Review Article

Pain Processing in Psychiatric Conditions: A systematic review

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Abstract

Objective: Pain is a universal, multidimensional experience with sensory emotional, cognitive and social components, which is fundamental to our environmental learning when functioning typically. Understanding pain processing in psychiatric conditions could provide unique insight into the underlying pathophysiology or psychiatric disease, especially given the psychobiological overlap with pain processing pathways. Studying pain in psychiatric conditions is likely to provide important insights, yet, there is a limited understanding beyond the work outside depression and anxiety. This is a missed opportunity to describe psychiatric conditions in terms of neurobiological alterations. In order to examine the research into the pain experiences of these groups and the extent to which a-typicality is present, a systematic review was conducted. *Methods:* An electronic search strategy was developed and conducted in several databases. *Results:* The current systematic review included 46 studies covering five DSM-5 disorders: autism, attention deficit hyperactivity disorder, schizophrenia, personality disorder and eating disorders, confirming tentative evidence of altered pain and touch processing. Specifically, hyposensitivity is reported in schizophrenia, personality disorder and eating disorder, hypersensitivity in ADHD and mixed results for autism. *Conclusions:* Review of the research highlights a degree of methodological inconsistency in the utilisation of comprehensive protocols; the lack of which fails to allow us to understand whether a-typicality is systemic or modality-specific.

Key words: Psychiatric, DSM-5, Pain, Quantitative Sensory Testing, QST.

Introduction

Pain is a universal, multidimensional experience with sensory emotional, cognitive and social components (A. C. d. C. Williams & K. D. Craig, 2016). Understanding pain processing in psychiatric conditions could provide unique insight into the underlying pathophysiology or psychiatric disease, especially given the psychobiological overlap with pain processing pathways (Bird et al., 2010; de la Fuente-Sandoval, Favila, Gómez-Martin, Pellicer, & Graff-Guerrero, 2010; Fan, Chen, Chen, Decety, & Cheng, 2014; Goesling, Clauw, & Hassett, 2013; Iannetti & Mouraux, 2010). For example, there is substantial literature on pain perception in anxiety and depression (for review, see (Thompson, Correll, Gallop, Vancampfort, & Stubbs, 2016) supporting a bidirectional relationship between these conditions and altered pain behaviours. From this literature, several examples have emerged that highlight the need to understand pain perception in psychiatric disorders. The co-occurrence of depression or anxiety and pain have an additive burden on the individual (Bair, Robinson, Katon, & Kroenke, 2003). Similarly, altered pain behaviours can lead individuals to look for somatic causes, potentially obscuring or delaying psychiatric diagnoses. There also seems to be important moderators between depression/anxiety and pain, specifically related to the exteroceptive or interoceptive nature of the stimuli and attentional resources allocated for painful stimuli, which provide insight into sensory processing in the disorder (Goesling et al., 2013; Thompson et al., 2016).

Studying pain in psychiatric conditions is likely to provide important insights, yet, there is a limited understanding beyond the work outside depression and anxiety. This is a missed opportunity to describe psychiatric conditions in terms of neurobiological alterations (Lautenbacher & Krieg, 1994). Indeed, a range of psychiatric conditions include core symptoms or associations with potentially pain-related behaviours, for example self-harm (Taylor, Hutton, & Wood, 2015). The absence of systematic study of pain responses in these conditions negates the possibility to understand the contribution of potential sensory changes to

these behaviours. Further, pain experience is critical in a number of aspects of environmental learning, allowing individuals to learn about dangers and threats and distinguish these from safety cues (Bastian, Jetten, Hornsey, & Leknes, 2014) as well as promoting social bonding with carers who provide pain relief (Krahé, Springer, Weinman, & Fotopoulou, 2013; Langford et al., 2010). Altered pain processing may therefore, underlie clinical features of a range of psychiatric conditions, especially those conditions which have associated threat-related or social features.

A first step in understanding how altered pain processing may contribute to these psychiatric conditions is to explore processing and responsivity to potentially nociceptive signals. There is an example of this altered pain responsivity in the diagnostic criteria for autism spectrum disorder, where the DSM includes "apparent indifference to pain/temperature" as an example of sensory reactivity (APA, 2013). Understanding whether pain behaviours are a cause, effect or epiphenomenon of a psychiatric condition would enable better diagnostic characterization. In the example of autism, more rigorous psychophysical investigation into these symptoms is likely to improve interventions that aim to reduce their occurrence or provide environmental adaptions to improve overall participation (Baranek, 2002). Additionally, while many psychiatric conditions co-occur with depression, first disentangling processing as a function of individual disorders is crucial to mechanistic-based understanding (Kendler, 2008; Savitz & Harrison, 2018; Vardeh, Mannion, & Woolf, 2016). As noted in depression, pain processing was moderated by exteroceptive/interoceptive nature of the stimuli (Thompson et al., 2016). Given the evidence of altered interoceptive processing in other psychiatric conditions (Quattrocki & Friston, 2014), understanding pain processing in this dimension may provide insight into bodily representation and emotional regulation in these disorders. In this way, understanding pain processing in psychiatric conditioning may also allow for more mechanism-based treatment.

Aims of the review

Characterization of pain processing may provide understanding into biological alterations related to psychiatric conditions, as well as, quality of life for these individuals. Importantly, Lautenbacher and Krieg (1994), published the only review in this area prior to the development of standardised protocols. Standardised protocols are essential in order to minimise variability (Backonja et al., 2013), produce reliable and comparable results, and improve clinical feasibility (Rolke et al., 2006). Recent attempts have been made to generate standardised psychophysical approaches to understand touch and pain sensitivity in the form of Quantitative Sensory Testing (QST) batteries i.e. Rolke et al. (2006). Hence, this review will include studies that have been conducted on psychiatric conditions with experimental pain, with particular reference to QST. It will also examine factors that have been shown to mediate the magnitude of pain response including clinical features of the conditions, medication status, or co-occurring symptoms. Indeed, the impact of clinical symptom management in altering pain precepts as well as the potential role for pain management strategies in altering clinical presentation is central in understanding health in these vulnerable groups.

This review includes quantification of peripheral afferents associated with pain processing as well as light touch; non-noxious stimuli like light touch, can sometimes be experienced as painful (IASP, 2012). This may be particularly relevant to psychiatric conditions where individuals have reported discomfort or pain to typically non-painful tactile inputs (Grandin, 1992, 1995). Responses such as these may mimic low-level allodynia, suggesting that a full assessment of the somatosensory system is necessary for a true comprehension of pain in psychiatric conditions.

Methods

Search Methods

An electronic search strategy was used, according to the Cochrane guidelines (Higgins & Green, 2011), through author consensus, in the following databases; Medline (1953-

Present), PsycINFO (1931-Present), PsycARTICLES (1955-Present), Science Direct (1966-Present) and Science Citation Index (1989-2014). To gain a list of potentially relevant publications, DSM-5 psychiatric condition terms were combined with "or", terms related to pain/somatosensation and QST were also combined with "or", and then the two groups of key words were combined using "and" (Table 1). Subsequently, reference lists from retrieved papers were scanned for further relevant publications and authors of poster abstracts were contacted for further information or full text articles.

[Table 1 here]

Eligibility

Types of Studies

Studies were eligible for inclusion if they 1) were explicitly experimental, 2) utilised psychophysically appropriate pain or touch sensitivity assessment and 3) included both a clinical and control group, or adequately compared clinical data values to published norms.

Studies were excluded if 1) there was poor quality control of stimuli (i.e. intensity of stimuli was variable or clear order effects might be present etc.) 2) they utilised poor or non-comparable pain induction tests, 3) they did not contain a control group or refer to published norms or 4) were animal studies on pain induction.

No publication date restrictions or publication status restrictions were imposed and only studies published in English were considered. No restrictions were put onto the participants within studies, other than it was imperative that they were human samples and had a diagnosis of a condition previously categorized as Axis I or Axis II (APA, 1994). Conditions that have a neurological or developmental origin i.e. not acquired or environmental, have significant public health implications, and have not appeared in multiple comprehensive reviews (i.e. anxiety and depression) were chosen. They included; autism spectrum disorder (ASD), obsessive

compulsive disorder (OCD), attention deficit hyperactivity disorder (ADHD), schizophrenia, eating disorders (inclusive of anorexia nervosa, bulimia nervosa and binge-eating disorder) and personality disorder (Borderline personality disorder: BPD/PD).

