Decreased Pain Sensitivity Among People with Schizophrenia: A Meta-analysis of Experimental Pain Induction Studies

Abstract

Schizophrenia patients report reduced pain sensitivity in clinical studies, but experimental studies are required to establish pain sensitivity as a potential endophenotype. We conducted a systematic review of electronic databases from database inception until 15/04/2015, including experimental studies investigating pain among schizophrenia-spectrum disorder patients versus healthy controls. A random effect meta-analysis yielding Hedges' g ±95% confidence intervals (CIs) as the effect size measure (ES) was conducted. Primary outcome was a pooled composite of pain threshold, pain tolerance, and sensory threshold; secondary outcomes included these parameters individually, plus physiological pain response, and pain intensity/unpleasantness. Across 17 studies, schizophrenia-spectrum disorder patients (n=387, age=30.7±6.9 years, female=31.9%, illness duration=7.0±5.7 years) were compared with controls (n=483, age=29.5±7.4 years, female=31.0%). Patients had elevated pain threshold/pain tolerance/sensory threshold versus controls (ES=0.493, 95% CI=0.145-0.839, p=0.005; studies=17). Results were similar in antipsychotic-free individuals (ES=0.599, 95% CI=0.291-0.907, p<0.0001; studies=8), with trend-level significance in antipsychotic-treated individuals (ES=0.428, 95%CI=-0.059-0.915, p=0.085; studies=11). Likewise, schizophrenia patients had increased pain tolerance (ES=0.566, 95% CI=0.235-0.897, p=0.0001; studies=6), sensory threshold (ES=1.16, 95% CI=0.505-1.727, p<0.0001; studies=5) and pain threshold (ES=0.696, 95% CI 0.407-0.986, p<0.001; studies=9), and reduced physiological response to painful stimuli (ES=0.456, 95%CI=0.131-0.783, p=0.006) and pain intensity/unpleasantness ratings (ES=0.547, 95% CI=0.146-0.949, p=0.008). Findings were similarly significant in antipsychotic-free schizophrenia patients (analyzable parameters=4) and antipsychotic-treated individuals (analyzable parameters=2). Finally, greater psychiatric symptoms and younger patient age moderated increased pain tolerance/threshold. Decreased pain sensitivity seems to be an endophenotype of schizophrenia-

spectrum disorders. How this alteration links to other dimensions of schizophrenia and physical comorbidity-related help-seeking behaviour/morbidity/mortality requires further study.

Key words: schizophrenia, pain, experimental pain, physical health, pain assessment, pain management

Decreased Pain Sensitivity Among People with Schizophrenia: A Meta-analysis of Experimental Pain Induction Studies

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Abstract

Schizophrenia patients report reduced pain sensitivity in clinical studies, but experimental studies are required to establish pain sensitivity as a potential endophenotype. We conducted a systematic review of electronic databases from database inception until 15/04/2015, including experimental studies investigating pain among schizophrenia-spectrum disorder patients versus healthy controls. A random effect meta-analysis yielding Hedges' g ±95% confidence intervals (CIs) as the effect size measure (ES) was conducted. Primary outcome was a pooled composite of pain threshold, pain tolerance, and sensory threshold; secondary outcomes included these parameters individually, plus physiological pain response, and pain intensity/unpleasantness. Across 17 studies, schizophrenia-spectrum disorder patients (n=387, age=30.7±6.9 years, female=31.9%, illness duration=7.0±5.7 years) were compared with controls (n=483, age=29.5±7.4 years, female=31.0%). Patients had elevated pain threshold/pain tolerance/sensory threshold versus controls (ES=0.493, 95% CI=0.145-0.839, p=0.005; studies=17). Results were similar in antipsychotic-free individuals (ES=0.599, 95% CI=0.291-0.907, p<0.0001; studies=8), with trend-level significance in antipsychotic-treated individuals (ES=0.428, 95%CI=-0.059-0.915, p=0.085; studies=11). Likewise, schizophrenia patients had increased pain tolerance (ES=0.566, 95% CI=0.235-0.897, p=0.0001; studies=6), sensory threshold (ES=1.16, 95% CI=0.505-1.727, p<0.0001; studies=5) and pain threshold (ES=0.696, 95% CI 0.407-0.986, p<0.001; studies=9), and reduced physiological response to painful stimuli (ES=0.456, 95%CI=0.131-0.783, p=0.006) and pain intensity/unpleasantness ratings (ES=0.547, 95% CI=0.146-0.949, p=0.008). Findings were similarly significant in antipsychotic-free schizophrenia patients (analyzable parameters=4) and antipsychotic-treated individuals (analyzable parameters=2). Finally, greater psychiatric symptoms and younger patient age moderated increased pain tolerance/threshold. Decreased pain sensitivity seems to be an endophenotype of schizophrenia-spectrum disorders. How this alteration links to other dimensions of schizophrenia and physical comorbidity-related help-seeking behaviour/morbidity/mortality requires further study.

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Introduction

Research has consistently demonstrated that people with schizophrenia experience an increased number of painful physical health comorbidities, including fractures [48], diabetes [50] and cardiovascular diseases, such as myocardial infarction [19; 37]. For over 60 years, numerous case reports and case series indicated that people with schizophrenia have reduced pain sensitivity [16] leaving clinicians perplexed when this population appears not to report pain in the face of ordinarily painful comorbidities. For instance, Lieberman [38] established that over 85% of patients with psychosis experiencing myocardial infarction did not report experiencing pain. This finding has been replicated numerous times since. For example, Hussar [27; 28] found that 60% of people with schizophrenia that died from a coronary heart disease reported no pain. This phenomenon persists to the present day and despite the high rates of cardiometabolic abnormalities in people with schizophrenia [52], it is noteworthy that there is a negligible increase of patients with schizophrenia presenting to hospitals with heart disease compared to the general population [35], which may contribute to the established increased premature mortality in people with schizophrenia [12; 41].

Consistent with the possibility of reduced pain sensitivity in schizophrenia, Stubbs et al [49] found that the prevalence of pain in those with schizophrenia was comparable to that of controls in a meta-analysis of over 5 million people (relative risk (RR)=0.99, 95% CI=0.83–1.19), despite the fact that schizophrenia is linked to a greater number of conditions ordinarily associated with pain [11; 12; 48]. Whilst the review of Stubbs et al [49] was helpful, the reliance on pain data from self-report and lack of pain severity measures in most studies might have introduced bias and noise. For example, cognitive deficits may impede the ability of people with schizophrenia to recognise and communicate the presence of pain [7]. In addition, the investigation of the prevalence of pain in schizophrenia patients is further complicated by the fact that antipsychotic medications have analgesic properties [45]. Nevertheless, understanding if people with schizophrenia have reduced pain sensitivity has important implications and poses a central clinical challenge, since a patient's inability to recognise pain may lead to increased risk for morbidity and ultimately mortality [29].

Experimental pain testing methods circumvent some of the concerns associated with data obtained from a purely clinical setting. Firstly, they allow for precise controllability of the noxious stimulus ensuring equivalent stimulation across groups. Secondly, they facilitate the recording of 'objective' non-verbal measures of pain, typically autonomic stress indices such as heart rate and pupillary dilation and thus offer a superior method for investigating algesia and hypoalgesia in people with schizophrenia. When considering experimental studies, it is important to establish the methods of pain induction (e.g., thermal, mechanical, chemical) and measurement including (1) pain threshold, (2) pain tolerance, (3) sensory threshold, (4) physiological responses to painful stimuli, and (5) ratings of pain intensity/unpleasantness [23]. It remains unclear to what extent people with schizophrenia have reduced pain sensitivity in each of these measures of pain.

