Pain Perception in Schizophrenia: Evidence of a Specific Pain Response Profile

Mylène Lévesque, BSc,* Stéphane Potvin, PhD,‡ Serge Marchand, PhD,* Emmanuel Stip, MD, MSc,§ Sylvain Grignon, MD, PhD,¶ Lalonde Pierre, MD,§ Olivier Lipp, MD,§ and Philippe Goffaux, PhD*

*Département de neurochirurgie and ‡Département de psychiatrie, Faculté de Médecine et des Sciences de la Santé, Université de Sherbrooke, Sherbrooke;
§Département de psychiatrie, Faculté de médecine, Hôpital Louis-H Lafontaine, Université de Montréal, Montréal, Canada
¶Département de psychiatrie, Faculté de médecine, Centre Hospitalier de l’Université de Montréal, Université de Montréal, Montréal, Canada

Reprint requests to: Philippe Goffaux, PhD, Équipe de recherche sur la douleur, Faculté de Médecine et des Sciences de la santé, Université de Sherbrooke, 3001 12e avenue Nord, Sherbrooke, Canada. J1H 5N4.
Tel: (819) 345-1110, ext. 13821; Fax: (819) 564-5446; E-mail: Philippe.Goffaux@usherbrooke.ca.

Abstract

Objective. Ever since the characterization of schizophrenia, clinicians have noted abnormal pain sensitivity in their patients. The published literature, however, is inconsistent concerning the nature of the change reported. The objective of this study was to characterize the pain response profile of schizophrenic patients by providing both acute and prolonged (i.e., rapidly repeating) painful stimuli to schizophrenic participants and control subjects.

Participants. Twelve schizophrenic subjects and eleven controls were included in the final analysis. Diagnosis was made according to Diagnostic and Statistical Manual of mental disorders-4th edition, text revision (DSM-IV-TR) criteria.

Methods. Intermittent, transcutaneous stimulations of the left sural nerve were administered to all participants. Painful sural nerve stimulations provoked a nociceptive flexion reflex response which was measured using an electromyographic recording of the bicep femoris muscle. Pain ratings were obtained using a 0–10 verbal numerical scale. Among schizophrenic participants, the relationship between subjective pain, reflex amplitude, and clinical features was investigated. The Positive and Negative Syndrome Scale, Calgary Depression Scale for Schizophrenia, and Subjective Scale to Investigate Cognition in Schizophrenia were used to evaluate clinical features.

Results. Compared with controls, schizophrenic subjects showed increased sensitivity to acute pain (i.e., lower pain thresholds; \( P = 0.019 \)), but decreased subjective pain sensitization (\( P = 0.027 \)). Group differences in subjective pain sensitization were not accompanied by group differences in nociceptive reflex activity (\( P = 0.260 \)), suggesting supraspinal origins to the change in pain experienced by schizophrenic subjects. Moreover, positive symptoms correlated negatively with pain threshold values among schizophrenic participants (\( r = -0.696, P = 0.012 \)), suggesting that distortions of thought and function relate to pain sensitivity in schizophrenic patients.

Conclusion. Results indicate that schizophrenic subjects present a specific experimental pain response profile, characterized by elevated sensitivity to acute pain but reduced sensitivity to prolonged pain.

