# Are Patients With Schizophrenia Insensitive to Pain? A Reconsideration of the Question

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**Objectives:** To review the scientific literature regarding pain and schizophrenia, examine the empirical basis for the reported pain insensitivity of schizophrenia, and to emphasize the distinction between behavioral responses to pain or self-reported pain and physiologic response to painful stimuli.

**Methods:** A Medline/Oldmedline search was conducted through 2006 using the key words schizophrenia and psychosis combined with pain and related terms designated by the International Association for the Study of Pain. Out of 431 articles initially identified, 57 were considered relevant and classified in 4 groups: case reports (n = 9), clinical studies (n = 23), experimental research (n = 20), and review articles (n = 5).

**Results:** Case reports and clinical studies reported reduced pain reactivity in patients with schizophrenia compared with healthy controls or other psychiatric patients. Similarly, experimental studies using self-report measures of pain reactivity generally reported higher pain perception thresholds in patients with schizophrenia. However, the only experimental study using a neurophysiologic measure of pain reactivity (the nociceptive RIII reflex) demonstrated a normal pain threshold in schizophrenia.

**Discussion:** Review of clinical and experimental data indicates that in most situations behavioral pain reactivity and self-reported responses to pain are reduced in schizophrenia. However, there is little or no physiologic evidence supporting pain insensitivity in schizophrenia. It can be suggested that the widely accepted notion of reduced pain sensitivity in schizophrenia is related more to a different mode of pain expression than to a real endogenous analgesia. Further studies are required and potential directions for future research are proposed to clarify this issue.

**Key Words:** pain, pain sensitivity, pain reactivity, schizophrenia

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The International Association for the Study of Pain (IASP) defines pain as ''an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.''[1] The IASP also notes that the inability to communicate verbally does not negate the possibility that an individual is experiencing pain and is in need of appropriate pain-relieving treatment. This applies to mental and medical disorders involving communication impairments and underlines the need to better take into consideration the expression of pain in these disorders and to develop adapted therapeutic perspectives.

Schizophrenia represents a frequent mental disorder (prevalence between 0.5% and 1%[2,3]) involving communication and other cognitive impairments. Sensory perception abnormalities including impairments in recognition of odors, perception of taste, and proprioceptive abilities have been reported in patients with schizophrenia.[4–7] Symptoms such as kinesthetic delusions, hypochondria, strange or delusion thoughts concerning internal organs, as described in the Cotard syndrome, suggest the presence of pain misperception in schizophrenia.

On the basis of clinical observations, it has been suggested that patients with schizophrenia are relatively insensitive to physical pain. Kraepelin[8,9] first described *Dementia Praecox*, which was included within the group of ''psychosis with deficit'' and reported that patients could burn themselves with cigarettes and experience needle pricks or injuries without showing adaptive and normal reactions. Bleuler,[10,11] who applied the modern name of ''schizophrenia'' to Kraepelin's *Dementia Praecox*, reported similar observations regarding decreased behavioral pain reactivity after painful stimuli on these patients' body or skin suggesting the ''presence of a complete analgesia.''

This paper reviews the scientific literature regarding pain and schizophrenia, and discusses prior studies in the context of neurodevelopmental hypotheses and vulnerability models. The literature regarding pain and schizophrenia has been reviewed once in the last 10 years,[12] and the review of Singh and colleagues[12] seemed to take pain insensitivity in schizophrenia as a given. This review updates the prior reviews and is focused on the critical distinction between behavioral responses to pain or self-reported pain and the physiologic response to painful stimuli. Keeping this distinction in mind is critical when addressing the fundamental and clinically significant question of whether pain sensitivity is altered in the schizophrenic patient. This review also includes detailed summaries of all the relevant studies in order that they may be fully considered.

## METHODS

To identify articles concerning pain perception in patients with schizophrenia, we searched on the Medline/Oldmedline database through 2006. The search strategy included the key words (in title, abstract, and key words list) schizophrenia and psychosis combined with pain and

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related terms designated by the IASP (allodynia, analgesia, anesthesia dolorosa, causalgia, dysesthesia, hyperesthesia, hyperalagia, hypoalgia, hypoesthesia, neuralgia, neuritis, neuropathy, nociceptor, noxious stimulus, and paresthesia). Furthermore, the reference lists of the articles obtained regarding our topic were screened to identify additional studies of interest. We found 431 articles and excluded 361, which were clearly not relevant to our topic or mentioned the topic only briefly. Out of the remaining 70 articles, 13 were general discussions on pain reactivity. In this latter category, the publications were considered secondary sources and were not included in our analysis. The remaining 57 articles were classified in 4 groups: case reports (n = 9), clinical and epidemiologic studies (n = 23), experimental studies (n = 20), and previous review articles (n = 5). Our review took into consideration these 5 previous reviews[12–16] and provides an update on the topic.