Study Selection and Data Collection

Study Selection

Sourced citations were transferred to Endnote. Eligibility assessment was first performed on article titles in an un-blinded standardised manner by 2 reviewers (SV and DM). The first reviewer (SV) checked all titles for relevance, with second reviewer (DM) auditing 10% of the total, with a 97% agreement rate. For those studies where authors disagreed, a third reviewer (HP) acted as a blinded arbitrator.

Eligible abstracts were then assessed for inclusion, under the same process by the first reviewer (SV). In this instance 10% of the abstracts were divided across three blinded authors (HP, FMcG, MF) with a fourth (DM) acting as a blinded arbitrator, with 100% agreement rate. Roles were allocated to ensure that the arbitrator was different for both phases.

Data Collection

Information extracted from each study included; 1) Participant characteristics (including age, gender, condition, diagnosis method, numbers in each group, matching criteria and psychometric measures), 2) Pain or touch method (including location and test parameters) and 3) Main data (including all inferential statistics, any subgroup analysis and mean values), placed into specifically designed extraction tables. Summary sheets were generated to compare information across conditions.

Results

[Figure 1]

Results of the search

A final search conducted on 04/02/18, which yielded 2167 potentially relevant records. The majority of studies have been conducted in the last decade, highlighting the growing interest of pain across these conditions. Figure 1 flow chart details the records found at each stage of the screening process. Study characteristics and data will be presented for each condition in the following sections. Meta-analysis was not possible due to the variability in the methods utilised and the lack of reported confidence intervals and effect sizes.

Autism Spectrum Disorder

Included studies.

Ten studies were included for ASD. These studies included pain responses to thermal, mechanical, pressure, vibratory and electrical stimuli; therefore, a number of somatosensory measures were missing. Given the range of available measures, research examining somatosensory and pain thresholds in ASD is presently limited.

Participant characteristics.

Although studies have been conducted using children (n=2) and adolescents (n=2) samples, the majority (n= 6) were conducted on adults. This bias is understandable given the nature of the tests administered, which require very precise reports from participants; they may also be distressing to younger children. Male participants were generally the majority in the experimental group, and two studies had an all-male sample. This distribution is in line with a three-time greater prevalence of ASD in males (Baxter et al., 2015).

Sensation thresholds.

Six studies examined somatosensory detection thresholds. Three studies examined thermal detection thresholds, two in adults (Cascio et al., 2008; Fründt et al., 2017) and another in adolescents (Duerden et al., 2015). All studies adopted a method-of-limits to determine

thresholds, with Cascio et al. (2008) and Fründt et al. (2017) having a change rate of 1°C/s and Duerden et al. (2015) using 0.5°C/s. Results are inconsistent. Cascio et al. (2008) and Fründt et al. (2017) reported no significant differences, while hyposensitivity was reported by Duerden et al. (2015). Furthermore, Duerden et al. (2015) report a significant correlation between autism severity (as measured by ADOS-G scores) and thermal detection thresholds, specifically to both the social and communication subscales, demonstrating that adolescents with greater autism severity and lower IQ had higher detection thresholds. However, it is of note that those studies, which utilised the DFNS standardised battery, report no-significant differences.

Four studies examined vibratory detection thresholds in adults (Blakemore et al., 2006; Cascio et al., 2008; Fründt et al., 2017) and children (Guclu, Tanidir, Mukaddes, & Unal, 2007). Blakemore et al. (2006) presented two frequencies of vibrotactile stimuli; 200Hz (stimulating rapidly adapting fibres) and 30Hz (stimulating slowly adapting fibres), in a method-of-limits. Whereas, Cascio et al. (2008) used a forced-choice paradigm at 33Hz; participants were asked to indicate in which of two time intervals a stimulus was presented. Guclu et al. (2007) used sinusoidal displacements at 40 and 250Hz, in a forward-masking paradigm; a 250Hz stimulus was applied prior to the test stimulus and Fründt et al. (2017) used the DFNS standardised protocol. Overall results indicate hyper-responsiveness to vibratory stimuli in adults with ASD, as lower vibrotactile thresholds were achieved (Blakemore et al., 2006; Cascio et al., 2008). Furthermore, these findings appear to be sensitive to both location (as differences were reported for the forearm but not the palm (Cascio et al., 2008), and the frequency at which the stimulus is presented (Blakemore et al., 2006). However, Guclu et al. (2007) and Fründt et al. (2017) report no significant difference between the vibrotactile thresholds, and the children with autism had the same detection and masking mechanisms as the neurotypical children.

Finally, Cascio et al. (2008) and Fründt et al. (2017) also examined punctate mechanical detection thresholds using von Frey hairs. Cascio et al. (2008) reported no significant group differences, suggesting typical static mechanical functioning in ASD. Whilst Fründt et al. (2017) reported a greater loss of function for MDT. Their methodologies differed slightly with the latter using the DFNS standardised protocol and the other utilising a two ascending and two descending block of trials methodology.

Overall, the findings for somatosensory detection thresholds for individuals with ASD are inconsistent. There are some signs of hyposensitivity in thermal sensations (Duerden et al., 2015), however, these findings are not reliable with no significant group differences reported by (Cascio et al., 2008) - these findings are duplicated for mechanical detection. Individuals with ASD may be hypersensitive to vibrotactile stimuli, though this may be frequency- and/or location-specific. A wider range of techniques than is presently used could confirm whether hyposensitivity for one modality may be present at the same time as hypersensitivity for another, i.e. thermal and mechanical. Additionally, it is not possible to consider somatosensory detection across the developmental course of ASD as studies in children and adolescents are limited.

Pain.

Seven studies examined pain thresholds in ASD. Cascio et al. (2008); Duerden et al. (2015); Fründt et al. (2017) used a method-of-limits to determine thermal pain threshold. While Duerden et al. and Fründt et al. (2017) reported no group differences, Cascio et al. (2008) reported hypersensitivity for both heat and cold pain thresholds in the ASD group compared to healthy controls. Contrary to previous reports that individuals with ASD are insensitive to pain (Militerni et al., 2000; Minshew & Hobson, 2008), these studies provide tentative indications that there is typical nociception processing.

Four studies investigated pressure pain thresholds; Fan et al. (2014) and Fründt et al. (2017) in adults, Chen et al. (2017) in adolescents and Riquelme, Hatem, and Montoya (2016) in children. Ramp rates are reported as 1kg/ cm^2 s or 50 kPa/cm^2 (~ 0.5kg/cm^2 s), or not at all, and probe sizes are either a non-standard probe size of 1.52cm^2 or the standard 1cm^2. Non-standardized probe sizes potentially affects comparison with the general pain research literature and within study, comparison is difficult to make for similar reasons. With the exception of Fründt et al. (2017) individuals with ASD are reported to have lower pressure pain thresholds compared to neurotypical controls (Chen et al., 2017; Fan et al., 2014; Riquelme et al., 2016). Although, decisive conclusions are problematical due to incomplete methodologies, or the differing stimuli presentations mentioned, as well as different age groups.

Lastly, two studies examined electrocutaneous pain thresholds. Bird et al. (2010) using square pulse waveform at 100Hz, with a 4ms pulse length and a 1s duration and report no significant group differences. Whilst Gu et al. (2017) report significantly lower stimulation levels in the ASD group, using a method-of-levels.

Results are inconsistent and reaching conclusions is difficult. The aforementioned studies do provide tentative insight into the possibility that the sensory abnormalities mentioned by the DSM can be quantified, but more investigation is required. From the 10 studies, of note is Fründt et al. (2017), who not only utilise the full DFNS QST battery, but also standardise their scores which extends results from simple group comparisons to clinically significant sensory losses or gains.

[Table 2 here]

Attention Deficit Hyperactivity Disorder

Included Studies & Participant Characteristics.