Key Words. Sensitization; Threshold; Positive Symptoms; Aberrant Salience

Introduction

Anecdotal reports and clinical case studies suggest that a change in pain perception occurs among patients who suffer from schizophrenia (Sz). In particular, patients with Sz seem to be less sensitive to pain than control subjects. This change in pain sensitivity is thought to explain why some patients present severe traumatic injury but fail to complain of pain or discomfort. It likely also contributes to explain why patients delay consulting their doctors, and, therefore, present a greater risk of morbidity and mortality [1]. Unfortunately, only a few experimental studies have investigated this issue and results to
date have been equivocal. Whereas some authors report evidence of decreased pain sensitivity in Sz [2–9], others report increased pain sensitivity [10–13] or no difference at all [14,15]. Methodological considerations, including inter-study differences in the type of stimulus used, stimulus duration, use of a comparison group, reliance on psychomotor responses, heterogeneity in disease profile, and treatment diversity, can all potentially explain why changes in pain sensitivity among Sz patients are still poorly understood. Despite all of this heterogeneity, a recent study published by Potvin et al. [16] reveals that even in cases where pain thresholds are unaffected, Sz participants remain less reactive to prolonged noxious insult. More specifically, that study demonstrated that following the repeat or continuous administration of a noxious stimulus (i.e., a circumscribed heat source), Sz participants showed very little pain enhancement. Control subjects, on the other hand, showed robust pain enhancement (also known as pain sensitization). Lack of pain sensitization in Sz patients suggests that their excitatory pain profiles (spinal and/or supraspinal) are significantly affected (see Woolf and Chong [17]). However, the findings reported by Potvin et al. [16] are based exclusively on subjective pain reports, and so, it is currently impossible to know if a lack of pain sensitization in Sz patients reflects a fundamental change in the way noxious afferents are treated by the spine, or, if a lack of pain sensitization captures the consequences of supraspinal pain-processing changes.

In order to study the contribution of spinal cord neurons to pain sensitization in humans, past studies have relied on the transcutaneous electrical pain paradigm [18]. This noninvasive paradigm supplies intermittent stimulations across the retromalleolar path of the sural nerve. When stimulation currents are strong enough to recruit Aδ fibers, a nociceptive-specific flexion reflex (NFR) response is triggered, whose amplitude correlates positively with subjective pain [19]. Importantly, when electrical stimulations are provided in rapid succession (i.e., 0.3 Hz or faster), both subjective pain and NFR amplitudes increase rapidly, indexing a temporary hyperexcitability of spinal cord neurons [20,21]. Thus, the transcutaneous electrical pain paradigm can be used to investigate the contribution of spinal process to pain sensitization [22]. This technique can be applied to better understand the contribution of spinal process to pain sensitization and to better understand the diminished reactivity to prolonged pain stimulation in Sz subjects.

The purpose of this study was to evaluate the contribution of spinal and supraspinal processes underlying the lack of pain sensitization observed among Sz patients. Four objectives were specifically pursued: 1) identify and compare the electrical pain and nociceptive reflex thresholds of Sz participants and age- and sex-matched control subjects; 2) replicate the finding of a lack of subjective pain sensitization in Sz participants; 3) identify spinal contributions to pain sensitization in Sz participants; and 4) correlate pain responses with clinical symptoms and antipsychotic drug use.

Methods

Participants

Outpatients suffering from Sz spectrum disorder were recruited at Louis-Hyppolite Lafontaine hospital (Montreal, QC, Canada) and invited to an experimental session at the Fernand-Seguin Research Center (Montreal, QC, Canada). Sz participants were diagnosed according to Diagnostic and Statistical Manual of mental disorders (DSM-IV) criteria by their treating psychiatrist. After carefully explaining the study, all participants provided free and informed consent. The study was approved by the local ethics committee.

Exclusion criteria were the following: the presence of a chronic pain condition, the presence of a substance use disorder, use of analgesic and/or benzodiazepine medication (last 24 hours), the presence of cardiac, respiratory, endocrine, or metabolic diseases, mental retardation or neurological deficits. Pregnant and/or breast-feeding women were also excluded. For Sz participants, exclusion criteria were verified following a physical exam and/or laboratory testing. For healthy controls, exclusion criteria were assessed via the administration of a health questionnaire (fully integrated in our intake socio-demographic questionnaire—see later). In the current study, chronic pain was defined as pain which persisted beyond normal healing times (typically 3 to 6 months—see Merskey and Bogduk [23]).