## RESULTS

Many case reports concerning patients with schizophrenia who had painful medical illnesses (acute abdomen pain, ruptured appendix, peritonitis, peptic ulcer, perforated bowel, compartment syndrome, fractures) without reports of pain, have contributed to the concept of pain insensitivity in schizophrenia (Table 1). The absence of pain reports can result in delayed treatment, as emphasized early by West and Hecker[17], and lead to greater morbidity and mortality.[18–25]

The absence of pain report was confirmed by clinical studies of pain reactivity conducted in large samples of individuals with schizophrenia in different medically painful conditions such as acute perforated peptic ulcer, acute appendicitis, or myocardial infraction (Table 2). More generally, clinical studies conducted on schizophrenic children or adult inpatients and outpatients, showed a high prevalence (52% to 80%) of patients without any pain.[26–29] In addition, no cases of schizophrenia were reported in large samples of inpatients with chronic pain.[30,31] However, studies reported low prevalence of schizophrenia (1.2% to 2%)[32–34] among psychiatric patients with chronic pain, these results need to be considered with regard to the prevalence of schizophrenia in the general population (0.5% to 1%[2,3]). Furthermore, some studies have reported relatively high (5.5%, 37.7%) prevalence of schizophrenia[27,35] among psychiatric inpatients and outpatients with headaches. Headaches, which were first described in schizophrenia by Kraepelin and Bleuler,[8–11] are also commonly (17%, 19.4%) observed in adult outpatients with chronic schizophrenia.[36,37] Other studies have even suggested that headaches might be an early symptom appearing frequently (17% to 23%) at the onset of schizophrenia.[38–40] Taken together, these clinical results are not consistent and need to be clarified by additional experimental studies.[41–47]

Experimental studies on pain perception in schizophrenia are mainly based on a psychophysical method (self-measurement of pain perception using a scale) or a method using the signal detection theory (the pain response is measured by the individual's ability to discriminate the sensory stimuli and by response criteria reflecting their attitude after painful stimuli). Most of the experimental studies that have examined the responses of individuals with schizophrenia to thermal, electrical, pinprick, cold pressor, and pressure pain have reported abnormal pain perception in terms of pain threshold, pain tolerance, sensation detection threshold, and sensory discrimination (Table 3). However, these experimental studies showed contradictory results. Thus, a few studies reported abnormally high pain perception thresholds or pain tolerance in patients with schizophrenia[48–51] which were not consistent with other studies.[52,53] One experimental study deserves special attention because it has used a neurophysiologic measure of pain reactivity, the nociceptive RIII reflex threshold. The RIII reflex is studied by applying percutaneous electrical stimulation on the sural nerve and recording the reflex motor response from the biceps femoris muscle (a flexor muscle). Studies conducted on healthy participants have shown that the amplitude of the RIII reflex is correlated proportionally with the participant's self-reported pain threshold.[54] Ten male patients with schizophrenia and 10 male healthy controls were recruited in the study. This study did find a slightly higher mean nociceptive RIII reflex threshold in the schizophrenia group ($11.55 \pm 2.01$ vs. $10.75 \pm 1.34$ mA) (Table 3). However, the difference was not significant by Mann-Whitney $U$ test (medians of 11.5 and 10.5, $z = 1.06$, $P = 0.289$), Student $t$ test ($t = 1.05$, $P = 0.31$), or paired $t$ test ($t = 1.57$, $P = 0.16$). In addition, values observed in the schizophrenia and control groups were extensively overlapped (Fig. 1). It