Only one previous review [43], with a last search date of almost a decade ago, investigated differences in experimental pain responses in people with schizophrenia versus controls. The authors aggregated all different types of pain measures together in a composite analysis and found that people with schizophrenia appeared to exhibit hypoalgesia. Whilst this review advanced the field, the authors included only 11 studies and 497 participants in a composite analysis in which they pooled any pain measures per study. Moreover, the authors were only able to pool data from 3 and 6 studies to investigate sensory threshold and pain threshold, respectively. Thus, only 2 of the 5 dimensions of pain sensitivity in people with schizophrenia were explored in that prior review. Other important facets of pain sensitivity, such as pain tolerance, physiological responses to painful stimuli, and ratings of pain intensity/unpleasantness were not explored, but may have important implications. In addition, pooling data on physiological responses to pain may offer a unique insight that circumvents concerns regarding cognitive and communication deficits when recognising and reporting pain in schizophrenia [7].

Given the importance of pain sensitivity in schizophrenia and lack of a comprehensive analysis of the available data of experimental pain studies, we aimed to investigate if people with schizophrenia-

spectrum disorders have reduced pain sensitivity under experimental pain conditions, assessing the different dimensions of pain. Based on the available data, we hypothesized that people with schizophrenia would exhibit decreased pain sensitivity in the form of reduced physiological response and ratings of pain and increased pain tolerance and threshold. We further hypothesized that these findings would be accentuated in antipsychotic-free patients.

Method

This systematic review was conducted in accordance with the MOOSE guidelines [47] and in line with the PRISMA statement [40], following a predetermined, but unpublished protocol.

Inclusion criteria

Included in this meta-analysis were studies that: (1) Included adult participants with schizophrenia-spectrum disorders (schizophrenia, schizoaffective disorder, schizophreniform disorder, as well as samples with >50% non-affective psychotic), diagnosed according to established criteria (e.g., DSM-IV, [2] or ICD-10, [42]); (2) Investigated any type of experimentally induced pain reporting data on (a) pain threshold, (b) pain tolerance, (c) sensory threshold, (d) physiological responses to noxious stimuli, or (e) ratings of pain intensity/ unpleasantness; (3) reports comparative data in a healthy control group; and (4) were published in an international peer-reviewed journal or conference abstract.

Information sources and searches

Three independent reviewers (BS, TT, SA) searched Academic Search Premier, MEDLINE, Psychology and Behavioral Sciences Collection, PsycINFO, SPORTDiscus, CINAHL Plus and Pubmed without language restrictions from database inception until April 15th, 2015, using the key words 'schizophrenia' or 'schiz*' or 'psychosis' or 'psychoses' or 'psychotic' and 'pain*' or 'nociception' or 'cold' or 'heat' or 'electrical' or 'thermal' or 'reflex' 'hypoalgesia'. In addition, reference lists of all eligible articles and reviews of pain in schizophrenia were screened to identify additional studies. We contacted corresponding/first authors up to 3 times over a month to clarify study eligibility and/or acquire additional data.

Study selection

After removal of duplicates, two independent reviewers screened the titles and abstracts of all potentially eligible articles. Two authors applied the eligibility criteria, and a list of full text articles was developed through consensus. Two authors (BS, TT) considered the full texts of included articles and a final list of included articles was reached through consensus.

Outcomes:

Primary outcome was a composite of selected measures of pain sensitivity that was derived by pooling the means and SDs of the following 3 individual parameters: (1) pain threshold, (2) pain tolerance, (3) sensory threshold. These 3 parameters were selected, as threshold and tolerance are typically correlated (e.g. [51]). Secondary outcomes were these three parameters by themselves plus two additional individual outcomes, namely (4) physiological responses to painful stimuli, and (5) ratings of pain intensity/unpleasantness.

Data Extraction

Two authors (TT, BS) extracted data using a data extraction form, including: study design, geographical location, details of schizophrenia participants (mean age, % males, diagnosis and utilized criteria, first episode, duration of illness body mass index, psychopathology scores, psychopharmacologic treatment, including % on antipsychotics (including type), antidepressants and mood stabilisers), and type and method of experimental pain measure assessment. We also abstracted details regarding the control group, including mean age, sex and body mass index. Finally, we extracted data on the mean and standard deviation (SD) for each experimental pain measurement.

When studies reported data from the same sample at different time points, we used the most recent data and/or the largest data set. From duplicate studies reporting experimental pain data in participants before and after antipsychotic medication treatment, we included the antipsychotic-free data for the overall pooled analyses, but also used the data in antipsychotic-treated patients in

subgroup analyses. Studies that employed sensory decision theory to determine pain threshold reported two measures: response criterion and d' (sensory discrimination). Response criterion was abstracted as the data of interest, as this measure is the most closely related to pain threshold used in the other included studies, which assessed pain threshold through verbal declaration [23].

Meta-analysis

Due to the anticipated heterogeneity, we adopted the random effects meta-analysis and calculated Hedges's g 95% confidence intervals (CIs) as the effect size measure (ES) comparing pain sensitivity between participants with schizophrenia-spectrum disorders (henceforward called "schizophrenia") and controls using Comprehensive Meta-Analysis (CMA, Version 3). In line with a previous meta-analysis [43], we examined the funnel plot of the composite outcome searching for extreme outliers and removed from the database and all analyses one extreme publication bias outlier [39]. Across the resultant sample of 17 studies, we first conducted a composite analysis pooling aggregated pain measure data on pain threshold, pain tolerance and sensory threshold together from all studies to establish an overall difference in pain sensitivity. We further pooled data separately for: (1) pain threshold, (2) pain tolerance, (3) sensory threshold, (4) physiological responses to painful stimuli, and (5) ratings of pain intensity/unpleasantness. We conducted subgroup analyses for the composite and each individual pain measure in patients who were antipsychotic-free or antipsychotic-treated at the time of experimental pain induction and assessment. Additional exploratory analyses compared the composite score in the same population off and on antipsychotics in those studies were patients were reassessed after antipsychotics were started. Heterogeneity was assessed with the I^2 statistic for each analysis [26]. Furthermore, we conducted meta-regression analysis with CMA when data were available in at least 3 studies, assessing the moderating effects of mean age, % females in both cohorts separately, and duration of illness and summary scores of psychiatric symptoms (measured with a standardised scale, e.g., PANSS [32]) in the schizophrenia cohort.

Publication bias was assessed with a visual inspection of funnel plots and with the Begg-Mazumdar Kendall's tau [4]and Egger bias test [17].

Results

Study selection, Study and participant characteristics

The initial search yielded 2532 hits. After removal of duplicates, 1989 abstracts and titles were screened. A further 20 abstracts were screened following a review of references from previous systematic reviews [7; 43]. At the full text review stage, 28 articles were considered and 11 were subsequently excluded (see Figure 1 for search results). Overall, 18 unique samples from 17 publications were included in the meta-analysis [1; 3; 5; 6; 8; 10; 13-15; 21; 22; 24; 30; 31; 34; 44; 46]. One publication [15] contained two unique studies with different samples and is henceforth considered as two unique studies. Full details of the included studies are summarised in Table 1.

Figure 1

Table 1

Across the 18 unique samples there were 387 participants with schizophrenia (mean age=30.7±6.9 years, females=31.9% (range=0%-70%), illness duration=7.0±5.7 (range=1.0-17.1). Altogether, 483 control participants were included (mean age=29.5±7.4 years, females=31.0% (range=0%-70%). Eight samples across seven studies were conducted in North America [8; 10; 15; 22; 31; 44], six studies in Europe [1; 3; 6; 21; 24; 30] and four were conducted in in other parts of the world [5; 13; 34; 46] (Table 1).