Only one study was identified for ADHD, which selectively covers cold pressor pain but not sensation (Treister, Eisenberg, Demeter, & Pud, 2015) . Thirty adults with ADHD, who were prescribed Ritalin and 30 healthy age- and gender-matched controls, took part. The use of adults is understandable given the nature of the tests administered, which require very precise reports from participants. However, given that ADHD is most prominent in childhood, and that adult ADHD has a different phenotype (Mannuzza, Klein, Bessler, Malloy, & LaPadula, 1993), a study on children is warranted in order to expand insight into pain processing in this disorder.

Pain.

A cold pressor water bath was set at 1°C, participants submerged their right hand, providing both threshold (time at which the cold stimulus began to elicit pain) and tolerance (latency to spontaneous hand removal) over two sessions. Participants were randomised to complete the task once following administration of Ritalin and once following no medication. Individuals who had not been administered Ritalin expressed shorter latencies to cold pain, providing psychophysical evidence of hypersensitivity compared with healthy controls. Although, both threshold and tolerance were significantly shorter in ADHD participants, no significant differences were reported for self-reported pain intensities –the intensity of the pain was similarly felt across the groups regardless of a physiological hypersensitive response.

Schizophrenia

Included studies.

Eleven studies were included for schizophrenia. Outcomes from these studies were limited to thermal, pressure and electrical stimuli, thus research examining somatosensory thresholds in schizophrenia is limited, with pain thresholds receiving more attention.

Participant characteristics.

All studies were conducted with adults and sample ages suggest that somatosensory assessment has been conducted across the time course of the condition covering early adulthood, which is a peak for the onset of schizophrenia (Sham, MacLean, & Kendler, 1994). A previous diagnosis of schizophrenia was accepted and studies did no further testing.

Sensation thresholds.

One study examined somatosensory thresholds, specifically warm detection thresholds (Jochum et al., 2006) using a method of limits paradigm and a change rate of 0.5°C/s. Patients with schizophrenia demonstrated hyposensitivity, with significantly higher warmth thresholds compared to healthy controls.

Pain.

Thermal pain thresholds were examined in six studies. Jochum et al. (2006) and Boettger, Grossmann, and Bar (2013) obtained warm and cold pain thresholds using a method-of-limits paradigm, however Boettger et al. (2013) used a temperature change rate of 0.5°C/s. Higher temperatures were required to achieve a heat (Boettger et al., 2013; Jochum et al., 2006) and lower to obtain cold (Boettger et al., 2013) pain threshold in patients with schizophrenia compared to controls.

Four studies obtained heat pain thresholds using other methods. Three studies asked participants to tolerate heat for a duration of 30s (de la Fuente-Sandoval, Favila, Gómez-Martín, León-Ortiz, & Graff-Guerrero, 2012; de la Fuente-Sandoval et al., 2010) and 120s (Potvin et al., 2008). The last, Dworkin et al. (1993) obtained thermal pain discrimination using a signal detection method; 48 stimuli were presented of four different intensities (35.5, 38.5, 46.4 and 48.5°C) and participants verbally rated these as “no-sensation”, “warm”, “hot” or “painful”. Higher temperatures were required to achieve a heat pain threshold in patients with schizophrenia compared to controls (de la Fuente-Sandoval et al., 2010). Furthermore,

individuals with schizophrenia were shown to be poorer at thermal pain sensory discrimination and showed no response-bias differences to their matched healthy controls. A significant correlation was reported for warm-hot stimuli and positive symptoms/affective flattening, indicating that higher criteria for reporting painfulness were associated with fewer positive symptoms (Dworkin et al., 1993). Two studies reported non-significant group differences (de la Fuente-Sandoval et al., 2012; Potvin et al., 2008). These differing results may be the product of differing methodologies. For example, a shift in response criterion might lead to a higher intensity required to generate a pain threshold. However, Dworkin et al. (1993) reported no shift in this criterion. Another explanation is that individuals with schizophrenia have a higher threshold for thermal pain but a lower endurance, which results in similar pain tolerance; this would be consistent with a central pain processing explanation for differences with a change in central sensitization (Kleinböhl et al., 1999). That is to say, that the magnitude of peripheral input required to induce a pain response (i.e. threshold) might be the same, but the process of temporal or spatial summation may be magnified. This suggests that, once pain is perceived, the magnitude of this experience grows to a point of being intolerable more quickly.

. However, there is tentative evidence that, for laboratory-induced thermal stimuli, individuals may have hyposensitivity towards noxious thermal stimuli. Furthermore, these effects might relate to threat perception. Tolerance is fundamentally a withdrawal response from a noxious cue and previous research in the visual domain has suggested that individuals with schizophrenia withdraw from visually threatening stimuli (Phillips, Senior, & David, 2000). Potentially the point at which the decision that threat is intolerable may be reduced due to this symptomology.

Two further studies utilised the cold pressor task to investigate thermal pain, with differing water temperatures. Atik, Konuk, Akay, Ozturk, and Erdogan (2007) used 1°C water and Potvin et al. (2008) reported water temperature range from 7 to 12°C, with participants

rating the pain every 30 seconds, rather than a threshold and tolerance measure. Atik et al. (2007) report patients to have higher pain tolerance than healthy controls, but pain threshold did not differ. Furthermore, Potvin et al. report no significant differences between patients and healthy controls in pain ratings.

Three studies investigated electrical pain stimulation. Methods differed across studies, with Lévesque et al. (2012) applying a TENS square wave pulse. Guieu, Samuélian, and Coulouvrat (1994) applied five shocks for a 13ms duration, with each train including increasing and decreasing stimulus intensities at a frequency of 0.16Hz. Kudoh, Ishihara, and Matsuki (2000) applied transcutaneous pulses at 2000Hz, 250Hz and 5Hz obtaining self-report pain intensity in response to each stimulus. Levesque et al. report significant group differences, in which individuals with schizophrenia showed hypersensitivity to electrical stimuli compared with healthy controls. Additionally, pain thresholds were negatively correlated to positive symptoms. Kudoh et al. contradict these findings, showing increased conduction thresholds for individuals with schizophrenia and lower VAS pain rating scores, suggesting hyposensitivity. Guieu et al. show no significant group differences. Results are conflicting and the methods employed by each of these studies are contradictory, making it difficult to identify the validity of each of the findings; or how they might reflect differences in populations.

Lastly, one study investigated pressure pain using an algometer with a $1cm^2$ pressure tip, applied in a static test of 160kPa and then in a method-of-limits (Girard, Plansont, Bonnabau, & Malauzat, 2011). Pain started significantly earlier for individuals with schizophrenia, requiring less pressure to achieve a pain rating, suggesting hypersensitivity.

A greater range of techniques was employed here, reflected by the age of the studies included, with many being conducted before guidance on pain research or relevant equipment had been developed. Results from thermal pain trend toward hyposensitivity, which is

tentatively supported by those from thermal sensation. These results are not mirrored in pressure stimuli, where hypersensitivity is reported, nor in electrocutaneous where results are inconclusive. There is evidence, as presented above, for different effects in different modalities, which a wider range of techniques may help, clarify (see Table 3 for detailed results of each study). Adopting a standardised approach will allow for the replicability of studies and better result comparisons across studies.

[Table 3 here]

Personality Disorder

Included studies.

Ten studies were included all of which focussed on BPD, one of the most common forms of personality disorder with a weighted prevalence rate of 0.7% of the general population (Coid, Yang, Tyrer, Roberts, & Ullrich, 2006). Outcomes from these studies were limited to thermal, mechanical, pressure, electrical stimuli, as well as two-point discrimination. Thus, with the range of available measures and types of personality disorder, research examining somatosensory and pain thresholds is presently limited.

Participant characteristics.

One study was conducted using a sample of adolescents, however the majority of studies were conducted with those in early adulthood (n= 10), which suggests that somatosensory assessment has been conducted in line with the pattern of onset. Some studies split the experimental group by personality disorder traits, such as self-injurious behaviour (Ludäscher et al., 2009) comparing BPD with and without self-injurious behaviour (SIB), and psychopathic to non-psychopathic prisoners (Fedora & Reddon, 1993).

Sensation thresholds.