**TABLE 1.** Case Reports of Patients With Schizophrenia Reporting no Pain in Various Painful Medical Conditions

| Authors | Sample Size | Age in Years (Sex) | Type of Painful Medical Conditions |
|---|---|---|---|
| Lewis[18] | 4 | Adults (male) | Acute abdomen |
| West and Hecker[17] | 33 | Adults (male) | Peptic ulcer |
| Geschwind[19] | 1 | 57 (female) | Ruptured appendix |
| Apter[20] | 1 | 24 (male) | Ruptured appendix |
| Fishbain[21] | 3 | Adults (male) | Perforation of peptic ulcer and fractures |
| Bickerstaff et al[22] | 5 | Adults (male) | Acute abdomen |
| Rosenthal et al[23] | 1 | 25 (male) | Perforated small bowel |
| Katz et al[24] | 7 | Range (20 to 78) (male) | Acute abdomen |
| Murthy et al[25] | 1 | 57 (male) | Fracture with compartment syndrome |

**TABLE 2.** Main Clinical Studies of Pain Reactivity/Sensitivity in Patients With Schizophrenia in Acute Painful Medical Conditions

| Authors | Sample Size | Age in Years | Type of Painful Medical Conditions | Percentage of Patients Reporting no Pain |
|---|---|---|---|---|
| Lieberman[41] | 56 | Adults mostly over 50 | Myocardial infarction | 87 |
| Marchand[42] | 51 | Adults mostly over 50 (4 were younger) | Myocardial infarction | 85 |
| Marchand et al[43] | 14 | Adults | Perforated peptic ulcer | 21 |
| | 19 | Mostly over 50 | Acute appendicitis | 37 |
| | 46 | (16 were younger) | Fracture of femur | 41 |
| Hussard[44,45] | 123 | All over 40 | Coronary heart disease leading to death | 60 |
| Ballenger et al[46] | 26 | Not given | Headache after lumbar puncture | 82 |
| Torrey[47] | 100 | Not given | Headache after lumbar puncture | 91 |

should be noted that all statistical analyses reported here for the Guieu et al[54] paper were performed using the reported raw data.[55–62]

## DISCUSSION

### Are Patients With Schizophrenia Less Sensitive Than Others to Pain or Rather Less Reactive to Pain?

Results from our review on clinical and experimental data suggest strongly a decrease of behavioral pain reactivity in individuals with schizophrenia, but there is a lack of evidence to prove that these individuals display a real analgesia. As schizophrenia is a severe mental disorder associated with communication and social impairments, it may be very difficult to demonstrate the decrease or absence of pain sensitivity. In their review of the literature, Lautenbacher and Krieg[14] concluded that the hypoalgesic changes observed in schizophrenia have still "not been verified unequivocally under experimental conditions," and that results remain ambiguous. Indeed, when we look carefully at the literature, some case reports and case series concern individuals with schizophrenia who displayed atypical pain (distorted perception of pain) which could be related to a different mode of pain expression due to cognitive impairments and disturbances of body schema.[13,15,24] Similar observations of atypical pain including hyperreactivity to pain have been described in patients with schizophrenia-like psychosis,[63,64] autistic disorder,[65] and intellectual or neurologic disabilities[66–69] involving cognitive and body schema impairments. In addition, Varsamis and Adamson[40] reported that 48% of their 64 hospitalized patients with schizophrenia report pain and it was the only subgroup of markedly withdrawn patients (social and communication withdrawal) who did not report pain, which underlines the importance of social communication in pain expression.

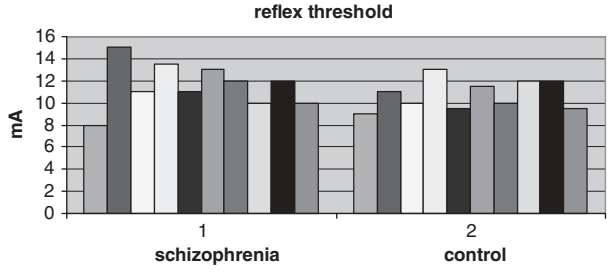


**FIGURE 1.** RIII reflex threshold for patients with schizophrenia and controls (in mA). From *Br J Psychiatry*. 1994;164;253–255