Twelve studies provided pain data for participants taking antipsychotic medication including 282 participants with schizophrenia (mean age 33.4 years±8.2 years, 38.9% female (range 17-70%) and 310 controls (31.7 years±7.9, 40.5% female (range 23-80%). Eight studies provided data for 140 individuals with schizophrenia who were antipsychotic free (31.8±4.4 years, 32% female (range 0-70%) and 215 controls (30.7±6.0 years, 29.5% female (range 0-70%). Ten studies induced pain with thermal methods [1; 3; 6; 13-15; 22; 30; 31; 44] and five used electrical inducement [5; 8; 10; 24; 34] whilst two induced pain mechanically [21; 46]. Details of each study, including medication data (where available), pain modalities and assessed parameters are summarised in table 1.

Table 2

Meta-analysis investigating pain sensitivity in people with psychosis

In the composite analysis of 17 unique samples, people with schizophrenia had reduced pain sensitivity versus controls (ES=0.493, 95% CI=0.145-0.839, p=0.005; I^2=81%, n=847; Table 2, figure 2). There was no evidence of publication bias (Begg=0.08, p=0.60, Egger test=4.56, p=0.18).

Figure 2 here

In a subgroup analysis, results were confirmed in antipsychotic-free patients (ES=0.599, 95% CI=0.291-0.907, p<0.0001, I^2=41%, studies=8, n=371 table 2, figure 3a), without evidence of publication bias (Egger test =3.6, p=0.26, Begg=0.25, p=0.36).

In contrast, antipsychotic-treated patients did not differ from controls regarding pain sensitivity (ES=0.428, 95%=-0.059-0.915, p=0.08, I^2=86%, studies=11, n=542, figure 3b; Begg =-0.018, p=1.0, Egger test =4.4, p=0.38, table 2, figure 3b).

In exploratory analyses of composite pain measures before and 5 weeks after antipsychotic initiation in the same patients from two studies (n=35), there was a significant reduction in pain sensitivity after antipsychotics were started (ES=-0.279, 95% CI -0.483 to -0.075, p=0.007, I^2=0%).

Figure 3 a and b here

Meta-regression of predictors of pain sensitivity

In meta-regression analyses of pain sensitivity across all studies, mean age, percentage of females, illness duration and psychopathology scores did not moderate significantly pain sensitivity (p>0.05, data not shown).

Meta-analysis investigating differences in different pain measures/modalities

Pain threshold

Across 9 studies (n=439), people with schizophrenia had significantly higher pain threshold than controls (ES=0.696, 95% CI 0.407-0.986, p<0.001, I^2=51%, Begg=0.35, p=0.26, Egger=3.7, p=0.25, table 2). In sub-group analyses, pain threshold was higher than in controls in both antipsychotic-free (ES=0.753, 95% CI 0.305-1.202, p<0.001, I^2=61%, studies=5, n=252) and antipsychotic-treated participants (ES=0.706, 95% CI 0.354-1.05, P<0.001, I^2=49%, studies=5, n=195, table 2).

Meta-regression of pain threshold

Only greater total psychiatric symptoms severity was a significant moderator of pain threshold (β=0.0156, 95%CI=0.0025-0.0286, z=2.34, p=0.019, R^2=1.0, studies=4, n=155), explaining the entire between-study variance.

Pain tolerance

Across 7 studies (n=366) pain tolerance did not appear reduced in people with schizophrenia (ES=0.393, 95%CI=-0.048-0.836, p=0.08, I^2=74%, table 2). However, the funnel plot identified one striking outlier [22] for pain tolerance . After removal of this study, schizophrenia patients had significantly greater pain tolerance than controls (ES=0.566, 95% CI=0.235-0.897, p=0.0001, I^2=49%, studies=6, Egger=2.26, p=-0.58, Begg=0.13, p=0.70, studies=6, n=330). Subgroup analyses with the outlier removed established similar results in antipsychotic-free (ES=0.342, 95%CI=0.03-0.645, p=0.02, I^2=41%, studies=4, n=190) and antipsychotic-treated participants (ES=0.745, 95%CI=0.461-1.02, p<0.0001, I^2=0%, studies=4, n=211) (table 2).

Meta-regression of pain tolerance

Only a higher mean age of schizophrenia participants significantly moderated pain tolerance (β=-0.058, 95% CI -0.1to-0.0161, z=-2.71, p=0.006, R^2=1.0, studies=6, n=330).

Sensory threshold

Across 5 studies (n=294), people with schizophrenia had a higher sensory threshold than controls (ES=1.16, 95%CI=0.505-1.727, p<0.0001, I^2=77%, Begg=0.33, p=0.46, Egger= -26.3, p=0.43, table 2). Similar results were found in antipsychotic-free participants (ES=0.807 (95% CI 0.168 to 1.446, p=0.01, I^2=71%, studies=3, n=165), whereas not data were available in antipsychotic-treated individuals (table 2).

Meta regression of sensory threshold

No significant moderators were identified.

Physiological responses to pain

Across 4 studies (n=190), the physiological response to pain was significantly reduced in people with schizophrenia compared to controls (ES=0.465, 95% CI=0.131-0.783, p=0.006, I^2=1%, Begg=0, p=1, Egger=5.1, p=0.73, table 2). Similar results were found in antipsychotic-free individuals (ES=0.505, 95%CI=0.072-0.941, p=0.02, I^2=28%, studies=3, n=145), whereas no data were available in antipsychotic-treated individuals (table 2).

Pain rating of intensity/ unpleasantness

Across 3 studies (n=95), all in antipsychotic-free patients, ratings of pain unpleasantness were lower compared to controls (ES=0.547, 95% CI=0.146-0.949, p=0.008, I^2=0%, Begg=0.33, p=0.60, Egger=0.69, p=0.95, table 2).

Discussion

Results of the largest and most comprehensive meta-analysis of experimental pain studies in schizophrenia-spectrum disorder patients indicate that 1) across all studies, using a composite outcome, patients had elevated pain threshold/pain tolerance/sensory threshold versus controls; 2) results were similar in antipsychotic-free individuals, but showed only trend level significance in antipsychotic-treated individuals; 3) in 2 longitudinal studies, antipsychotic initiation significantly decreased pain sensitivity; 4) pooling results across individual outcomes, patients had increased pain tolerance, sensory threshold and pain threshold, yet reduced physiological response to painful stimuli and ratings of pain intensity/unpleasantness; 5) after removal of one marked outlier, findings regarding individual outcomes were similarly significant in antipsychotic-free and antipsychotic-treated individuals; and 6) in meta-regression analyses, greater psychiatric symptoms and younger patient age moderated increased pain tolerance/threshold.

Our results are consistent with a more preliminary prior meta-analysis [43]. In this paper, the authors had reported hypoalgesia to experimentally induced pain that was independent of antipsychotic treatment using a composite analysis in which any pain measure, albeit very divergent parameters were pooled together. However, that prior quantitative review included only 11 studies and 497 participants compared to our meta-analysis in which we were able to analyse data from 18 unique samples including 870 participants. Furthermore, the prior meta-analysis was only able to pool data individually for sensory threshold and pain threshold, i.e., for only 2 of the 5 specific pain sensitivity dimensions that we were able to analyse separately, which enabled us to confirm and extend the results of decreased pain sensitivity across different pain measures and both in samples on and off antipsychotics.