A total of 23 Sz subjects were eligible to participate. Twenty-one subjects suffered from paranoid Sz and two suffered from schizoaffective disorder. Of the 23 participants recruited, 12 were retained in the final analysis. Eight subjects were excluded because of unreliable electrophysiological recordings (extremely poor signal-to-noise ratio on the tachogram), one participant had taken analgesic medication prior to testing, one participant reached his/her pain tolerance threshold before a reflex response could be evoked, and one participant did not use the pain scale properly. The eight Sz subjects excluded because of unreliable electrophysiological data did not differ in terms of socio-demographic (age, sex) or clinical/medical data (pain threshold, antipsychotic drug use, and symptom severity [see later for a description of the tests used to evaluate symptom severity]) from the 12 Sz subjects retained for final analysis (all Ps > 0.05 on Fisher’s exact test and Mann–Whitney test). Average time since symptom onset for all retained Sz participants was 7.67 ± 1.76 years. Sz subjects were treated with one or more of the following antipsychotic drugs: ziprasidone (N = 1), olanzapine (N = 4), clozapine (N = 2), trifluoperazine (N = 2), aripiprazole (N = 2), risperidone (N = 2), loxapine (N = 1), and perphenazine (N = 1).

At recruitment, the control group included 13 subjects with no history (or family history) of Sz spectrum disorder. Control subjects were submitted to the same exclusion criteria as Sz participants. One control subject was excluded because of unreliable electrophysiological data.
and one because sural nerve stimulations did not reliably evoke pain during testing. As a result, 11 control subjects were retained for final analysis. Control and Sz subjects were paired as a function of age and sex. There were eight men and four women in the Sz group and eight men and three women in the control group ($\chi^2 = 0.1; P = 0.752$). Mean age for Sz participants was $31.33 \pm 0.62$ and $31.55 \pm 0.85$ for control subjects ($U = 62; P = 0.833$).

**Measures**

**Sural Nerve Stimulations**

Painful sensations were evoked through transcutaneous electrical stimulations of the sural nerve (across the retro-malleolar path of the left leg). Stimulations consisted of a volley of five electrical pulses (square waves, each 1 mil-lisecond long) administered at a rate of 240 Hz using a constant current stimulator. A stimulation volley lasted 21 milliseconds. Stimulations produced an NFR response that was measured via an electromyographic (EMG) recording of the biceps femoris (i.e., knee-flexor muscle). Reflex threshold was determined using an iterative staircase method [24]. EMG activity was considered reflexive when its amplitude exceeded baseline activity levels by at least 1.5 standard deviations. Withdrawal reflex activity was quantified by calculating the integral of the rectified EMG signal between 90 and 180 milliseconds.

**Pain Rating**

A verbal numerical rating scale was used to evaluate the intensity of pain during testing. The scale ranged from 0 (no pain) to 10 (pain tolerance). It is important to point out that the 0–100 pain intensity scale typically used in experimental pain research [25] was not used here because pilot testing conducted prior to this experiment confirmed that Sz participants found this scale more difficult to use than the 0–10 scale. As a result, we opted for the latter.

**Symptom Evaluation and Medication**

Psychiatric symptoms were measured using three questionnaires. The Positive and Negative Syndrome Scale (PANSS) was used to evaluate positive symptoms (e.g., delusion, hallucinatory behavior), negative symptoms (e.g., blunted affect, emotional withdrawal), and general symptoms of Sz (e.g., anxiety, disturbed volition). The PANSS consists of 30 items administered using a semi-structured clinical interview and has strong psychometric properties [26]. The Calgary Depression Scale for Schizophrenia (CDSS) was used to assess depression symptoms in Sz subjects. The CDSS is a nine-item interview questionnaire derived from the Hamilton Depression Rating Scale [27]. Finally, Sz participants’ cognitive complaints were assessed using the Subjective Scale to Investigate Cognition in Schizophrenia (SSTICS). The SSTICS is composed of 21 Likert-type questions evaluating the subjective dimension of cognitive deficits in Sz [28].

Antipsychotic drug doses were standardized using chlorpromazine equivalents [29,30]. This technique gives an estimation of therapeutic chlorpromazine dose equivalence for each antipsychotic drug and is frequently used to statistically control for the effects of medication.

**Pre-Experimental Procedure**

Prior to testing, Sz participants completed the PANSS, the CDSS, the SSTICS, and a socio-demographic questionnaire, whereas control subjects completed only the socio-demographic questionnaire. All participants were then fitted with EMG electrodes. Pain and withdrawal reflex thresholds were subsequently measured.