Four studies were identified which examined somatosensory thresholds. Ludäscher et al. (2009) considered thermal sensory thresholds in adults with BPD with and without SIB and Ludäscher et al. (2014) examined these effects in adolescents. Both studies used a method-of-limits with a 1^0C/s change rate. Results from these studies show no significant group differences. A further experiment conducted by Ludäscher et al. (2009) utilised Infra-red thulium-YAG-laser. Individuals with SIB require a greater energy intensity for detection compared to BPD without SIB and healthy controls, although both BPD groups had higher thresholds than healthy controls. This suggests that SIB may have a role to play in somatosensation, independent of BPD.

One study examined two-point discriminability using a forced-choice paradigm (Pavony & Lenzenweger, 2014). During the task, a two-point (6mm experimental stimuli or 10mm control stimuli) or one-point (intended for the detection of false alarms) stimulus was presented. Participants were then asked to indicate how many points were felt with no significant differences reported between BPD and control participants.

Overall results for somatosensory detection thresholds suggest normal functioning in BPD, with the exception of laser radiant heat stimuli where individuals may have hyposensitivity (Ludäscher et al., 2009). However, this effect may be specific to individuals who practice self-injury, and therefore be, at least, partially attributable to the complexity of the behaviours involved. These findings were not replicated under an alternative method of producing thermal stimuli within the same study, nor in adolescents (Ludäscher et al., 2014). Furthermore, results suggest normal tactile discrimination.

Pain.

Ten studies examined pain thresholds in BPD. Thermal pain thresholds were examined in five studies (Ludäscher et al., 2009; Ludäscher et al., 2014; Schmahl et al., 2006; Schmahl et al., 2004; Schmahl et al., 2010). Ludäscher et al. (2009) used a method of limits with

418 1^0C/second change rate, Schmahl et al. (2010) and Ludäscher et al. (2014) used a 1.5°C/s
419 change rate, with Schmahl et al. (2006) using 2°C/s. Compared to healthy controls, individuals
420 with BPD required higher temperatures for heat (Ludäscher et al., 2009) and lower
421 temperatures for a cold pain threshold (Ludäscher et al., 2009; Schmahl et al., 2010),
422 suggesting hyposensitivity. This was additionally supported by results from the Laser Radiant
423 Thermal Stimuli Test (parameters previously discussed (Ludäscher et al., 2009; Schmahl et al.,
424 2004). More specifically, Ludäscher et al. (2009) showed that individuals engaging in SIB had
425 the highest thresholds, supporting the role of this behaviour in attenuating sensory deficits .
426 Additionally, SIB symptom severity was negatively correlated with pain ratings, showing that
427 individuals who have high symptomology rate the stimulus intensity as lower. Ludäscher et al.
428 (2014) provide further support to these findings, reporting similar hyposensitivity in
429 adolescents with BPD. Schmahl et al. (2006) also report hyposensitivity in a group of BPD
430 adults with SIB using their tonic heat methodology. These converging results suggest that for
431 laboratory-induced thermal stimuli, individuals with BPD may experience hyposensitivity to
432 noxious thermal stimuli, specifically when engaging in self-injurious behaviour.

433 Three further studies investigated thermal pain through use of a cold pressor (Bohus et
434 al., 2000; McCown, Galina, Johnson, DeSimone, & Posa, 1993; Pavony & Lenzenweger,
435 2014). Water temperatures were different across studies; one used 1°C water (Pavony &
436 Lenzenweger, 2014), with Bohus et al. (2000) using 10°C and McCown et al. (1993) stating an
437 approximate temperature of 0°C. Procedural methodologies also differed between these
438 studies. Bohus et al. (2000) asked participants to have their hand submerged for 4 minutes and
439 to rate the pain intensity every 15 seconds, whereas McCown et al. (1993) and Pavony and
440 Lenzenweger (2014) obtained threshold, tolerance and endurance. McCown et al. (1993)
441 reported no significant group differences on baseline tolerance levels, however, Pavony and
442 Lenzenweger (2014) report that individuals with BPD show significant higher tolerance and
443 endurance levels, compared with healthy controls. Bohus et al. (2000) reported lower intensity

and unpleasantness ratings by individuals with BPD compared to healthy controls. Specifically, those individuals self-reported as under distress of SIB had the lowest pain ratings, followed by individuals who felt calmer. This suggests that those individuals who self-injure perceive pain as less severe or may experience hyposensitivity.

One study investigated mechanical pain thresholds using punctate probes (Magerl, Burkart, Fernandez, Schmidt, & Treede, 2012). BPD threshold estimations are reported as significantly higher compared to healthy controls. The recency of SIB and pinprick threshold were significantly correlated. Analysis of the suprathreshold pain measures also revealed similar self-injurious behaviour-dependent losses of pain sensitivity, occurring in all pain measures. Overall, patients in the frequent SIB subgroup were significantly less-pain sensitive than healthy controls and less sensitive than BPD individuals who rarely engaged in SIB, suggesting hyposensitivity.

Two studies reported electrocutaneous thresholds; both utilised constant current stimulation although methods differed. Fedora and Reddon (1993) applied an ascending series of stimulation using a Tursky concentric electrode to prisoners. Ludäscher et al. (2007) applied a continuous stimulation of a pulse with a frequency of 10Hz and 0.5ms duration to the right index finger, with a 2 ring electrode, to individuals with BPD and healthy controls. Both studies report significant group differences, in which both prisoners and individuals with BPD have higher pain thresholds than healthy controls. Additionally, Fedora and Reddon (1993) show a negative correlation between pain thresholds and the degree of monotony avoidance, with highest thresholds found in those who are the lowest thrill seekers. In contrast, Ludäscher et al. (2007) report a positive correlation between pain thresholds and both state and trait dissociation, as well as aversive arousal; the more avoidant an individual with BPD is, the higher their pain thresholds. This has important connections with SIB and reinforces the relationship previously discussed.

As can be seen from Table 4 results across both sensation and pain tend towards hyposensitivity in individuals with BPD. This conclusion is limited due to the varied methodologies used. Adopting standardised techniques in future studies will allow for the replicability of studies and better result comparisons, which is the factor vitiating any statistically significant conclusions. Another important consideration is the characterisation of stress levels during sensation and pain testing. Evidence suggests that pain sensitivity is altered by mood induction in BPD (Ludäscher et al., 2007).

[Table 4 here]

Eating Disorders

Included studies.

Fourteen studies were included for Eating Disorders. Outcomes from these studies were limited to thermal, mechanical, pressure, vibratory stimuli and two-point discrimination. Thus, with the range of available measures, research examining somatosensory and pain thresholds in eating disorders is presently limited, although it is one of the conditions that has received greater interest.

Participant characteristics.

Eating disorders include anorexia nervosa, bulimia nervosa, restrictive anorexia and binge-purge anorexia (APA, 2013). Twelve studies used an adult sample, with only one study specifically employing adolescents. Eleven of the 14 studies had an all-female participant sample. This is in line with increased prevalence in females, or the underreporting of males with eating disorders (Hackler, Vogel, & Wade, 2010). One study reported the use of both male and female sample (Bär, Berger, Schwier, Wutzler, & Beissner, 2013).

Sensation thresholds.

Two studies examined tactile sensitivity (Faris et al., 1992; Keizer, Smeets, Dijkerman, van Elburg, & Postma, 2012) via mechanical detection, with the addition of sensory discrimination to one study. Tactile acuity and size estimation were tested using two-point discrimination. For tactile acuity, the trial consisted of either one-point (33% of the trials) or two-point stimuli (66%). Blindfolded participants indicated whether they perceived one single stimulus or two distinct stimuli. Responses were recorded with a forced-choice one-up two-down staircase method, with starting distances of 43 and 33mm, for the right underarm and abdomen, respectively. Participants then estimated the distance of the two points on a touchpad computer. In a second phase, mechanical detection was measured using calibrated von Frey hairs, a method mirrored by Faris et al. (1992). Patients with anorexia nervosa had a higher two-point discrimination threshold, regardless of body site tested, and compared with healthy controls. Furthermore, distance estimation was larger in this group for both sites; this effect was largest for the abdomen (Keizer et al., 2012). Rather than a purely sensory effect, the cognitive processing of somatosensory input may in fact be altered in individuals with eating disorders, in line with the expression of their condition. A lower threshold for mechanical detection on the abdomen is reported, but no significant group differences were found for the arm (Keizer et al., 2012), or the hand (Faris et al., 1992).