In the same vein, Kuritzky et al[36] found that 19.4% of their 108 adult outpatients with chronic schizophrenia had migraines and were able to give a precise description of it in a self-report questionnaire, but they tended to refrain from reporting spontaneously about their migraine due to social communication impairments. Furthermore, a dissociation is found in schizophrenia between decreased psychophysical and behavioral responses contrasting with increased physiologic responses after a painful stimulus; Malmo et al[57] reported decreased volitional responses to thermal stimuli, but an association with increased heart rate, blood pressure, and muscle tension in 17 patients with schizophrenia compared with 21 healthy controls. In fact, as reported in the Results section, the only experimental study of pain sensitivity in schizophrenia based on measuring the nociceptive RIII reflex threshold did not find any differences between individuals with schizophrenia and healthy comparison participants. The authors concluded that, in most cases, any observed increase in pain perception threshold was the result of "attitude," but not alteration in brain function.[54] Guieu and colleagues in their study found that objectively measured pain thresholds not to differ significantly between patients and controls, with extensive overlap observed between the 2 groups.[54] Although replication of this study is warranted, it adds support to the observations suggesting that there is not a real endogenous analgesia in schizophrenia and that pain sensitivity is not altered in this disorder. Most prior reports did not distinguish pain reactivity from pain sensitivity, and absence of pain reactivity does not mean absence of pain sensitivity. Hence, as proposed by some authors,[14] it is safer to state that pain experience in schizophrenia is disturbed or distorted than absent.

In addition, a number of limitations to the previous studies must be acknowledged. Most of these studies, especially those before 1970, have methodologic problems. First, samples were often very small ($N \leq 10$ patients) or were not compared with appropriate control groups. Moreover, the diagnosis was not precisely ascertained or the study did not take into account the subtype or severity of schizophrenia (positive or negative symptoms), which

 

**TABLE 3.** Main Studies on Pain Sensitivity or Reactivity in Patients With Schizophrenia

| Authors | Type of Painful Stimulus | Pain Assessments and Measures | Sample Size: Patients With Schizophrenia/ Controls | Age of Patients With Schizophrenia (years) | Results |
|---|---|---|---|---|---|
| Bender and Schilder[55] | Electric stimulation: light signal associated with electric shock compared with light signal only | Clinical description of behavioral pain reactivity | 16 (mostly catatonic)/no control group | Adults (23 to 58 for those described) | Reactivity is retarded and incomplete. Emotional and breathing reactions are present |
| May[56] | Painful pinch on the face near mastoid process | Pupillary dilatation considered as positive response | 343/100 healthy controls | All < 55 | Positive response in 66% of patients versus 83% of controls |
| Malmo et al[57] | Thermal stimulation | Participant pressing a button when heat applied to the forehead became too painful | 17/27 healthy controls | All < 60 | Patients with schizophrenia pressed the button and displayed withdrawal less frequently than controls |
| Hall and Stride[49] | Thermal stimulation | Pain level verbally reported and observation of behavioral pain reactivity | 14/256 neurotic patients | 18 to 70 | Increased verbal report of pain and pain reaction in patients with schizophrenia (312 and 32, respectively) when compared with neurotic patients (260 and 283, respectively). |
| Earle and Earle[33] | Cold pressor test: blood pressure measure after immersion in water at 37°C and 4°C | Increased blood pressure produced by the cold water immersion (cold pressor response) | 36/10 patients with nonschizophrenic psychosis/15 healthy controls | Mean: 34.6 Range: (15 to 73) | 33% of patients with schizophrenia showed no cold pressor (especially the paranoid patients) response, 66% showed a response of 5 mm or less (especially the hebephrenic patients). The 2 control groups showed a higher response than the schizophrenic group |
| Merskey et al[34] | Soft pinprick in several areas and pressure algometer (wooden plumber) | Behavioral reactivity scales (0 to 5) | 80 (12 with paranoid symptoms and 18 with high phenotiazine dose)/no control group | Range: (25 to 64) | Paranoid and high phenotiazine dose patients (mostly oldest patients) react less than other patients (paranoid vs. nonparanoid: 0.90 vs. 1.52, $P < 0.02$ and high phenotiazine vs. other patients: 0.93 vs. 1.38, $P < 0.05$). |
| Collins and Stone[52] | Electric stimulation | Verbal report, sensation and pain threshold, length of tolerance | 18/56 healthy controls | Mean ± SD: 32.82 ± 13.14 Range: (20 to 54) | Increased sensation threshold in patients compared with controls (06 ± 0.34 vs. 0.3 ± 0.15, $P < 0.01$). No difference between the 2 groups for pain threshold and tolerance |
| Kane et al[58] | Thermal stimulation | Verbal report | 30/15 healthy controls | Mean: 32.6 (Range: 20 to 62) | Compared with controls, paranoid patients were less sensitive and hebephrenic patients were more sensitive (more verbal report) |
| Sappington[31] | Electric stimulation | Verbal report and pain tolerance (self-selected voltage level) | 30 paranoid/30 hebephrenic/ no control group | Mean: 29.6 Range: (22 to 70) | Shock tolerance of hebephrenic patients was significantly greater than paranoid (21/30 vs. 16/30 had a self-selected |