**Experimental Protocol**

Testing consisted of a series of sural nerve stimulations that were administered repeatedly for 3 minutes and 40 seconds. Stimulation intensity was set at reflex threshold and remained constant throughout testing. During the first 3 minutes, sural nerve stimulation volleys were provided at a fixed frequency of 0.14 Hz (i.e., once every 7 seconds). During the last 40 seconds, however, stimulation frequency increased to 1 Hz (i.e., one per second). Thus, the first testing period represented the low-frequency condition and the last testing period represented the high-frequency condition. Consistent with previous research focusing on the interaction between stimulation frequency and pain, change in response from the low- to high-frequency condition was used as our metric of pain sensitization [18]. Verbal pain intensity ratings were recorded every 30 seconds during the low-frequency condition and every 10 seconds during the high-frequency condition. Each rating reflected the pain intensity felt on the last shock received.

**Data Analysis**

All data are given as mean ± standard error Comparisons made between groups were conducted using Mann–Whitney tests, a nonparametric approach appropriate for small samples. Within-group analyses were conducted using the Wilcoxon signed rank test. To further reduce the risk of interpreting empirically over-fitted results (arising from a relatively small number of subjects per group) and to better appreciate the significance of our data, a measure of effect size ($\eta^2$) was provided. Relationships between our different outcome variables were looked at using Spearman correlations. Group differences in the strength of the relationship between outcome variables were assessed using a Fisher r to z transform. $P < 0.05$ (two-tailed) was considered statistically significant.

**Results**

**Pain Threshold**

A significant difference in pain threshold was found between Sz participants and control subjects ($U = 28.5, P = 0.019, \eta^2 = 0.245$), such that Sz participants had a much lower pain threshold ($9.73 \pm 1.16$ mA) than control subjects ($14.41 \pm 1.38$ mA).
Lévesque et al.

Reflex Threshold

There was no significant difference in withdrawal reflex threshold between Sz participants and control subjects (U = 35.5, P = 0.059, \( \eta^2 = 0.179 \)). However, there was a near-significant trend in the data demonstrating lower withdrawal reflex thresholds for Sz participants compared with controls (13.48 ± 1.17 mA for Sz subjects and 18.19 ± 1.91 mA for control subjects).

Pain Sensitization: Subjective Intensity Ratings

Within-Group Analysis

Comparison of the average pain intensity score calculated during low- and high-frequency conditions confirmed that average verbal pain ratings increased significantly as a function of increasing stimulation frequency for Sz participants (passing from 3.78 ± 0.70 on average to 5.3 ± 0.82 on average; \( U = 3.06, P = 0.002, \eta^2 = 0.795 \)) and controls (passing from 2.79 ± 0.57 on average to 5.24 ± 0.81 on average; \( U = 2.93, P = 0.003, \eta^2 = 0.776 \)).

Between-Group Analysis

Before comparing pain sensitization scores between groups, it was important to first control for inter-group differences in baseline pain (i.e., the pain felt during the low-frequency condition). This was done by detrending low-frequency pain scores from the change in pain intensity observed when passing from the low- to the high-frequency condition (i.e., the pain sensitization score). Detrending was done for all participants and carried out using linear regression analysis such that low-frequency pain scores were entered as predictors of pain sensitization. The unstandardized residual calculated during low- and high-frequency conditions confirmed that average verbal pain ratings increased significantly as a function of increasing stimulation frequency for Sz participants (\( r = 0.346 \)), but not in Sz participants (\( r = 0.298, P = 0.346 \)). The regression coefficient emerged as marginally stronger in control subjects than in Sz participants (\( Z = 1.15, P = 0.12 \)). Results also showed that pain intensity ratings were significantly correlated with NFR amplitudes during low- (\( P = 0.738, r = 0.01 \)) and high-frequency conditions (\( r = 0.743, P = 0.009 \)) in control subjects, but not in Sz participants (both \( Ps > 0.3 \); both \( r s < 0.2 \)). Here, regression coefficients were significantly larger in control subjects than in Sz participants (both \( Zs > 2.04, both Ps < 0.02 \)).

