bundle, the corpus callosum. In the absence of this structure, one cerebral hemisphere can be unaware of the nature, or even the presence, of an ipsilateral stimulus [4,5].

Both classical and contemporary theories of pain have emphasized that crossed pathways subserve the sensory and affective dimensions of pain. Yet some of the neurons in these pathways (e.g., spinothalamic and spinoreticular) that respond to frankly noxious stimuli can be activated from either side of the body [10,16]. Furthermore, there

are clinical research reports that pain from both sides of the body can still be perceived after extensive damage to one cerebral hemisphere [1–3,15] or after almost total spinal cord transection, sparing a small portion of one (e.g., left side) spinoreticular/spinothalamic pathway [12]. The combination of these reports strongly suggests that at least some aspects of pain perception of the ipsilateral body surface do not require the inter-hemispheric transfer of information.

In the present experiments, we examined the relative contribution of ascending ipsilateral pathways to pain, as well as the possibility that some dimensions of pain perception (like those of speech, etc.) might be lateralized in the brain. A patient with a total transection of the corpus callosum and capable of comprehending language in both hemispheres provided the unusual opportunity to explore these issues in a conscious human [7]. The methodological approach used was similar to previous analyses of contributions of

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various ipsilateral and contralateral visual and somatosensory pathways to sensory perception. While noxious ipsilateral thermal stimuli evoked all components of the experience of pain in this subject, they did so only at intensity levels well above the normal thermal pain threshold. When the subject used only neural inputs that were ipsilateral to the responding cerebral hemisphere, perception of the intensity, presence and location of stimuli within the lower end of the range of nociceptive stimulus intensities (for normal subjects) was shown to be markedly impaired. Furthermore, when he acknowledged the presence of these low intensity nociceptive stimuli (43–47°C), they were rarely reported as painful.

Methods

Patient

J.W. is a 33-year-old male who underwent callosal surgery in 1979 [9]. Midline section of the corpus callosum was performed in 2 stages. The posterior half of the corpus callosum, including the splenium, was sectioned first, with the remaining portion sectioned in a second operation 10 weeks later. The complete section of the corpus callosum (the anterior commissure was spared) was demonstrated by magnetic resonance imaging (MRI) [9]. Postoperatively, J.W. demonstrated the capacity to comprehend language in both his left and right hemispheres and was cooperative and articulate. However, only J.W.'s language-dominant left hemisphere was shown to be capable of generating speech [9].

Experimental paradigms

The subject was presented with 3 experimental paradigms. The first was a simple task of non-noxious tactile localization requiring a verbal response. With the feet and the experimenter hidden from view by a table, the subject was required to verbally identify which of 5 toes of which foot was touched with a plastic probe by the experimenter. The specific toe and foot were randomly varied. Since the subject's speech center was in his left hemisphere [8], this paradigm examined perception only via the left hemisphere.

In the second and third experimental paradigms, the subject was required to rate the intensities and/or the unpleasantness of noxious thermal stimuli in one of two ways. In the second paradigm, the subject was instructed to rate *pain sensation intensity* and *unpleasantness* of each stimulus on 10-point scales, where 10 represented 'the most intense pain sensation imaginable' and 'the most unpleasant feeling imaginable' for sensation intensity and affect scales, respectively. Standardized typewritten instructions used in several previous studies were used to clarify the distinction between ratings of sensory intensity and affective dimensions of pain [13]. In addition, the subject was told that he could use any numbers between 0 and 10 to represent the relative magnitudes of these two dimensions of pain and that he could use fractions [11,14]. As noted above, such a paradigm examines perception only via the left hemisphere. A total of 13 blocks of 20 stimuli each were presented. In the third paradigm (6 blocks of 20 trials), the subject rated the intensities of the same stimuli by pointing along a line that appeared on a TV screen (the visual analogue scale or VAS). The VAS consisted of 10 cm lines presented on a TV monitor (as shown in Fig. 1) and was anchored by the same verbal descriptors used in verbal ratings. On each trial, the subject fixated on an illuminated point in the center of the screen. The thermal stimulus was then presented, after which a VAS appeared within his peripheral right or peripheral left visual field for 150 msec. The subject rated the intensity of the thermal stimulus by pointing along the VAS with his right or left hand. In an effort to rule out cross-cueing strategies [6] as well as other strategies [9], the directional orientation of the VAS was systematically varied from trial to trial. Left-handed/left visual field-related ratings were presumed to be related to right cerebral hemispheric responses and vice versa.