The exact reasons for the observed deficits in pain sensitivity in people with schizophrenia are complex, likely multifactorial [7; 29] and may, given the heterogeneous nature of schizophrenia, vary

from patient to patient and over time. Importantly, however, the finding of a blunted physiological response to noxious stimuli confirms for the first time that individuals with schizophrenia genuinely appear to exhibit hypoalgesia rather than simply failing to report pain. Thus, hypoalgesia appears to be an endophenotype of schizophrenia, which could be explained by several neurobiological processes. First, impaired prefrontal and medial temporal functioning in schizophrenia [33] may result in a reduced pain experience. Specifically, prefrontal cortex hypofunctioning may result in alterations in the motivational affective processing of pain [18] which may translate into difficulties in recognising and expressing pain [7; 53]. Second, impairments within the mediodorsal thalamus and hippocamapus (both central parts of the medial pain system) may play a role in modifying affective and cognitive evaluative processes of pain among people with schizophrenia [20], translating into decreased pain experience. Third, alterations in the cortical dopamine system and higher vulnerability of COMT Met allele may account for reduced pain sensitivity in people with schizophrenia [29]. Fourth, there may also be decreased primary sensory-discriminative pain processing functioning. For example, one study included in our meta-analysis [13] utilised functional magnetic resonance imaging to explore blood oxygen level dependent changes (BOLD) in response to experimentally induced pain in 12 antipsychotic-free people with schizophrenia. The authors found a greater BOLD response in patients in the primary sensory-discriminative pain processing region (S1) compared to controls, and noticed reduced activity in the posterior cingulate cortex, insula and brain stem, suggesting abnormal central processing during painful stimuli. Taken together, these findings suggest decreased pain sensitivity as a potential endophenotype of schizophrenia, which may be relevant to enhance diagnostic precision in general, or predictive validity during the ultra-high risk syndrome for psychosis [9]. Furthermore, studies should investigate if symptomatic response to antipsychotic treatment is related to a normalization of pain sensitivity and/or if baseline values could be predictive of future symptomatic response.

Moreover, due to increased sensory and pain thresholds as well as greater pain tolerance, individuals with schizophrenia may not register potentially harmful stimuli that are related to often

co-occurring physical comorbidities until they becomes more advanced, which could possibly contribute to the low help-seeking among people with schizophrenia [11; 12], since pain is the primary reason that people seek medical help,[25] . Given that people with schizophrenia already experience multiple barriers in accessing medical care [11; 12] these results are concerning. Antipsychotics are known to be analgesic [45], which was reflected by our exploratory finding of two longitudinal studies [13; 14; 30], in which antipsychotic initiation further reduced pain sensitivity. Nevertheless, hypoalesia was clearly apparent in antipsychotic free individuals, indicating that reduced pain sensitivity appears to be a trait marker that is independent of antipsychotic effects.

Finally, for the first time, we investigated moderators that may explain the reduced pain sensitivity in people with schizophrenia. In meta-regression analyses, greater psychiatric symptoms and younger patient age moderated increased pain tolerance/threshold. Curiously, the inverse age effect is in contrast to increases in pain threshold in older adults in the general population [36].

Whilst this is the most comprehensive meta-analysis of experimental pain research in participants with schizophrenia to date, a number of limitations need to be considered. First, although we increased the number of studies and participants compared to the previous meta-analysis by 39% and 43%, this meta-analysis still only contains a modest number of studies and participants, especially when considering individual pain parameters. Second, there were insufficient data to investigate pain sensitivity among people with first episode psychosis. Third, there were insufficient details within the included studies to determine if the antipsychotic-free participants were actually antipsychotic-naïve or (more likely) had stopped prior treatment for some (unknown) duration. Moreover, other psychotropic medications may also have influences pain sensitivity, but data were too sparse to examine this further. Fourth, too few studies examined pain sensitivity in patients before and after antipsychotic treatment, and none examined the relationship between changes in pain sensitivity and psychopathology over time. Finally, some results were heterogeneous. However, we were able to explain this heterogeneity in a number of our meta-regression analyses.

Future experimental research is required to better understand the interaction between different dimensions of schizophrenia and decreased pain sensitivity, such as various aspects of psychopathology, including negative symptoms and cognition, and medication effects (both before and after treatment and in those truly antipsychotic-naïve). Meta-regression analyses suggested that greater global psychiatric symptom severity contribute to reduced pain sensitivity, but it was not possible to investigate the influence of negative symptoms or cognitive deficits within our analyses due to paucity of data. Future work is required to understand these potential interactions. Research investigating physiological responses to painful stimuli should be increased, given that decreased pain sensitivity may be an endophenotype of schizophrenia and related disorders and that decreased identification and reporting of pain may be directly related to the low help-seeking and insufficient treatment of medical comorbidities in patients with schizophrenia [11; 12]. Finally, research is needed that investigates methods to assist clinicians to identify people with schizophrenia with painful comorbidities and ultimately seeks to demonstrate how this increased detection of pain may improve patient care, morbidity, quality of life and mortality.

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Conflict of Interest

BS, TT and SA have no conflict of interest

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References

[1] Albus M, Ackenheil M, Engel RR, Müller F. Situational reactivity of autonomic functions in schizophrenic patients. Psychiatry Research 1982;6(3):361-370.

[2] American Psychiatric Association AP. Diagnostic and Statistical Manual of Mental Disorders – DSM-IV-TR. 4th edition: American Psychiatric Association, 2000.

[3] Atik L, Konuk N, Akay O, Ozturk D, Erdogan A. Pain perception in patients with bipolar disorder and schizophrenia. Acta Neuropsychiatrica 2007;19(5):284-290.

[4] Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics 1994;50(4):1088-1101.

[5] Blumensohn R, Ringler D, Eli I. Pain perception in patients with schizophrenia. Journal of Nervous and Mental Disease 2002;190(7):481-482.

[6] Boettger MK, Grossmann D, Bär KJ. Increased cold and heat pain thresholds influence the thermal grill illusion in schizophrenia. European Journal of Pain 2013;17(2):200-209.

[7] Bonnot O, Anderson GM, Cohen D, Willer JC, Tordjman S. Are patients with schizophrenia insensitive to pain? A reconsideration of the question. Clinical Journal of Pain 2009;25(3):244-252.

[8] Collins LG, Stone LA. Pain sensitivity, age and activity level in chronic schizophrenics and in normals. The British Journal of Psychiatry 1966;112(482):33-35.

[9] Correll CUHMAMCBA. Research in people with psychosis risk syndrome: a review of the current evidence and future directions. Journal of Child Psychology & Psychiatry 2010;51(4):390-431.

[10] Davis GC, Buchsbaum MS, Bunney WE, Jr. Analgesia to painful stimuli in affective illness. The American Journal Of Psychiatry 1979;136(9):1148-1151.

[11] De Hert M, Cohen D, Bobes J, Cetkovich-Bakmas M, Leucht S, Ndetei DM, Newcomer JW, Uwakwe R, Asai I, Möller H-J, Gautam S, Detraux J, Correll CU. Physical illness in patients with severe mental disorders. II. Barriers to care, monitoring and treatment guidelines, plus recommendations at the system and individual level. World Psychiatry: Official Journal Of The World Psychiatric Association (WPA) 2011;10(2):138-151.

[12] De Hert M, Correll CU, Bobes J, Cetkovich-Bakmas M, Cohen D, Asai I, Detraux J, Gautam S, Möller H-J, Ndetei DM, Newcomer JW, Uwakwe R, Leucht S. Physical illness in patients with severe mental disorders. I. Prevalence, impact of medications and disparities in health care. World Psychiatry: Official Journal Of The World Psychiatric Association (WPA) 2011;10(1):52-77.