(*continued*)

**TABLE 3.** (*continued*)

| Authors | Type of Painful Stimulus | Pain Assessments and Measures | Sample Size: Patients With Schizophrenia/ Controls | Age of Patients With Schizophrenia (years) | Results |
|---|---|---|---|---|---|
| | | | | | voltage level above 2.9 volts, $P < 0.05$). |
| Maricq and Edelberg[30] | Two sessions of cold pressor test (during a maximum of 60 s unless participant stopped the test) separated by a period of elevated temperature in the exam room | Verbal report for cold pressor test and electrodermal recovery rates | 28 unmedicated patients/27 healthy controls | Mean ± SD: 43.0 ± 7.6 | No significant difference between patients and controls for ERR and verbal report after cold pressor tests |
| Davis et al[32,59,60] | Electric stimulation: 1 ms computer-controlled stimulation on the left forearm | Verbal reports: response: milli-amperage noxious level assessed by participants. Insensitivity is defined by the absence of discrimination between the pleasant and unpleasant conditions. Electrophysiologic measures: somatosensory evoked potentials (SEP) | 17 unmedicated patients/17 healthy controls | Mean: 26 | Patients were significantly more insensitive to painful stimuli than controls ($P < 0.01$). Verbal report was lower in patients compared with controls ($P < 0.01$). Patients had lower amplitude-intensity slopes for SEP than controls ($P < 0.05$) |
| Albus et al[61] | Cold pressor test: each foot in ice water for 40 s | Electromyogram (EMG), electroencephalogram (EEG), skin conductance level, and response (PSCR). Finger temperature and pulse amplitude (FPA) heart rates (HRs) and respiratory volume (RV) Plasma cortisol by catheter | 12/63 healthy controls | Mean ± SD: 34 ± 8.5 | No difference was found between patients and controls for EEG, PSCR, FPA, and RV. When compared with controls, patient had significantly higher measures of SCL (26.63 ± 16.17 vs. 18.4 ± 13.05, $P < 0.05$), EMG ($P < 0.001$) and cortisol ($P < 0.05$). HR was not significantly higher in patients than in controls |
| Buchsbaum et al[62] | Electric stimulation: patients are receiving a 34 min 1/s series of unpleasant electrical stimuli to the right forearm | Scanner analysis of cerebral glucose in the brain | 16 unmedicated patients/11 with affective disorder /19 healthy controls | Mean ± SD: 28.3 ± 7.7 | Less significant anteroposterior glucose gradients in patients compared with controls (1.02 ± 0.08 vs. 1.08 ± 0.11, $P < 0.05$). Relative hypofrontal function in patients compared with controls |
| Dworkin et al[53] | Thermal stimulation by brief pulse of increasing or decreasing heat on the forearm | Verbal report of pain: signal detection theory classical measures: (1) Sensory discrimination (2) Response criterion (RC) | 13 unmedicated patients for at least 4 weeks/ 19 healthy controls | Mean: 35 | Patients showed significantly poorer sensory discrimination than controls (0.66 ± 0.10 vs. 0.77 ± 0.09, $P < 0.01$) but no differences in RC. Higher RC was present in patients with more intense affective clinical experience |
| | Thermal stimulation by a dolorimeter. Six stimuli of different intensity were randomized | Same as above | 13/13 patients with mood or bipolar disorders/32 | Mean: 26.6 | There were no significant differences for any measures between patients with |

(*continued*)