Thermal nociceptive stimulation procedures

Each stimulus consisted of a 5 sec heat pulse delivered via a 1 cm diameter contact thermal probe [also see 12, 13]. Stimulus intensities (the range was 43–49°C in 1° increments and 51°C) were presented in random order and randomly to

VISUAL ANALOGUE SCALE (VAS) PARADIGM

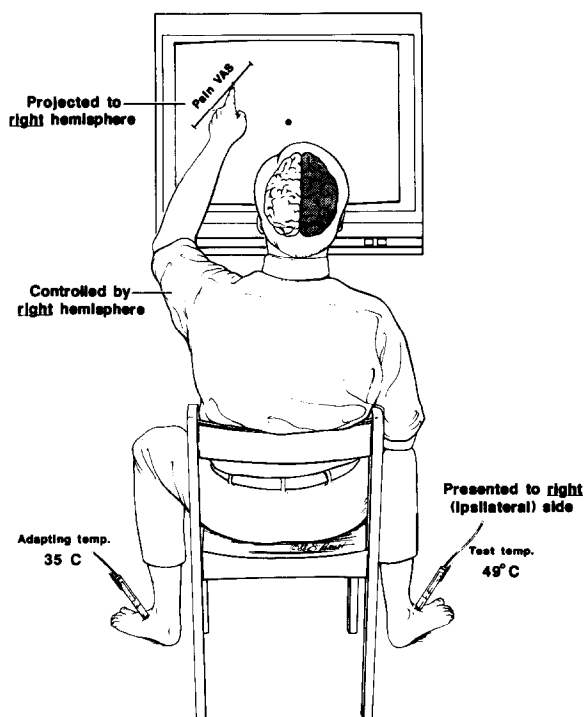


Fig. 1. Experimental paradigm wherein subject rates pain intensity on a visual scale (VAS). On each trial, the subject fixated on an illuminated point in the center of the TV screen, as shown. The thermal stimulus was then presented, after which a VAS appeared within his peripheral right or peripheral left visual field for 150 msec. The subject rated the intensity of the thermal stimulus by pointing along the VAS with his right or left hand. As shown here, *left-handed/left* visual field-related ratings were presumed to be related to *right* cerebral hemisphere responses and vice versa. Here the subject is responding to an intense (49°C) nociceptive stimulus presented *ipsilateral* (right) to the responding (right) cerebral hemisphere. Both the intensity of the stimulus (its temperature) and the side of the body stimulated were randomly varied in these experiments.

the right and left sides of the body. The thermode-skin temperature rose rapidly ($10^{\circ}\text{C}/\text{sec}$) from a baseline of 35°C to a peak of 43 – 51°C for 5 sec and then returned to baseline by an active cooling mechanism [2]. Two thermodes were positioned on homologous body parts so that the subject would be unaware of which thermode would present the thermal stimulus on a given trial. Stimuli were presented to the masseter area

of the face, the wrist, the dorsum of the hand and the dorsum of the foot. To avoid sensitization or suppression of nociceptors induced by rapid and repeated stimulation of the same or adjacent areas of skin, stimuli were presented to separate spots distributed over the surface of the chosen body area with interstimulus intervals of 5 min for any given spot and at least 30 sec between successive stimuli in general [2].

Statistical methods

All data are presented as means. Statistical significance on verbal and VAS ratings was assessed using 2-tailed unpaired *t* tests at each stimulus temperature. $P < 0.05$ was chosen as the minimum level of statistical significance and comparisons were made separately for the sensory and affective data presented in Fig. 2B. For results presented in Fig. 2C, the contralateral data from the two hemispheres were combined and tested against the ipsilateral data.

Results

In the first experimental paradigm, which required the localization of non-noxious tactile stimuli, the subject was able to correctly detect and verbally identify the toe stimulated on the right (contralateral) side with 75% accuracy (40 trials). However, his performance with stimuli on the left side (24%) was not significantly above chance (chi-square, $P > 0.2$). The difference in performance between the two sides was statistically reliable ($P < 0.01$, chi-square).