[13] de la Fuente-Sandoval C, Favila R, Gómez-Martin D, Pellicer F, Graff-Guerrero A. Functional magnetic resonance imaging response to experimental pain in drug-free patients with schizophrenia. Psychiatry Research: Neuroimaging 2010;183(2):99-104.

[14] de la Fuente-Sandoval C, Favila R, Gómez-Martín D, León-Ortiz P, Graff-Guerrero A. Neural response to experimental heat pain in stable patients with schizophrenia. Journal of Psychiatric Research 2012;46(1):128-134.

[15] Dworkin RH, Clark WC, Lipsitz JD, Amador XF, Kaufmann CA, Opler LA, White SR, Gorman JM. Affective deficits and pain insensitivity in schizophrenia. Motivation and Emotion 1993;17(3):245-276.

[16] E B. Textbook of Psychiatry. New York: E and S Livingstone, 1951.

[17] Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ (Clinical Research Ed) 1997;315(7109):629-634.

[18] Engels G, Francke AL, van Meijel B, Douma JG, de Kam H, Wesselink W, Houtjes W, Scherder EJA. Clinical Pain in Schizophrenia: A Systematic Review. The Journal Of Pain: Official Journal Of The American Pain Society 2013.

[19] Fan Z, Wu Y, Shen J, Ji T, Zhan R. Schizophrenia and the risk of cardiovascular diseases: A meta-analysis of thirteen cohort studies. Journal of Psychiatric Research 2013;47(11):1549-1556.

[20] G E, E S. Clinical Pain in Schizophrenia: A Forgotten Area. Chapter 14 in Pain, emotion and cognition: A complex nexus. Pickering G & Gibson, S.: Springer, London ISBN 978-3-319-12032-4, 2015.
[21] Girard M, Plansont B, Bonnabau H, Malauzat D. Experimental pain hypersensitivity in schizophrenic patients. The Clinical Journal of Pain 2011;27(9):790-795.
[22] Goldman MB, Gnerlich J, Hussain N. Neuroendocrine responses to a cold pressor stimulus in polydipsic hyponatremic and in matched schizophrenic patients. Neuropsychopharmacology 2007;32(7):1611-1621.
[23] Gracely RH. Studies of pain in human subjects. In R. Melzack & P. Wall (Eds.), *Textbook of pain* (5th ed., pp. 267-289). London, Elsevier, 2005.
[24] Guieu R, Samuélian JC, Coulouvrat H. Objective evaluation of pain perception in patients with schizophrenia. The British Journal Of Psychiatry: The Journal Of Mental Science 1994;164(2):253-255.
[25] Hasselström J, Liu-Palmgren J, Rasjö-Wrååk G. Prevalence of pain in general practice. European Journal of Pain 2002;6(5):375-385.
[26] Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ (Clinical Research Ed) 2003;327(7414):557-560.
[27] Hussar AE. CORONARY HEART DISEASE IN CHRONIC SCHIZOPHRENIC PATIENTS: A CLINICOPATHOLOGIC STUDY. Circulation 1965;31:919-929.
[28] Hussar AE. Leading causes of death in institutionalized chronic schizophrenic patients: a study of 1,275 autopsy protocols. The Journal Of Nervous And Mental Disease 1966;142(1):45-57.
[29] Jarcho JM, Mayer EA, Jiang ZK, Feier NA, London ED. Pain, affective symptoms, and cognitive deficits in patients with cerebral dopamine dysfunction. Pain (03043959) 2012;153(4):744-754.
[30] Jochum T, Letzsch A, Greiner W, Wagner G, Sauer H, Bär K-J. Influence of antipsychotic medication on pain perception in schizophrenia. Psychiatry Research 2006;142(2-3):151-156.
[31] Kane EM, Nutter RW, Weckowicz TE. Response to cutaneous pain in mental hospital patients. Journal of Abnormal Psychology 1971;77(1):52-60.
[32] Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophrenia Bulletin 1987;13(2):261-276.
[33] Keshavan MS, Tandon R, Boutros NN, Nasrallah HA. Schizophrenia, 'just the facts': What we know in 2008: Part 3: Neurobiology. Schizophrenia Research 2008;106(2-3):89-107.
[34] Kudoh A, Ishihara H, Matsuki A. Current perception thresholds and postoperative pain in schizophrenic patients. Regional Anesthesia & Pain Medicine 2000;25(5):475-479.
[35] Laursen TM, Munk-Olsen T, Agerbo E, Gasse C, Mortensen PB. Somatic hospital contacts, invasive cardiac procedures, and mortality from heart disease in patients with severe mental disorder. Archives Of General Psychiatry 2009;66(7):713-720.
[36] Lautenbacher S, Kunz M, Strate P, Nielsen J, Arendt-Nielsen L. Age effects on pain thresholds, temporal summation and spatial summation of heat and pressure pain. Pain 2005;115(3):410-418.
[37] Li M, Fan Y-L, Tang Z-Y, Cheng X-S. Schizophrenia and risk of stroke: a meta-analysis of cohort studies. International Journal Of Cardiology 2014;173(3):588-590.
[38] Lieberman AL. Painless myocardial infarction in psychotic patients. Geriatrics 1955;10:579-580.
[39] Lévesque M, Potvin S, Marchand S, Stip E, Grignon S, Pierre L, Lipp O, Goffaux P. Pain Perception in Schizophrenia: Evidence of a Specific Pain Response Profile. Pain Medicine 2012;13(12):1571-1579.
[40] Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Clinical Trials 2009;6(7):1-6.
[41] Nielsen J, Juel J, Al-Zuhairi KSM, Friis R, Graff C, Kanters JK, Jensen SE. Unrecognised myocardial infarction in patients with schizophrenia. Acta Neuropsychiatrica 2015:1-7.

[42] World Health organisation Wh. The ICD-10 Classification of Mental and Behavioural Disorders – Diagnostic Criteria for Research, 1993.
[43] Potvin S, Marchand S. Hypoalgesia in schizophrenia is independent of antipsychotic drugs: A systematic quantitative review of experimental studies. Pain 2008;138(1):70-78.
[44] Potvin S, Stip E, Tempier A, Pampoulova T, Bentaleb LA, Lalonde P, Lipp O, Goffaux P, Marchand S. Pain perception in schizophrenia: No changes in diffuse noxious inhibitory controls (DNIC) but a lack of pain sensitization. Journal of Psychiatric Research 2008;42(12):1010-1016.
[45] Seidel S, Aigner M, Ossege M, Pernicka E, Wildner B, Sycha T. Antipsychotics for acute and chronic pain in adults. The Cochrane Database Of Systematic Reviews 2013;8:CD004844.
[46] Song JY, JH Y. Pain insensitivity and pressure pain thresholds in patients with schizophrenia. J Korean Neuropsychiatr Assoc, 39:14–21., 2000.
[47] Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, Moher D, Becker BJ, Sipe TA, Thacker SB. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA: The Journal Of The American Medical Association 2000;283(15):2008-2012.
[48] Stubbs B, Gaughran F, Mitchell AJ, De Hert M, Farmer R, Soundy A, Rosenbaum S, Vancampfort D. Schizophrenia and the risk of fractures: a systematic review and comparative meta-analysis. General Hospital Psychiatry 2015;37(2):126-133.
[49] Stubbs B, Mitchell AJ, De Hert M, Correll CU, Soundy A, Stroobants M, Vancampfort D. The prevalence and moderators of clinical pain in people with schizophrenia: A systematic review and large scale meta-analysis. Schizophrenia Research 2014;160(1-3):1-8.
[50] Stubbs B, Vancampfort D, De Hert M, Alex JM. The prevalence and predictors of type two diabetes mellitus in people with schizophrenia: A systematic review and comparative meta-analysis. Acta psychiatrica Scandinavica, 2015 (in press).
[51] Thompson T, Keogh E, French CC, Davis R. Anxiety sensitivity and pain: Generalisability across noxious stimuli. Pain 2008;134(1-2):187-196.
[52] Vancampfort D, Wampers M, Mitchell AJ, Correll CU, De Herdt A, Probst M, De Hert M. A meta-analysis of cardio-metabolic abnormalities in drug naïve, first-episode and multi-episode patients with schizophrenia versus general population controls. World Psychiatry: Official Journal Of The World Psychiatric Association (WPA) 2013;12(3):240-250.
[53] Wojakiewicz A, Januel D, Braha S, Prkachin K, Danziger N, Bouhassira D. Alteration of pain recognition in schizophrenia. European Journal of Pain 2013;17(9):1385-1392.