A third study examined thermal and vibration thresholds (Pauls, Lautenbacher, Strian, Pirke, & Krieg, 1991) using a method-of-limits. No significant group differences were reported for patients with anorexia nervosa or bulimia nervosa compared to healthy controls.

Overall, the findings for somatosensory detection thresholds are inconsistent. When considering tactile acuity and mechanical detection individuals with eating disorders were shown to display both hypo- and hyper-sensitivity, which may be stimulus specific. Furthermore, there is potential evidence of a psychogenic effect on somatosensation, with the largest effect reported for the abdomen, an area of cognitive focus for those suffering from an

eating disorder. It is not possible to consider somatosensory detection in its entirety, as studies are limited, impeding comparisons.

Pain.

Thirteen studies examined pain thresholds in eating disorders. Thermal pain thresholds were examined in eleven of these. Seven studies measured heat pain in a method-of-limits, with varying temperature change rates 0.5°C/s, 0.7°C/s and 1.5°C/s (Bär et al., 2013; Bär et al., 2006; Krieg, Roscher, Strian, Pirke, & Lautenbacher, 1993; Lautenbacher, Pauls, Strian, Pirke, & Krieg, 1990, 1991; Pauls et al., 1991; Schmahl et al., 2010). Significant increased heat pain thresholds were observed in eating disorders compared to healthy controls (Bär et al., 2013; Bär et al., 2006; Lautenbacher et al., 1990, 1991; Pauls et al., 1991). These results were shown to decrease after weight had been regained (Bär et al., 2006) for both tonic and phasic thermal stimuli (Lautenbacher et al., 1990). However, Krieg et al. (1993) and Schmahl et al. (2010) reported no significant group differences. This may be due to the use of recovering anorexics and may provide tentative support to Bär et al. (2006) in which individuals who had gained weight and therefore assumed to be in a phase of recovery, showed that threshold levels decreased. Results from these studies suggest individuals, when in an acute phase, are likely to experience hyposensitivity.

The last four studies that examined heat pain thresholds used radiant heat stimuli, specifically laser (de Zwaan, Biener, Bach, Wiesnagrotzki, & Stacher, 1996; de Zwaan, Biener, Schneider, & Stacher, 1996) and thermal latency with a constant stimulus (Papezova, Yamamotova, & Uher, 2005; Yamamotova, Papezova, & Uher, 2009). Patients with eating disorders had higher threshold for thermal pain (de Zwaan, Biener, Bach, et al., 1996; de Zwaan, Biener, Schneider, et al., 1996) compared with healthy controls. Thermal pain threshold latencies were longer (Yamamotova et al., 2009) in bulimia nervosa than healthy controls. As well as a general group of individuals with eating disorders (patients with eating

542 disorders; restrictive anorexia, binge-purge anorexia and bulimia nervosa), specifically those
543 with binge purging symptomatology (Papezova et al., 2005). Providing further evidence of
544 hyposensitivity in respect of noxious thermal stimuli that may be symptomology related.

545 Five studies investigated pressure pain thresholds (de Zwaan, Biener, Bach, et al., 1996;
546 de Zwaan, Biener, Schneider, et al., 1996; Faris et al., 1992; Raymond et al., 1995; Raymond et
547 al., 1999) using a method-of-limits. Individuals with eating disorders, including anorexia, had
548 higher pressure-pain (de Zwaan, Biener, Bach, et al., 1996; de Zwaan, Biener, Schneider, et al.,
549 1996; Faris et al., 1992) and detection thresholds (Raymond et al., 1995) compared to healthy
550 controls. Though no significant difference at suprathreshold tolerance (Raymond et al., 1999).
551 This may be due to pressure pain threshold being entered as a covariate. There is tentative
552 evidence for hyposensitivity towards laboratory-induced pressure pain.

553 Results for thermal pain, tactile stimuli, pressure detection and pain suggest that
554 individuals with eating disorders experience hyposensitivity, which may be specific to acute
555 phases (see Table 5 for detailed results of each study). However, conclusions are difficult to
556 make in regards to this. The aforementioned studies do provide tentative insight into the
557 possibility that the sensory abnormalities can be quantified, but more investigation is required,
558 specifically as there is a focus on thermal stimuli.

559 [Table 5 here]

560 **Discussion**

561 The purpose of this review was to provide an overview of research that investigated
562 pain processing in a number of psychiatric conditions where this has not been a focus
563 previously. The most notable global observation is the lack of utilisation of detailed testing
564 procedures and particularly standardised protocols such as those published by Rolke et al.
565 (2006). Even when these have been used, small variability in the methods, such as temperature

ramp rate, still compromise the ability to compare results and draw definitive conclusions. Thermal test procedures remain the most widely used form of sensory testing and mechanical testing remains, for the most part, unused, including; mechanical detection threshold, mechanical pain sensation, dynamic mechanical allodynia and wind-up ratio. This may be due to how user-friendly, safe and easily applicable thermal testing is. Furthermore, the absence of research examining wind-up ratio reduces the possibility of gaining insight into whether there is a central processing component. Specifically, central sensitization manifests as dynamic tactile allodynia, secondary punctate or pressure hyperalgesia, and enhanced temporal summation rather than thermal cutaneous pain, with most clinical pain states involving these aspects (Woolf, 2011). Therefore, to exclude these from a battery of tests is to exclude the possibility of understanding alterations in peripheral and central mechanisms that can contribute to the development and maintenance of pathological states.

Additionally, only one paper (Fründt et al., 2017) in the 46 eligible papers, utilised the DFNS QST battery (Rolke et al., 2006). Utilizing comprehensive psychophysical procedures across a range of modalities would allow for better across-study comparisons. It would also allow the development of sensitive indices whilst providing consistency in the approach to understanding these phenomena across conditions. The DFNS battery in particular provides this opportunity and is a valuable starting point, as it provides the potential for systematically comparing the function of small and large sensory afferents, quantification of the full sensory axis and comparison to known normative values. Although, it must be noted that this particular battery has been developed through considerable research to identify the most sensitive indices for neuropathic pain. Without such rigour it is not possible to fully appreciate the extent of any abnormality, specifically whether it may be systemic or modality specific.

Although such a definitive understanding is still not available, results of the reviewed studies indicate that pain processing may be altered in certain psychiatric groups. When considering the overarching question of whether changes in pain processing are present in

psychiatric conditions, it would appear that for individuals with schizophrenia, BPD and eating disorders, there is moderate evidence for hyposensitivity to pain and touch. A single study on ADHD (Treister et al., 2015) suggests that individuals may have a hypersensitivity to pain, however given the lack of further data, this needs to be considered very carefully. Lastly, for individuals with ASD the findings are inconsistent, with the possible exception of a hypersensitivity to vibrotactile stimuli. Furthermore, findings from each of these conditions suggest that these effects may be more complex, specifically, that effects are specific to a single site, stimulus intensity or are reliant on some other behaviour.

In the case of ASD, the psychophysical methods used to investigate pain sensations reveal no systematic evidence for hypo- or hyper-sensitivity in this population, and run contrary to current diagnostic criteria (APA, 2013), as well as clinical and parent reports that suggest a pain experience to stimuli (Militerni et al., 2000; Moore, 2014; Wing, 1976). While this may be in large part due to lack of investigation, it highlights the need for systematic protocols. The most reliable results stem from those studies which have utilised the standard QST protocol, specifically those by Fründt et al. (2017). This study not only utilised the methodology it standardised scores based on the published normative values, which means that a clinically significant hypo- or hyper-sensitivity can be determined. This is not to discount the other papers who utilised psychophysically robust methods of testing; Cascio et al. (2008); Duerden et al. (2015); and Fan et al. (2014), however, the utilisation of standard group comparisons may not be enough to determine true alterations. It is, therefore, clear that more research is required to understand further the nature of any differences and to reconcile the differences between *objective* measures and *observations* of behaviour.