The results of the second and third paradigms are illustrated in Fig. 2, which shows the striking differences in verbal (i.e., left, or 'speaking' hemisphere, Fig. 2A, B) and VAS (either hemisphere, Fig. 2C) ratings of the noxious thermal stimuli presented to the left and right sides of the body. Ratings of the intensity (sensory) or unpleasantness (affective) of the stimuli were far lower for the ipsilateral (left) side than for the contralateral (right) side except at the highest stimulus intensities. This difference occurred with both testing methods (verbal rating and VAS) and is most apparent in Fig. 2A, where similar verbal judg-

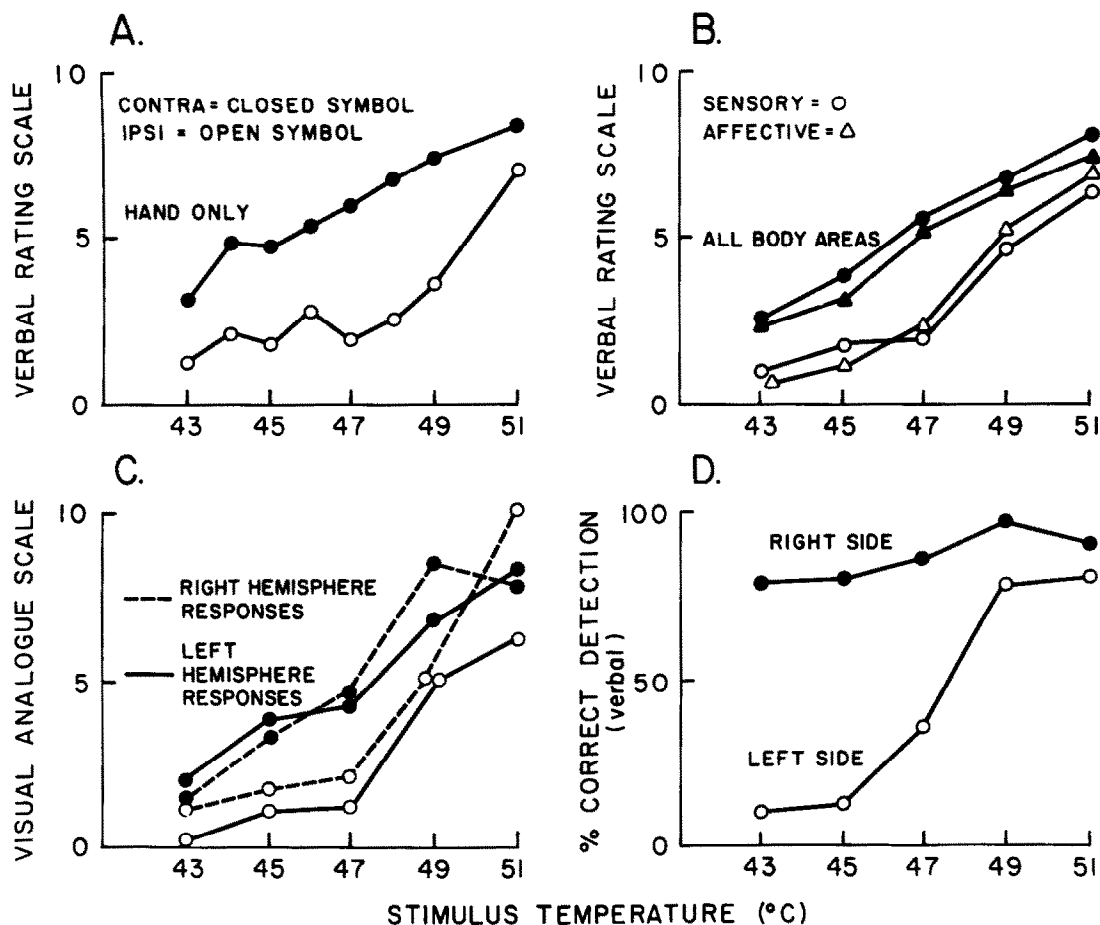


Fig. 2. Psychophysical responses to thermal stimuli within the noxious range presented ipsilateral and contralateral to the responding cerebral hemisphere. In A, the mean verbal ratings (made via the left hemisphere) of the pain sensation intensities of nociceptive thermal stimuli delivered to right (contralateral, closed symbols) and left (ipsilateral, open symbols) hands are compared. Note that ratings are generally much higher ($P < 0.05$, 2-tailed t test) for the contralateral than for the ipsilateral hand at all temperatures except the highest (51°C) tested. This contralateral-ipsilateral difference was apparent regardless of the area of the body tested, the nature of the response (verbal or VAS) or the hemisphere responding. In B, the mean contralateral sensory (closed circles) and affective (closed triangles) ratings are compared to ratings of the same stimuli on the ipsilateral (open symbols) side of the body using the same verbal rating scale. Here, data from all body areas tested (hands, feet and face) are combined for each side of the body. As in A, contralateral judgments are far higher than are ipsilateral ($P < 0.05$ except affective ratings at $49-51^{\circ}\text{C}$). Also note the close correspondence of intensity (sensory) and unpleasantness (affective) ratings. In C, the visual analogue scale is used to compare intensity ratings of stimuli contralateral and ipsilateral to the responding hemisphere. Here, both right- and left-hand responses (which use opposite hemispheres) were used to rate stimuli on each side of the body. Once again, and regardless of the hemisphere involved, contralateral judgments were far higher than ipsilateral ($P < 0.05$) except at the highest and lowest temperature. In D, verbal responses were used to determine the percent correct detection of the side of the body stimulated as a function of stimulus temperature. Note the poor detection of ipsilateral (open symbols) as opposed to contralateral (closed symbols) stimuli except at the highest temperatures.