Figure 1 prisma search flow results

Figure 1. PRISMA 2009 flow diagram for search strategy

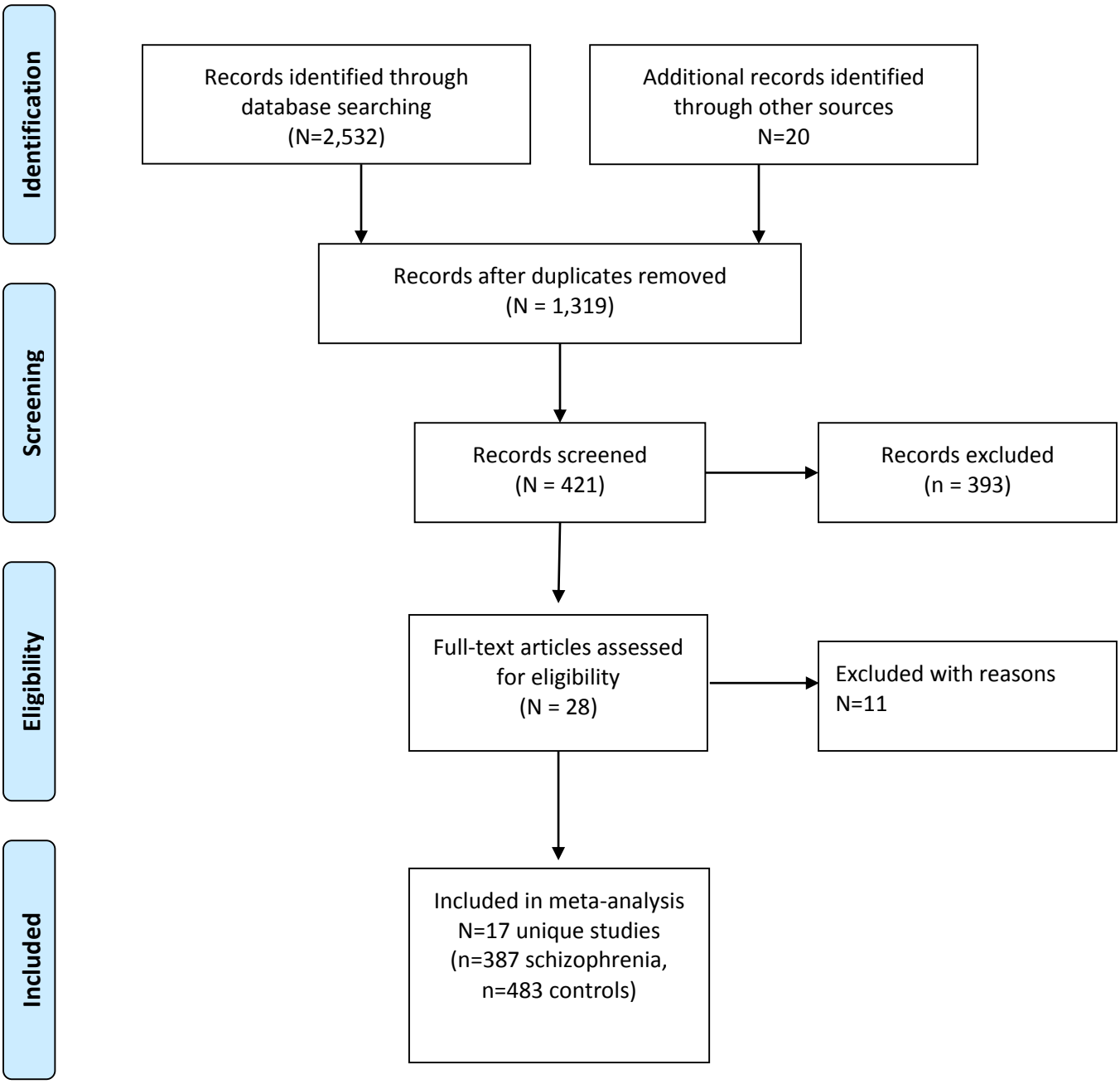

Figure 2 meta analysis

Figure 2. Pooled Analysis of All Studies Comparing Experimentally Induced Pain Sensitivity in Schizophrenia-Spectrum Patients Versus Controls

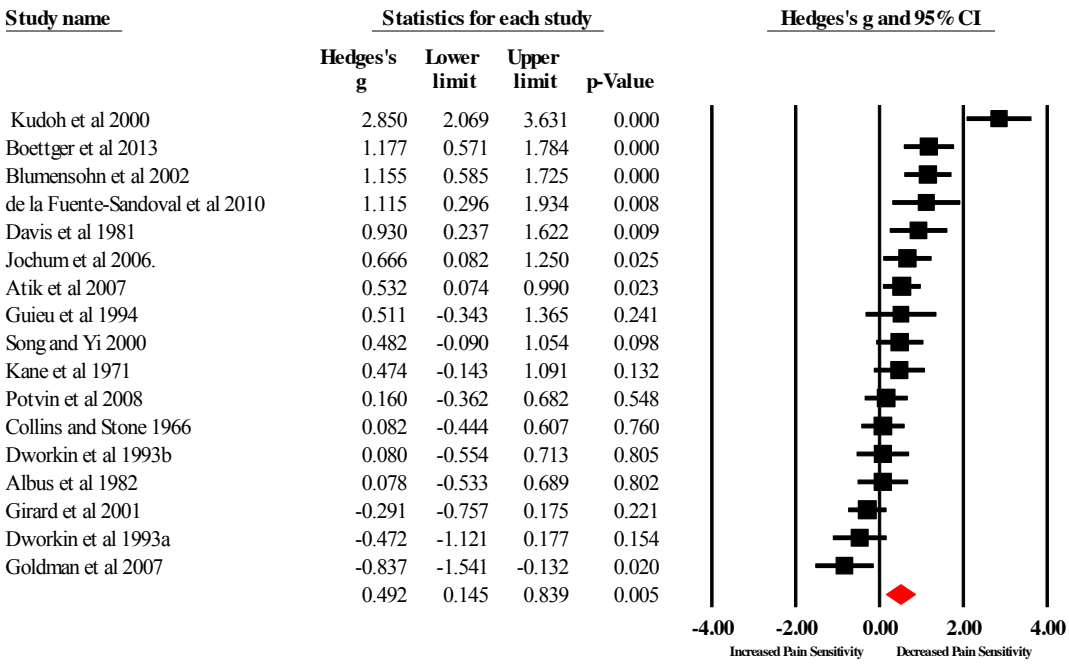

Figure 3 meta analysis

Figure 3a. Differences in Experimentally Induced Pain Sensitivity in Antipsychotic-Free Patients Compared to Controls