The hyposensitivity reported in each of the other conditions appears to have different potential explanations. In eating disorders, changes in both tactile acuity and pressure detection thresholds appear more pronounced when examined on the abdomen (Keizer et al., 2012). Specifically, individuals had larger distance estimations and poorer tactile perception,

618 as measured by two-point discrimination, as well as a sensitivity to pressure detection. Both
619 these tests potentially indicate a cognitive deficit rather than sensitivity, however, those studies
620 reporting thermal hyposensitivity (Bär et al., 2013; de Zwaan, Biener, Schneider, et al., 1996;
621 Lautenbacher et al., 1990, 1991; Papezova et al., 2005; Yamamotova et al., 2009), at least for
622 this modality, suggest a true physiological deficit. Since recovering anorexic patients showed
623 thresholds returning to healthy control level during weight gain, altered thresholds appear to be
624 confined to acute phases of the condition, as reported by Bär et al. (2006). Symptom specific
625 effects are also relevant in considering individuals with BPD. During acute BPD episodes,
626 self-injury is a common behavioural dysregulation and those individuals under distress of self-
627 injury required higher temperature for thermal detection and pain thresholds (Ludäscher et al.,
628 2009; Schmahl et al., 2006), as well as reporting higher mechanical pain thresholds (Magerl et
629 al., 2012) than those not under distress of self-injury and healthy controls. Therefore, these
630 sensory deficits might, similarly be, acute phase specific. Unlike eating disorders, where
631 recovery is possible, there is no evidence that sensory changes return to typical levels once
632 symptoms reduce, as those who are not under distress of self-injury still have hyposensitivity in
633 comparison to healthy controls. This symptom effect is similarly present in schizophrenia
634 (Boettger et al., 2013; Jochum et al., 2006) and those with fewer positive symptoms e.g.
635 hallucinations and delusions required greater temperatures to report pain (Lévesque et al.,
636 2012).

637 Given the limited range of studies at present, it is premature to presume specific
638 mechanisms, which might underlie these psychiatric conditions. Understanding the specific
639 mechanisms behind these findings will however, be integral in utilizing pain behaviours to
640 further understand each disorder. Given the role of somatosensory processing and behavioural
641 differences in each disorder, altered pain behaviours may also be an extension of altered
642 somatosensory processing or associated with alterations in emotional regulation (Keefe,
643 Lumley, Anderson, Lynch, & Carson, 2001) or interoceptive abilities (Craig, 2003). Pain and

644 touch have inherent affective and motivational components (Williams & Craig, 2016) as well
645 as being a signal of problems in homeostatic regulation (Panerai, 2011). As these can all be
646 seen to be symptoms within psychiatric conditions it is possible therefore, that with the correct
647 application of individual differences research that pain might help to understand aspects of
648 these challenges in these conditions. Further, models have proposed pain and touch to be a
649 critical component of interoceptive abilities (Craig, 2003), suggested to be regulated by lamina
650 I spinal pathways (Craig, 2002), which are thought to be affected in a range of psychiatric
651 conditions (Mash et al., 2017; Murphy, Brewer, Catmur, & Bird, 2017). This provides a
652 potential mechanism for future research to explore, within understanding of susceptibility of
653 psychiatric conditions.

654 Rather than providing definitive answers to questions related to pain processing in
655 psychiatric conditions, this review more comprehensively highlights a number of implications
656 for researchers and clinicians. The first consideration for future research relates to the potential
657 role of general cognitive and emotional states in these populations. Specifically, as it is already
658 well established for depression and anxiety that mood is associated with pain responses
659 (Goesling et al., 2013), it would be prudent for future research into the psychiatric conditions
660 mentioned above to consider the relationship between mood and pain processing. This is
661 further in light of the fact that recent evidence has suggested that the relationship between
662 autism symptoms and pain behaviours was mediated by symptoms of anxiety and depression
663 (Garcia-Villamisar, Moore, & Garcia-Martinez, 2018). Additionally, difficulties with general
664 cognitive processing, specifically with executive control; an attentional system, is a hallmark of
665 many of these psychiatric conditions (Galimberti et al., 2013; Hill, 2004; Niendam et al., 2012)
666 and there are known links to pain experience (Eccleston & Crombez, 1999; Moore, Keogh, &
667 Eccleston, 2012). The somatosensory changes observed in eating disorders may also reflect
668 such a cognitive change. Here an attentional bias towards areas of bodily concern (i.e. the
669 abdomen) may increase sensitivity at this site. This may also explain why individuals no

longer show these hypersensitivities as they recover. More general cognitive processes, may therefore, mediate responses on these pain assessment measures. Evidence for this in the context of this review comes from Treister et al. (2015) who found that participants with ADHD who were currently un-medicated with Ritalin, showed hypersensitivity to pain, however, when these individuals were given medication these thresholds moved into the normal range. One potential explanation of these differences might be that clinical groups find it harder to attend to the task at hand, indeed effects often changed when the ramp rate of stimuli was also changed, suggesting that attention might be an important factor (Cascio et al., 2008; Duerden et al., 2015). It may also be the case that treatment with Ritalin helps to normalize homeostatic set-points across sensory and cognitive systems. For example, previous studies have suggested that rapid changes in attention, increased motor activity, and enhanced sensory sensitivity, may all be part of an auto-regulatory attempt to increase stimulation, in order to maintain homeostasis of brain arousal (Geissler, Romanos, Hegerl, & Hensch, 2014). Effective treatment (with Ritalin, for example) may obviate the need for such autoregulation, reducing sensory sensitivity, as well as behavioural and attentional hyperactivity (Geissler et al., 2014).

Medication being taken by these populations therefore, also might directly affect pain processing. Specifically, it opens up questions regarding any analgesic effects present. Given the percentage of individuals with a range of psychiatric conditions, who use pharmacological substances; which are known to act on the serotonergic system (Hurwitz, Blackmore, Hazell, Williams, & Woolfenden, 2012; Singh, Singh, Kar, & Chan, 2010). As well as many of these medications having known analgesic effects (Mico, Ardid, Berrocoso, & Eschalier, 2006), it is important to consider the role of these agents in altering pain processing. Several studies included in this review explicitly mention the use of non-medicated participants. However, few mention medication use, therefore, discounting the possibility of investigating this phenomenon thoroughly. More is needed regarding the management of challenging

behaviours, including both those thought to be related to pain (i.e. self-injurious behaviours) as well as other symptoms, to identify how management of clinical symptoms may alter pain response and how pain management strategies may help with clinical symptoms.

A further consideration is to carefully select appropriate control groups. Comparing psychiatric or pain patients with healthy controls can result in artificial amplification of QST differences that are unrelated to clinical state, as they do not represent the general population who are typically fraught with issues that can affect QST results for e.g. obesity (Coghill & Yarnitsky, 2015). This can confound significant results, especially considering the number of additional diagnosed or undiagnosed co-morbidities present in psychiatric conditions (Gillberg & Fernell, 2014). One potential approach could be to go beyond examining psychiatric groups' thresholds in relation to healthy controls and compare them with other experimental groups with specific psychiatric conditions. Several studies within this review considered a range of conditions or additionally looked at traits within these conditions. This approach could solve the amplitude issue and provide other areas of interest to be explored.

The present research however, is limited by this reliance on condition-based research and group-level analysis. Current research trends are moving away from such an approach with The National Institute of Mental Health (NIMH) developing a taxonomy, which proposes a trans-diagnostic approach to understanding mental health conditions. It might therefore be of value to examine for the underlying mechanisms which may result in these differences or pain processing more broadly, as a result of symptoms or traits, rather than conditions (Insel et al., 2010). There are also large individual differences within the general population with reference to somatosensory thresholds (Fillingim, 2005) that should be considered when investigating similar differences in individuals with a diagnosis; variability may be typical regardless of the diagnosis therefore caution should be adopted to ensure that such variability extends beyond that which is typically expected. Given these observations, future research may benefit from a more individualistic approach in examining these. Comparison with published normative

values (Magerl et al., 2010) allows for individual profiles to be developed and an understanding of potential links between individual psychiatric symptoms and somatosensory differences. As well as an understanding of the number of individuals within each condition who might be experiencing altered somatosensory interactions with external stimuli (either hyper- or hypo- sensitivity), including any individuals with typical function.