ments were made for identical stimuli delivered to either hand only when the temperature was 51°C . At each of the other 7 temperatures tested, equivalent temperatures on the ipsilateral hand were

rated much lower compared to the contralateral hand and each of these differences was statistically significant (all $P < 0.05$). This contralateral-ipsilateral difference was also evident when

the data from all body parts were combined (Fig. 2B): similar verbal judgments were made for identical stimuli on both sides of the body only when the highest temperatures were presented. *Both* cerebral hemispheres, tested independently, responded very similarly to contralateral stimuli by VAS rating (see Fig. 2C). However, similar to verbal ratings, VAS responses to contralateral stimuli were significantly greater than those to ipsilateral stimuli except at the lowest and highest temperatures tested. This combination of results indicates that the statistically significant differences between ratings of stimuli contralateral and ipsilateral to this subject's responding hemisphere are not likely to be the result of intrinsic differences in cerebral hemispheric responses to pain in general. Thus, there does not appear to be lateralization of either the sensory or affective dimensions of pain in this patient. Furthermore, these contralateral–ipsilateral differences in responses cannot be a result of differences in pain sensitivity between right and left sides of the body. Consistent with the deficits in localizing ipsilateral non-noxious tactile stimuli described earlier, localizing the ipsilateral side of the body stimulated with the lower intensity thermal stimuli (43–47°C) also was impaired (Fig. 2D). However, similar to VAS and verbal rating responses, the ability to use ipsilateral inputs to the responding hemisphere to correctly detect the side of the body stimulated increased radically at higher (49–51°C) temperatures.

Perhaps most unexpected was the finding that ipsilateral nociceptive input contributes to *both* sensory and affective dimensions of pain, albeit at very high stimulus intensities. The contribution of ipsilateral input to affective responses was attested to not only by verbal ratings of unpleasantness (Fig. 2B), but by several verbal statements made by the subject indicating that 49–51°C stimuli to the ipsilateral (left) side were bothersome, annoying and, therefore, clearly aversive.

Discussion

These experiments show that somehow each cerebral hemisphere can be made aware of noci-

ceptive stimuli on both sides of the body in the absence of the corpus callosum. Neurons with bilateral receptive fields in medial thalamic nuclei that project to cerebral cortex [10,16] are prime candidates to subserve this function. They may receive their ipsilateral nociceptive input via a recrossing of ascending nociceptive pathways at supraspinal levels, or via lamina VII spinothalamic neurons that already have bilateral receptive fields [10,16]. This latter possibility is consistent with the high nociceptive thresholds of these lamina VII cells [10,16]. Regardless of how this input is received, these results indicate that nociceptive neural activity in pathways *other than* the classical crossed spinothalamic pathway (that represents the contralateral body surface, synapses in the VPL_c of thalamus, and then projects directly to primary somatosensory cortex on the same side) is sufficient to evoke the complete complex of responses associated with pain when stimuli are frankly noxious (49–51°C). Alternate central pathways that represent the ipsilateral body surface somehow contribute to the intensity of a painful sensation, its unpleasantness and its location. However, these pathways do not contribute much to these aspects of pain at the lower end of the nociceptive range (43–47°C), where they often fail to subserve the detection of stimulus location and appreciation of stimulus intensity, functions normally subserved by contralateral and inter-hemispheric pathways.

It is likely that during normal behavior, innocuous and weakly noxious stimuli have access to contralateral (and interhemispheric) pathways only. However, when noxious stimuli are sufficiently intense, ipsilateral pathways are also recruited. Presumably, the recruitment of all possible inputs capable of signaling potential harm allows such stimuli maximal access to consciousness and produces the maximal motivation to escape.

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