**TABLE 3.** (*continued*)

| Authors | Type of Painful Stimulus | Pain Assessments and Measures | Sample Size: Patients With Schizophrenia/ Controls | Age of Patients With Schizophrenia (years) | Results |
|---|---|---|---|---|---|
| | | | healthy controls | | schizophrenia and patients with bipolar disorder or depression and between patients and healthy controls. There was a significant correlation between the schizophrenia premorbid adjustment rates and the RC (Bravais-Pearson $r = 0.59$, $P < 0.05$) |
| Guieu et al[54] | Electric stimulation: reflex motor activity recorded near the ipsilateral femoral biceps | Nociceptive RIII reflex threshold (gives an neurophysiologic measure of pain reactivity) | 10/10 healthy controls | Mean ± SD: 35 ± 12.9 | There was no significant difference between patients (11.6 ± 2) and controls (10.7 ± 1.3) for the RIII nociceptive threshold ($U = 3.9$, $P = 0.07$) |
| Hermesh et al[50] | Thermal stimulation by walking on a motor-driven treadmill in a chamber with elevated temperature (40°C) | Rectal temperature, HR, skin temperature, and blood pressure | Eight patients with antipsychotic drugs/8 healthy controls | Mean ± SD: 31.5 ± 6.5 | Significantly higher rise in rectal ($P < 001$) and skin temperature ($P < 0.02$) in patients compared with controls. No difference in other measures |
| Kudoh et al[51] | Electric stimulation: transcutaneous electric stimulation (0 to 10 mA, 5-250-2000 Hz) | Verbal report of pain: (1) Current perception threshold (CPT) (2) Visual analogue scale (VAS) | 25 patients with pentazocine (A)/25 patients with pentazocine + -haldol (B)/25 healthy controls with 30 mg pentazoline alone (C) | Mean ± SD: 47.0 ± 2.1 (A) Mean ± SD: 45.5 ± 1.6 (B) | When compared with controls, patients had an increased CPT at 2000, 250, and 5 Hz (334.2 ± 112.2 vs. 198.9 ± 43.9, 303.9 ± 117.1 vs. 62.0 ± 15.7, and 165.0 ± 772.3 vs. 35.3 ± 12.4, respectively, $P < 0.001$ for all measures) and a lower VAS score (3.9 ± 1.6 vs. 5.1 ± 1.9, $P < 0.05$). No differences where found between the 2 groups of patients |
| Blumensohn et al[48] | Electric stimulation: acute pain stimulation by electric tooth vitality scanner | Verbal report of pain: (1) Sensation threshold indicated by the subject (Sth) (2) Pain threshold and pain tolerance (Pth and PT, respectively.) (3) VAS | 25/29 healthy controls | Mean ± SD: 19.1 ± 2 | Sensation threshold, pain threshold, and tolerance levels were significantly higher in patients compared with normal controls (Sth: 29.7 ± 15.4 vs. 17.8 ± 6.7, Pth:41.0 ± 21.5 vs. 21.7 ± 6.9, PT: 47.0 ± 22.1 vs. 28.7 ± 9.9, respectively; $P < 0.001$ for all measures). VAS measures showed no significant differences |

ERR indicates Electrodermal Recovery Rates; PSCR, Palmar Skin Conductance Response.

may be important in the perception and verbalization of painful stimuli. Indeed, it has been reported that schizophrenic patients with paranoia or catatonia seemed to be less sensitive to pain than those with other subtypes of schizophrenia.[11,34] In the same line, we have no idea if patients were able to understand the instructions of the examiner. Additionally, the chronic course of the disorder may confound results in that individuals with chronic schizophrenia seemed to be less reactive to electrical shocks and thermal stimulus than individuals with acute schizophrenia.[31,58] Concerning pain measures, assessments were not comparable from one study to another. Furthermore, the 2 experimental methods for measuring pain have been criticized. Indeed, the psychophysical method has been considered potentially unreliable especially in individuals with verbal impairments.[70] The method of signal detection has been criticized because sensory discrimination might measure nonsensory processes like context effects, and response criteria can be interpreted in different ways based on conceptual, judgmental, emotional, motivational, and sociocultural factors.[71] Finally, medications taken by patients were not always indicated. Indeed, neuroleptics bind to opiate receptors and therefore may modify pain sensitivity. Thus, it has been suggested that neuroleptics may play a key role in the pain insensibility phenomenon.[15,21,72] However, clinical observations of apparent pain insensitivity had been reported in schizophrenia before the therapeutic use of neuroleptics.[8,11,18,55]