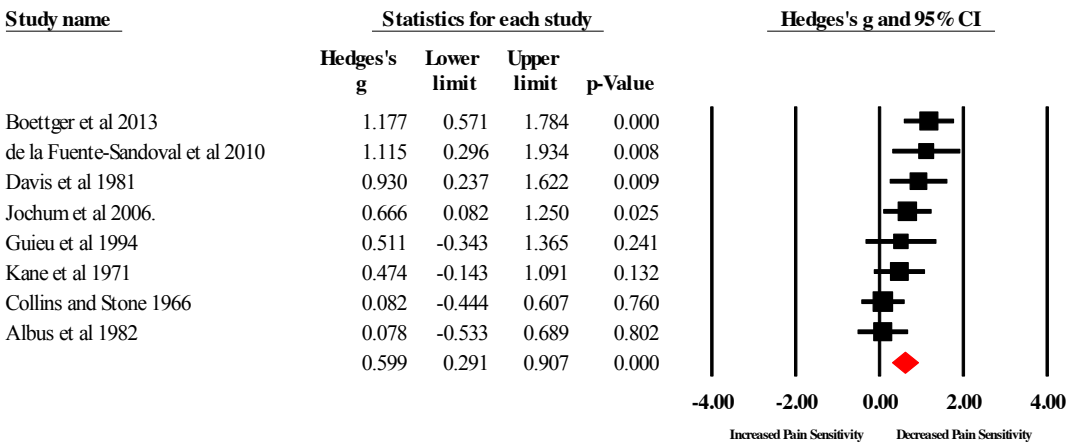

Figure 3b. Differences in Experimentally Induced Pain Sensitivity in Patients Taking Antipsychotics Compared to Controls

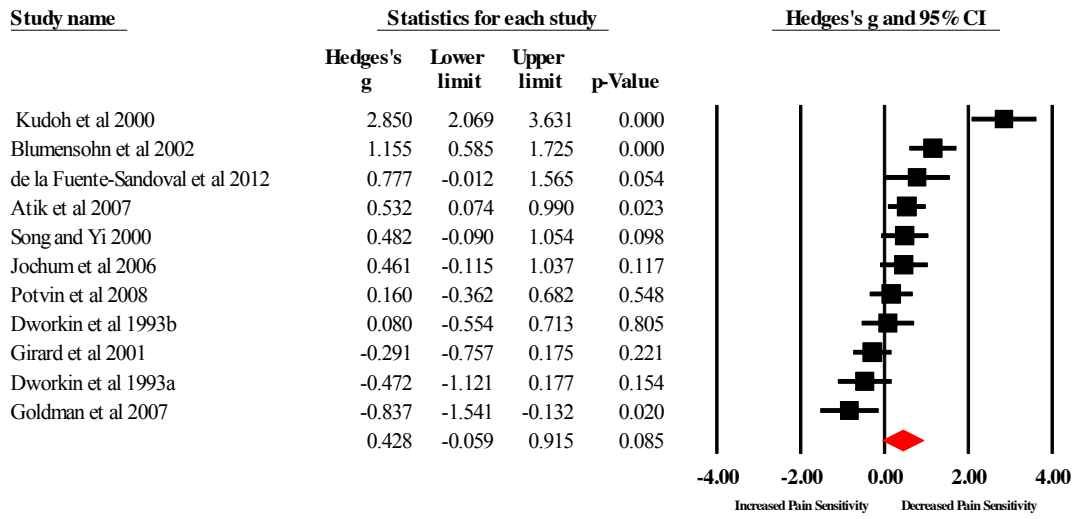

Table 1 summary of included studies

Author	Location & Setting	Schizophrenia participants	Antipsychotic Treatment	Control participants	Pain modality	Pain measure used
Antipsychotic-Treated Individuals						
Atik et al 2007	Turkey, outpatients	N=27, schizophrenia, 51.9% female, age=31.7 years, 10.7 years illness duration. , 25% taking antidepressants BPRS= 22.1	83% taking various antipsychotics	N=59, 45.8% female, age=32.0 years,	Thermal	Pain threshold Pain tolerance Pain intensity
Blumensohn et al 2002	Israel, inpatients	N=25, schizophrenia acute, 48% female, age=19.1 years.	100% taking various antipsychotics	N=29, 48.3% female, age=19.9 years	Electrical	Pain threshold Pain tolerance Sensory threshold
Dworkin et al. 1993 (A)	US, inpatients	N=17, 15 schizophrenia, 2 schizoaffective disorder, age=35 years.	100% taking various antipsychotics	N=19, age=30.4 years,	Thermal	Sensory discrimination Response criterion
Dworkin et al. 1993 (B)	US, inpatients	N=13, 8 schizophrenia, 3 schizoaffective disorder, 2 schizotypal disorder, age=26.6 years	Details not stated but treated as medicated	N=32, age=23.1 years	Thermal	Sensory discrimination Response criterion
Goldman et al 2007	US, mixed setting	N=24, 20 schizophrenia, 4 schizoaffective disorder, 33% female, age=41.6 years, 17.1 years illness duration, PANSS total 59.55	100% taking haloperidol or olanzapine	N=12, 42% female, age=38.3 years,	Thermal	Pain intensity Pain tolerance Blood pressure change
*Jochum et al 2006**	Germany, inpatients	N=23, schizophrenia, 70% female, age=34.4 years, 8.6 years illness duration, SAPS 47.4, SANS 32.5,	100% taking various antipsychotics	N=23, 70% female, 37.8 years	Thermal	Pain threshold Pain tolerance Sensory threshold
Kudoh et al 2000	Japan, unclear setting	N=50 schizophrenia, age=46.3 years.	100% taking various antipsychotics	N=25, age=45.3 years	Electrical	Sensory threshold Pain intensity
Potvin et al 2008	Canada, mixed (91% outpatients)	N= 23,18 schizophrenia, 5 schizoaffective disorder, 22% female, age=36.9 years, 5.2 years illness duration	100% taking various antipsychotics	N=29, 28% female, age=32.6 years,	Thermal	Pain intensity
*de la Fuente-Sandoval et al 2010**	Mexico, mixed setting	N=12, schizophrenia, 17% female, age=23.6 years, 1.4 years illness duration, PANSS total 86.7.	100% taking various antipsychotics*	N=13, 23% female, age=26.1 years	Thermal	Pain tolerance Pain intensity Pain unpleasantness