Correlation Between Pain Rating and NFR Activity

Subjective pain threshold and the NFR threshold were significantly correlated in control subjects (\( r = 0.70, P = 0.016 \)), but not in Sz participants (\( r = 0.298, P = 0.346 \)). The regression coefficient emerged as marginally stronger in control subjects than in Sz participants (\( Z = 1.15, P = 0.12 \)). Results also showed that pain intensity ratings were significantly correlated with NFR amplitudes during low- (\( P = 0.738, r = 0.01 \)) and high-frequency conditions (\( r = 0.743, P = 0.009 \)) in control subjects, but not in Sz participants (both \( Ps > 0.3 \); both \( r s < 0.2 \)). Here, regression coefficients were significantly larger in control subjects than in Sz participants (both \( Zs > 2.04, both Ps < 0.02 \)).

Correlation Between Pain, Clinical Symptoms, and Antipsychotic Drug Use in Sz Subjects

Among Sz participants, symptomatology was evaluated using three different questionnaires: PANSS, CDSS, and SSTICS. Clinical symptom scores are provided (and interpreted) in Table 1. Spearman correlations revealed that pain threshold was negatively correlated with positive symptoms in Sz subjects (\( r = -0.696, P = 0.012 \); Figure 3). Pain sensitization, however, was not related to any of our clinical variables (i.e., positive, negative, and general symptoms of Sz [PANSS], depression [CDSS],...
cognitive symptoms [SSTICS], and antipsychotic drug use [chlorpromazine equivalents]; all rs < |0.457|, all P < 0.073).

Discussion

Results from this study demonstrate that Sz participants have a lower pain detection threshold than control subjects, suggesting that Sz participants remain acutely attuned to acute pain in this experimental setting. This is consistent with some of the earliest studies published on this issue [10,11,13] which found that Sz participants were more sensitive to pain than control subjects. Interestingly, these early studies showed that, depending on clinical subtype, pain response profiles varied widely among Sz participants. Thus, Sz participants suffering from reactive Sz, but not from process Sz, were found to have hyperalgesic responses [11,13]. Reactive Sz is characterized by the presence of acute psychotic episodes, depressive features, states of excitement, and a favorable prognosis [31]. On the other hand, process Sz is characterized by the presence of apathy, dissociation of affect, disorganization, and a poor prognosis [31]. Reactive and process Sz are old diagnostic terms, which today, would correspond more closely to brief reactive psychosis and continuous Sz, respectively. Given the difference in response

Table 1 Clinical scaled scores for symptomatology evaluation among schizophrenic patients

<table>
<thead>
<tr>
<th>Instruments</th>
<th>Mean ± Standard Error</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive PANSS</td>
<td>15.20 ± 0.97</td>
</tr>
<tr>
<td>Negative PANSS</td>
<td>14.50 ± 1.30</td>
</tr>
<tr>
<td>General PANSS</td>
<td>35.00 ± 1.85</td>
</tr>
<tr>
<td>Total PANSS</td>
<td>64.67 ± 3.69</td>
</tr>
<tr>
<td>SSTICS</td>
<td>48.58 ± 6.63</td>
</tr>
<tr>
<td>CDSS</td>
<td>1.58 ± 0.63</td>
</tr>
</tbody>
</table>

PANSS = Positive and Negative Syndrome Scale; SSTICS = Subjective Scale to Investigate Cognition in Schizophrenia; CDSS = Calgary Depression Scale for Schizophrenia. Each item of the PANSS can present a score varying from 1 (absent) to 7 (extreme). The general PANSS score varies between 30 and 210 and provides information concerning overall illness severity; a score of 64 indicates the presence of mild-to-moderate severity. SSTICS can vary from 0 (no cognitive complaints) to 84 (very often report cognitive complaints). The average SSTICS score obtained in our sample represents the presence of moderate cognitive complaints. CDSS can vary from 0 (no symptoms of depression) to 27 (severe symptoms of depression). Our sample can be characterized as showing no, or few, symptoms of depression.
Lévesque et al.