By taking an account of these observations, it could be suggested that the apparent pain insensitivity reported in schizophrenia is related more to a different mode of pain expression than to a real endogenous analgesia. It should be taken into consideration that individuals with schizophrenia have communication and thinking impairments,[73] nonadapted social skills,[74] and also lack of body representation,[75] all of which could lead to altered, decreased or absent pain expression. Rigorously designed research should be conducted to identify and to understand the phenomenon of apparent insensibility to different types of painful stimuli in patients with schizophrenia. Such studies need to consider and compare subjective aspects of pain (perceived pain measured on a visual analogue scale), behavioral observational scales, neurovegetative reaction (heart rate, breath, or palmar skin conduct), functional magnetic resonance imaging, and the physiologic pain threshold measured by the nociceptive RIII threshold. It is by contrasting the different measures of pain response and expression that the picture can be clarified. The examination of verbal reporting by schizophrenics of other sensory modalities may be a fruitful approach. The demonstration of altered communication in other domains would tend to support the idea that communication deficits underlie altered pain reactivity (behavioral responses and reported pain) in schizophrenia. In addition, future studies on the effects of neuroleptic administration on pain reactivity and sensitivity may provide an approach for testing the hypothesis that the altered pain reactivity arises from disturbances in communication. Normalization of communication after neuroleptic treatment would be expected to lead to more normal pain reactivity. Interpretation of the results of such studies would be complicated due to the possible direct effects of neuroleptics on pain mechanisms; other interventions or therapies targeting communication deficits may offer less confounded approaches.

## Is There a Biochemical Dysfunction Related to Pain in Schizophrenia?

The case reports, clinical, and experimental studies regarding pain insensitivity in schizophrenia[12] have prompted opioid and *N*-methyl-D-aspartate (NMDA) theories in schizophrenia. Thus, some authors have invoked pain insensitivity in support of theories of a dysfunction of NMDA receptor-mediated neurotransmission in schizophrenia,[76,77] considering that NMDA antagonists have analgesic properties. In a parallel fashion, other authors have posited abnormally high activity of central endorphins, which led to the therapeutic use of the opiate antagonist naltrexone in individuals with schizophrenia.[12,78,79] However, as in autism, the studies measuring endorphins in schizophrenia offered conflicting results.[75,78–80] Similarly, studies conducted by Davis et al[32] correlating elevated endorphins or high endorphin binding to decreased pain perception in patients with schizophrenia, are not consistent with most reports.[81–85] Further studies are required to clarify the opioid or NMDA issues. However, consideration of the past research and any future work in this specific area should take into account that the underlying rationale (of reduced pain sensitivity in schizophrenia) may be in doubt.

## Is the Decrease of Behavioral Pain Expression Relevant to the Stress Vulnerability Model of Schizophrenia?

A decrease of behavioral pain expression may play a role in a comprehensive theory of schizophrenia in line with the stress-vulnerability model.[86–90] In this model, anxiety and stress are the factors which have been suggested to induce the onset of schizophrenia.[89,90] This model also suggests that a dimensional approach involving characteristic symptom clusters of schizophrenia would be more appropriate than a categorical approach. These symptom clusters could be clinical (eg, persecution feelings, social withdrawal or anxiety),[86,91] psychologic with cognitive variables (eg, impairments in attention, executive function, memory, or verbal and nonverbal communication),[92] biologic,[87] electrophysiologic (eg, catch-up saccade in examination of ocular movement or impairment in late evoked potential, such as P300),[87] genetic (eg, genetic risk factors of schizophrenia in patients' offspring or sibling),[93] or anatomic (eg, asymmetry in brain areas, enlargement of ventricular volumes).[87] Trait markers are reported to be present before the onset of the disorder in vulnerable patients.[87] Identification of a marker and assessment of its predictive value is an important issue for research. A recent study conducted by Hooley and Delgado[94] showed that individuals with a family history of schizophrenia showed significantly higher pain perception thresholds and pain tolerance to finger pressure than controls with no mental disorder in their family history. This study suggests that reduced pain expression may be a potential state marker with vulnerability to schizophrenia.

We hypothesize that painful stimuli would provoke noxious psychologic and physical stress which could not be released and expressed through normal behavioral responses in patients with schizophrenia or vulnerable patients by regular regulation mechanisms of stress responses. This phenomenon could reflect a key mechanism and be a part of the onset or relapse factor of schizophrenia. Exploration of pain reactivity and of possible

 

discrepancies between self-reported pain and physiologic responses to pain in patients at risk to schizophrenia could be of interest in vulnerability studies. Further research is required to test this hypothesis

## Summary

On the basis of this review of the literature, it can be merely suggested that the widely accepted notion of reduced pain sensitivity in schizophrenia is related more to a different mode of pain expression than to a real endogenous analgesia. Although an open question at this time, objective measures of pain sensitivity should be especially useful in determining with any certitude whether pain sensitivity is essentially normal in schizophrenia. If this is determined to be the case, there would be important theoretical ramifications and practical implications.

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