Table 1 summary of included studies

Author	Location & Setting	Schizophrenia participants	Antipsychotic Treatment	Control participants	Pain modality	Pain measure used
Girard et al 2011	France, inpatients	N=35, 37% female, age 41.9 whole sample, 11.3 years illness duration, SAPS 36.3, ,	? all taking various antipsychotics	N=35, no data on gender or age	Mechanical	Pain intensity Mechanical Pressure Time
Lévesque et al 2012	Canada, outpatients	N=12, schizophrenia, 33% female, 31.3 years, .6 years illness duration, PANSS total 64.7,	100% taking various antipsychotics	N=11, age=31.5 years, 27% female	Electrical	Pain threshold Withdrawal reflex Pain intensity
Song and Yi 2000	Asia, unclear setting	N=21; schizophrenia, no data on gender or age	All taking antipsychotics	N=23, no data on gender or age	Mechanical	Pain threshold
Subtotal Antipsychotic-Treated	Studies=12; Region: USA=3, Other=3, Canada=2, Europe=2, Asia=2; Setting: Outpatient=5, Inpatients2=, Mixed=3, Unclear=2	N=282, age=33.4 years±8.2 years, females=38.9% (range=17-70%).	Antipsychotic-Treated=11; Unclear=1	N=310, age=31.7 years±7.9, 40.5% female (range 23-80%)	Thermal=7; Electrical=3; Mechanical=2	Pain intensity=7; Pain threshold=5; Pain tolerance=5; Sensory threshold=3; Physiological response=2; Sensory discrimination=1; Response criterion=1
Antipsychotic-Free Individuals						
Collins and Stone 1966	US, inpatients	N=18, schizophrenia, 0% female, age=32.8 years, 0% taking antidepressant or mood stabilisers	Antipsychotic-free	N=56, 0% female, age=27.1 years,	Electrical	Pain threshold Pain tolerance Sensory threshold
Davis et al 1981	US, inpatients	N=17, schizophrenia, 33% female, age=26 years, 0% taking antidepressant or mood stabilisers	Antipsychotic-free	N 17, matched for age and gender, but data not given	Electrical	Pain threshold Response criterion EEG
Guieu et al 1994	France, unclear setting	N=10 , schizophrenia, 60% female, age=35.4 years, 0% taking antidepressant and mood stabiliser, 6.1 years illness duration	Antipsychotic-free	N=10, 40% female, age=31.6 years,	Electrical	Pain threshold

Table 1 summary of included studies

Author	Location & Setting	Schizophrenia participants	Antipsychotic Treatment	Control participants	Pain modality	Pain measure used
*Jochum et al 2006**	Germany, inpatients	N=23, schizophrenia, 70% female, age=34.4 years, 8.6 years illness duration, SAPS 47.4, SANS 32.5,	Antipsychotic-free (and retested with 100% taking various antipsychotics*)	N=23, 70% female, 37.8 years	Thermal	Pain threshold Pain tolerance Sensory threshold
Kane et al 1971	Canada, inpatients	N=30, schizophrenia , 0% female, age=34.4 years,3 years illness duration	Antipsychotic-free	N=15, 0% female, age=21.6 years,	Thermal	Pain threshold Pain tolerance Sensory threshold
Albus et al 1982	Germany, inpatients	N=12 schizophrenia, 34 years	Antipsychotic-free	N=63, age=37 years,	Thermal	Heart rate change EEG
Boettger et al 2013	Germany, inpatients	N=18, schizophrenia, 44% female, age=34 years, PANSS total 86	Antipsychotic-free	N=18, 44% female, age=34 years,	Thermal	Pain threshold Pain intensity Pain unpleasantness
*de la Fuente-Sandoval et al 2010 **	Mexico, mixed setting	N=12, schizophrenia, 17% female, age=23.6 years, 1.4 years illness duration, PANSS total 86.7.	Antipsychotic-free (and retested with 100% taking various antipsychotics*)	N=13, 23% female, age=26.1 years	Thermal	Pain tolerance Pain intensity Pain unpleasantness
Subtotal Antipsychotic free	Studies=8; Region: Europe=4, USA=2, Canada=1, Other=1; Setting: Inpatients=6, Outpatient=1, Unclear=1	N=140 schizophrenia, age=31.8±4.4 years, females=32% (range=0-70%)	Antipsychotic-free=8 (and retested with 100% taking various antipsychotics*=2)	N=215, age-30.7±6.0 years, 29.5% female (range 0-70%)	Thermal=5; Electrical=3	Pain threshold=6; Pain tolerance=4; Sensory threshold=3; Pain intensity=2; Pain unpleasantness=2; Physiological response=2; EEG=2 Response criterion=1
TOTAL	Studies=18; Region: USA=5,	N=387 participants with schizophrenia spectrum, mean age=30.7±6.9 years, females=31.9% (range=0%-70%),	Antipsychotic-Treated=11; Antipsychotic-	N=483 control participants, mean age=29.5±7.4	Thermal=10; Electrical=6; Mechanical=2	Pain threshold=10; Pain intensity=8; Pain tolerance=7;

Table 1 summary of included studies

Author	Location & Setting	Schizophrenia participants	Antipsychotic Treatment	Control participants	Pain modality	Pain measure used
	Europe=5, Canada=3, Other=3, Asia=2; Setting: Outpatient=6 Inpatients=7, Mixed=2, Unclear=2	illness duration=7.0±5.7 (range=1.0-17.1).	free=8 (and retested on antipsychotic=2); Unclear=1	years, females=31.0% (range=0%-70%)		Sensory threshold=5; Physiological response=4; Pain unpleasantness=1; EEG=2 Response criterion=2 Sensory discrimination=1

Key: BPRS= Brief Psychiatric Rating Scale, EEG= electroencephalography, PANSS= Positive and Negative Syndrome Scale, SANS= Scale for the Assessment of Negative Symptoms, SAPS= Scale for the Assessment of Positive Symptoms, US= United States, *=authors published two papers on same participants, one in antipsychotic-free individuals and one in people taking antipsychotic medications. Dworking et al 1993 A and B are two unique studies contained in one publication.

Table 2 Summary of pain sensitivity results within meta-analysis

Pain Measure	Overall hedges g (95% CI) P value	Number studies (N) and number participants (n)	Hedges g AP free (95% CI) P value	Number studies (N) and number participants (n)	Hedges g Medicated (95% CI), P value	Number studies (N) and number participants (n)
Composite analysis	0.493 (95% CI 0.145-0.839) p=0.005	N=17 n=847	0.599 (95% CI 0.291 - 0.907) p<0.0001	N=8 n=371	0.428 (95%0.059 - 0.915) p=0.08	N=11 n= 542
Pain threshold	0.696 (95% CI 0.407-0.986) p<0.001	N=9 n=439	0.753 (95% CI 0.305-1.202) p<0.001	N=5 n=252	0.706 (95% CI 0.354-1.05) P<0.001	N=5 n=195
Pain tolerance	0.393, (95%CI=-0.048-0.836), p=0.08	N=7 n=366	0.342 (95% CI 0.03-0.645) p=0.02	N=4 n=190	0.453 (95% CI -0.135 – 1.04) P=0.1	N=5 n=237
*Pain tolerance with Outlier Removed**	0.566 (95% CI 0.235-0.897) p=0.0001	N=6 n=330	0.342 (95% CI 0.03-0.645) p=0.02	N=4 n=190	0.745 (95% CI 0.461-1.02) p<0.0001	N=4 n=211
Sensory Threshold	1.16 (95% CI 0.505-1.727) p<0.0001	N=5 n=294	0.807 (95% CI 0.168-1.446) p=0.01	N=3 n=165	N/A	N/A
Pain ratings of unpleasantness	0.547 (95% CI 0.146-0.949) p=0.008	N=3 n=95	0.547 (95% CI 0.146-0.949) p=0.008	N=3 n=95	N/A	N/A
Physiological response to painful stimuli	0.465 (95% CI 0.131-0.783) P=0.006	N=4 n=190	0.505 (95% CI 0.072-0.941) P=0.02	N=3 n=145	N/A	N/A
Pain sensitivity changes before and after antipsychotic medication	-0.279 (95% CI -0.483 - -0.075) P=0.007	N=2 n=35				

Key: g=hedges g, N=number of studies, n=number of participants, CI=confidence interval, *=outlier remover details and reason in manuscript text, N/A= not available for meta-analysis

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5-7
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6-7
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	8
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	8
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	8-9
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	8-9
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	8-9
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	8-9
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	8-9
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	9-10
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	10-11
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	10-11

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	10-11
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	10-11
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	12
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	12-13
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	12-13
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	12-15
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	12-15
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	12-15
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	12-15
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	16
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	16-19
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	16-19
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	19

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097