Another feature, which has received only limited indirect attention, is that of the developmental time course of the somatosensory symptoms in psychiatric conditions. Almost all studies included in this review examined participants in the age range of 18-30 years with IQ in the normal range. This is wholly understandable given that the tasks being presented require very specific responses, as well as being potentially distressing to younger children or individuals without the capacity to fully understand the procedures. This does, however, limit the generalisability and utility of these findings. Understanding the experience of pain in childhood is important, as it could clarify the development of any hyper- or hypo-sensitivity, or the change from an early a-typicality to a potentially more typical somatosensory profile in adulthood, or the reverse. Further, it is well known that conditions associated with pain have a progression into old age (Brattberg, Parker, & Thorslund, 1997), and it appears that both sensory and pain thresholds increase with age (Magerl et al., 2010). It would therefore be beneficial to further understand the progression of pain sensitivity and response into older adulthood in individuals with psychiatric conditions.

In conclusion, this review highlights the needs for ongoing work that has methodological rigour. Researchers utilising sound psychophysical methods and carefully reporting the methods can achieve this. In doing so, research can develop individual profiles, as well as facilitate comparisons across studies that involve other psychiatric conditions, physical health conditions and healthy controls. This will provide the more precise results required to form conclusions that are more definitive. Experimental investigations of pain can detect or verify altered processing as a symptom and can provide insights into the behavioural

748 consequences (Lautenbacher & Krieg, 1994), which in turn would help to provide the grounds
749 for accurate interventions to assist in alleviating symptoms. Overall, the findings in the current
750 review suggest somatosensory hyposensitivity in schizophrenia, eating disorders, and
751 personality disorders. More investigation that is systematic will correct views based on
752 inconsistent research, anecdotal and clinical case study views, or support these findings and
753 potentially lead to better clinical pain management in vulnerable groups.

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Figure Legend

Figure 1. Number of identified publications at each phase of the screening process. Adapted 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.

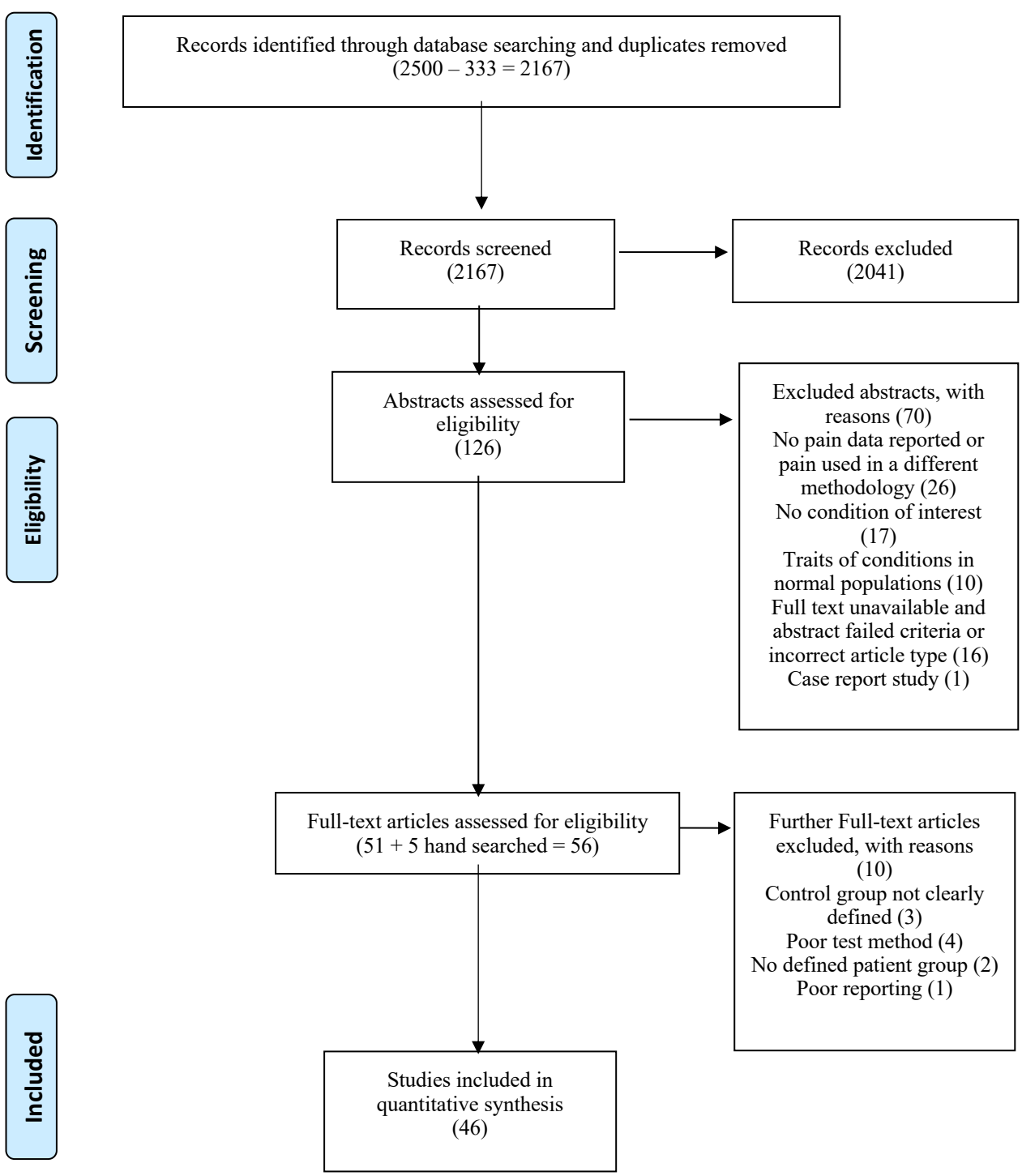

Table 1: Electronic search strategy.

PHASE	TERMS
1. SPECIFIC SEARCH TERMS FOR DSM-5 PSYCHIATRIC CONDITIONS.	ASD Autism Spectrum Disorder Autism Asperger's ADHD Attention Deficit Hyperactivity disorder ADD Attention Deficit Disorder PD Personality Disorder BPD Borderline Personality Disorder Schizophrenia Anorexia Nervosa Bulimia Nervosa Binge-eating disorder OCD Obsessive Compulsive Disorder Post-traumatic Stress Disorder PTSD Depression Anxiety
2. SPECIFIC SEARCH TERMS FOR PAIN/SOMATOSENSATION AND QST.	QST Quantitative Sensory Testing Experimental pain Nociception Nociceptors Aδ A-delta C-fibres C-fiber Thermal pain Somatosensation Pain thresholds Thermal detection Tactile detection Mechanical pain Dynamic mechanical allodynia Wind-up ratio Vibration detection Pressure pain Two point discrimination Electrocutaneous Cold pressor
3. COMBINATION OF PHASES 1 AND 2.	----
DSM = DIAGNOSTIC STATISTICAL MANUAL QST= QUANTITATIVE SENSORY TESTING	

1108 **Table 2: Detailed reported results for each study listed by QST test for autism spectrum disorder (ASD).**

Test	Citation	Sample	Control	Matched	Results
CDT	Cascio et al. (2008)*	8 ASD	8 HC	Age Gender	No significant main effects, group differences or interactions.
	Duerdan et al. (2015)*	20 ASD	55 HC	Age Gender	Significant group differences, ASD lower threshold than HC.
	Frundt et al. (2017)*	13 ASD	13HC	Age Gender IQ >70	No significant group differences.
WDT	Cascio et al. (2008)*	8 ASD	8 HC	Age Gender	Showed lower threshold for palm (1.61°C) than forearm (2.91°C) no significant group differences.
	Duerdan et al. (2015)*	20 ASD	55 HC	Age Gender	Significant group differences, ASD increased threshold compared to HC.
	Frudnt et al. (2017)*	13 ASD	13 HC	AGE Gender IQ >70	No Significant group differences
TSL	Frundt et al. (2017)*	13 ASD	13 HC	Age Gender IQ >70	No significant group differences
PHS	Frundt et al. (2017)*	13 ASD	13 HC	Age Gender IQ >70	No significant group differences
CPT	Cascio et al. (2008)*	8 ASD	8 HC	Age Gender	Main effect of site and group; ASD threshold 16.68°C compared to HC 9.04°.
	Duerdan et al. (2015)*	20 ASD	55 HC	Age Gender	No significant group differences.
	Frundt et al. (2017)*	13 ASD	13 HC	Age Gender IQ >70	No significant group differences
HPT	Cascio et al. (2008)*	8 ASD	8 HC	Age Gender	Sig group effect; ASD lower threshold 43.66°C than HC 46.58°C, paired with lower thresholds on the thenar palm than the forearm. Interaction effect reflected ASD had higher thresholds (by 1.86°C, on average) on the second day of testing as compared to the first, HC remained stable.