to pain observed between reactive and process Sz, and the set of clinical features that distinguish these subtypes, it is possible to propose that positive symptoms play a key role in explaining why some Sz patients are more sensitive to pain than others. This proposition would be consistent with our data because we found that pain thresholds were negatively related to the presence of positive symptoms in Sz participants. A negative relationship between pain threshold and positive symptoms further suggests that distortions of thought and function predict increased pain sensitivity in Sz. Interestingly, early findings in support of this claim were published by Malmo and Shagass [10]. In their seminal study, the authors showed that early-onset Sz participants demonstrated elevated auditory hallucinations, inappropriate affect, anxiety, compulsions, delusions, and, importantly, lower pain thresholds than control subjects and unselected psychiatric participants. Unfortunately, this original finding has languished in obscurity and researchers have failed to appreciate the increased sensitivity to pain displayed by some Sz patients. It is important to note, however, that a recent study published by Girard et al. [12] also reported heightened pressure- and ischemic-pain sensitivity in Sz participants. Moreover, the increased sensitivity noted by Girard et al. [12] was closely associated with hallucination production. Together with our results, this finding would argue that hyperalgesia in Sz cuts across different types of pain stimuli and is closely linked with the presence of positive symptoms.

Although we currently ignore why positive symptoms and pain sensitivity are closely associated in Sz, our nociceptive-specific withdrawal reflex recordings suggest that spinal processes may play a role. This is because the withdrawal reflex threshold of Sz subjects was lower than the withdrawal reflex threshold of control subjects, as confirmed by a statistical trend in our data ($P < 0.06$). Despite this potentially promising trend, however, we warn against drawing strong conclusions from this near, but nonsignificant result. Here, strong conclusions should be tempered because sample size was relatively small. As a result, near-significant effects may emerge solely because of spurious associations. Moreover, correlations conducted as supplementary measures of association failed to return a significant relationship between spinal nociceptive activity and perceived pain in our Sz participants. Thus, prudence should be exercised when considering the possible, but currently uncertain, spinal origins of hyperalgesia in Sz. Replication of this original finding using a larger sample of Sz participants is warranted to ensure that neither a Type I nor a Type II error is being committed.

As mentioned earlier, a unifying theory linking positive symptoms and heightened pain sensitivity in Sz is still lacking. Despite this lack of a unifying theory, a biological framework underlying the development of positive symptoms in general, and psychotic states in particular, has recently been developed. This biological framework is known as the aberrant salience hypothesis and proposes that psychotic states arise out of the aberrant assignment of salience to external stimuli or to the internal representation made of these stimuli [32]. Essential to this hypothesis is the idea that chaotic firing of dopaminergic afferents to the striatum contributes to altered states of consciousness in Sz [33]. From a pain-processing perspective, the aberrant salience hypothesis would predict that hyperalgesic responses occur because Sz patients are excessively attuned to stimulus-reinforcement associations, making them indiscriminately vigilant to external events and afferent stimulations. This hypothesis has been confirmed in Sz using: 1) operant discrimination tasks [34]; 2) visuospatial working memory paradigms with inserted distracters [35]; and 3) aversive Pavlovian learning [36]; but has never been formally tested using noxious somatosensory stimuli. Although our findings agree nicely with the predictions made by the aberrant salience hypothesis (e.g., lower thresholds for Sz participants than for control subjects), a future study designed specifically to address this issue is necessary.

Despite clear evidence of hyperalgesia among Sz participants, we also found that Sz subjects show less subjective pain sensitization when painful stimuli repeat frequently. This is consistent with previous results from our lab which showed that Sz participants have lower subjective pain enhancement than control subjects when a painful, tonic heat source is applied to the forearm [16]. Importantly, results from the current study demonstrate that the decrease in pain sensitization observed among Sz subjects does not depend on disease-induced changes occurring at the spinal level. This is because shock-evoked withdrawal reflex responses were found to be comparable between Sz and control subjects. In other words, the percentage increase in reflex amplitude provoked by the increase in stimulation frequency was comparable between groups. Interestingly, our analyses failed to find a significant association between subjective pain sensitization and various measures of clinical symptom severity, including extent of antipsychotic drug use. Again, this is consistent with our previous findings (see Potvin et al. [16]) and suggests that decreased subjective pain sensitization may be an intrinsic feature of the disease. Its role as a pathophysiological marker, however, remains to be demonstrated.

To our knowledge, elevated sensitivity to acute pain in combination with decreased sensitivity to prolonged pain constitutes a specific pain response profile—never documented in any other psychiatric condition or pain-related disorder. Surprisingly, this unique response profile has only been observed once before, namely, in an experimental study published by Kuehl et al. [37]. In their study, the authors purposely blocked cortisol synthesis before administering painful stimuli to control subjects. The authors found that when cortisol synthesis was blocked, pain sensitivity increased (i.e., pain thresholds decreased), whereas pain sensitization was attenuated. This finding closely mirrors the results we obtained when testing Sz participants and agrees with previous findings demonstrating that Sz participants secrete less cortisol than control subjects when exposed to psychological and/or
When interpreting the results of our study, it is difficult to understand why physicians anecdotally remark less pain sensitivity in Sz patients [1]. Given the threshold results obtained in the current study, the opposite would be expected. A number of reasons can explain this apparent contradiction. First, the supposed insensitivity to pain expressed by Sz patients in clinical settings may have very little to do with patient response to acute noxious insult and perhaps much more to do with their response to prolonged pain, which we found to be significantly diminished. Second, subjective pain may not be spontaneously voiced by patients when they are exposed to painful stimuli, despite their actual experience of pain [41]. This would explain why physicians generally describe their patients as insensitive to pain. This would also be consistent with the lack of emotional and facial expression that we regularly observed when testing patients (but did not formally test), and suggests that the experience of pain among Sz subjects must be directly queried if we are to fully appreciate their private experience. It also argues for the expenditure of greater research efforts into a possible (dis)concordance between physiological, facial, and subjective pain responses in Sz.

One potential limitation of the current study is worth noting and concerns the role of antipsychotic medications. In our study, antipsychotic medications were controlled for using chlorpromazine equivalents. Despite being a popular and ethically acceptable method of controlling for antipsychotic medications, chlorpromazine equivalents cannot entirely rule out medication-induced effects from our findings. Drug washouts are perhaps better suited to address this issue but carry important ethical concerns. Thus, chlorpromazine equivalents remain, to date, the accepted standard. Interestingly, a meta-analysis conducted by our team confirmed that antipsychotic medications have an effect on pain sensitivity, but cannot explain all differences between control and Sz subjects [42]. Another possible limitation of the current study concerns the causal relationship between disease onset and pain response. In other words, our data cannot tell us whether or not the change in pain sensitivity observed among Sz patients is related to the presence of their condition, the severity of their symptoms, or simply to the existence of genetic vulnerabilities. Longitudinal designs and studies which include next of kin as control subjects could help address this important issue. Finally, it is important to point out that our results suggest supraspinal origins to the change in pain sensitivity observed in Sz patients. In our study, supraspinal origins are supported by a comparable degree of spinal hyperexcitability in Sz and control subjects and by a dissociation between spinal responses and verbal responses in Sz participant only. Clearly then, ascending contributions and subjective experience in Sz are not as closely intertwined as they are in control subjects. Some form of cognitive reappraisal and/or disengagement must be responsible for this difference. Given this possibility, future studies should include neuroimaging data in order to better understand the neural network associated with change in pain in Sz.

In conclusion, our study demonstrates that Sz participants have a unique pain response profile, characterized by increased sensitivity to acute pain and decreased sensitivity to prolonged pain. These changes appear unrelated to spinal noxious processing, and thus, suggest a supraspinal etiology. The contribution of the neuroendocrine system should also be investigated further. Finally, clinicians should be aware that apparent indifference to pain among Sz patients may not mean actual insensitivity to pain. As a result, a careful clinical workup and a thorough examination of the patient remains, to date, the most valuable way for clinicians to know if pain is present and if additional tests are necessary.

Acknowledgments

This work was supported by grants from the Fonds de la Recherche en Santé du Québec (SP and PG are holder of a junior 1 young investigator award) and by an unrestricted grant from Servier Pharmaceutical Laboratories. The authors would like to thank Vesela Zaharieva, Marc Lavoie, Antoine Escher, Vongmaly Rattanavong, and Nathalie Brissette for their precious help. No conflict of interest.

References