	Duerdan et al. (2015)*	20 ASD	55 HC	Age Gender	No significant group differences.
	Frundt et al. (2017)*	13 ASD	13 HC	Age Gender IQ >70	No significant group differences
MDT	Cascio et al. (2008)*	8 ASD	8 HC	Age Gender	Sig lower on palm than forearm for both groups with a significant increase seen on the second day.
	Frundt et al. (2017)*	13 ASD	13 HC	Age Gender IQ >70	Significant group difference with a greater loss of function for mechanical detection in ASD patients that, nevertheless, did not survive Bonferroni correction
	Riquelme et al. (2016)	27 ASD	30 HC	Age	Significant group*body location*body side interaction. HC had significantly higher thresholds than ASD in the left face and right hand dorsum. Three body locations sig different (face< hand palm< hand dorsum) in HC, whereas only face< hand palm and, face< hand dorsum sig diff in ASD. No sig difference in body side in ASD.
MPT	Frundt et al. (2017)*	13 ASD	13 HC	Age Gender IQ >70	No significant group differences
MPS	Frundt et al. (2017)*	13 ASD	13 HC	Age Gender IQ >70	No significant group differences
DMA	Frundt et al. (2017)*	13 ASD	13 HC	Age Gender IQ >70	No significant group differences
WUR	Frundt et al. (2017)*	13 ASD	13 HC	Age Gender IQ >70	No significant group differences
VDT	Blakemore et al. (2006)	32 HF ASD	41 HC	Age IQ	AS hypersensitive to 200Hz compared to HC.
	Cascio et al. (2008)	8 ASD	8 HC	Age Gender	Main effect of site for 33Hz with ASD having 34% lower thresholds than HC on the forearm, decreasing on 2nd day.
	Guclu et al. (2007)	6 ASD	6 HC	Age Gender	No sig group difference at the unmasked 40Hz, 250Hz unmasked or masked 40Hz.
	Frundt et al. (2017)*	13 ASD	13 HC	Age Gender	No significant group differences

				IQ >70	
PPT	Fan et al. (2014)*	44 ASD	41 HC	Age Gender IQ	ASD individuals more sensitive than HC.
	Frundt et al. (2017)*	13 ASD	13 HC	Age Gender IQ >70	No significant group differences
	Riquelme et al. (2016)	27 ASD	30 HC	Age	Main group effect, showing lower thresholds in ASD than HC.
	Chen et al. (2017)	37 ASD 26 CDS	34 HC	Age Gender IQ >90	Significant difference between all groups, mean rank from lowest to highest ASD, HC and CDS.
ELE	Bird et al. (2010)*	18 AS	18 HC	Alexithymia Age IQ	Main effect of pain. No group diff. Unpleasantness for low and high pain main effect of pain Sig interaction pain*group. Sig group differences for ratings of low pain self and other. ASD judged unpleasantness of stimulation to be zero compared to controls.
	Gu et al. (2017)	17 ASD	17 HC	Age Gender IQ >80	Significant group differences with ASD lower stimulation levels than HC.
Psychometrics	Duerdan et al. (2015)	20 ASD	55 HC	Age Gender	Significant correlation with Autism severity and WDT as well as CDT. IQ was correlated to WDT, CDT and HPT.
	Guclu et al. (2007)	6 ASD	6 HC	Age Gender	Sig correlation between sensory profile and touch inventory and between the tactile and emotional subsets of the Sensory Profile. Significant correlation between the touch inventory test and the tactile subset of the sensory profile. Those individuals who scored higher, suggesting emotional problems (according to the SP), have more tactile problems (according to the SP) and display more tactile defensiveness behaviours according to the TI.

NOTES: * indicates standardised DFNS QST protocol used. ASD (Autism Spectrum Disorder), AS (Asperger's) and HC (Healthy Control). CDT (Cold Detection Threshold), WDT (Warm Detection Threshold), PHS (Paradoxical Heat Sensations), TSL (Thermal Sensory Limen), CPT (Cold Pain Thresholds), HPT (Heat Pain Threshold), MDT (Mechanical Detection Threshold), MPT (Mechanical Pain Threshold), MPS (Mechanical Pain Sensation), DMA (Dynamic Mechanical Allodynia), WUR (Wind-Up Ratio), VDT (Vibration Detection Threshold), PPT (Pressure Pain Threshold), and ELE (Electrical Pain Stimulation).

Table 3: Detailed reported results for each study listed by QST test for Schizophrenia.

Test	Citation	Sample	Control	Matched	Results
WDT	Jochum et al. (2006)	23 SCH	23 HC	Age Gender Handedness	Significant group differences, Schizophrenic patients indicated perception for warmth later than controls.

CPT	Boettger et al. (2013)	18 SCH	18 HC	Age Gender	Significant group differences on both palms, with SCH showing higher thresholds than HC. No significant group differences on VAS scores.
HPT	Boettger et al. (2013)	18 SCH	18 HC	Age Gender	Significant group differences on both palms, with SCH showing higher threshold than HC No significant differences on VAS scores. Significant group differences on thermal grill thresholds, with greater temperature differentials required by SCH group to elicit a painful response. No significant group differences on VAS scores instead the stimulus response curve of TGI pain perception was shifted towards higher stimulus intensities.
	de la Fuente-Sandoval et al. (2010)	12 SCH	13 HC	Age Gender Handedness	SCH reported higher WPT than HC, but no group differences for intensity or unpleasantness ratings.
	de la Fuente-Sandoval et al. (2012)	12 SCH	13 HC	Age Gender Handedness	No group differences for thermal pain tolerance or intensity and unpleasantness ratings
	Dworkin et al. (1993)		19 HC	Age	Sig group differences for thermal d' at lower (warm) and higher (hot-pain), showing SCH poorer at sensory discrimination. No group differences on response bias Inβ.
	Jochum et al. (2006)	13 SCH	23 HC	Age Gender Handedness	Significant group differences with SCH showing higher threshold for heat pain.
	Potvin et al. (2008)	23 SCH	29 HC	Age Gender Ethnicity	No sig group differences for tonic thermal pain but scores were lower in SCH. Windup ratio, time was a positive significant predictor of pain in controls, but not SCH. Diffuse noxious inhibitory control effects in patients and controls, showed a sig effect of time, however, the interaction between time and group did not emerge as significant.
		23 SCH			
PPT	Girard et al. (1994)	35 SCH	35 HC	Age Gender	For the fixed pressure, VAS score was higher in SCH than HC. Step by step pressure and P3 (p is the pressure relating to 3 on the VAS scale) was lower for schizophrenics than HC. Ischemia induction test showed schizophrenics were more sensitive than HC.
ELE	Guieu et al. (1994)	10 SCH	10 HC	Age Gender	Correlation between nociceptive flexion reflex threshold and subjective pain threshold for individuals with SCH. No group differences in Pain threshold.
	Kudoh et al. (2000)	50 SCH	25 HC	Age	Cutaneous thresholds for 2,000 Hz, 250 Hz, and 5 Hz in SCH were significantly higher than HC. No significant differences in conduction thresholds between SCH groups. VAS scores for SCH at 2 and 5 hours post operatively were significantly lower than HC.
	Levesque et al. (2012)		11 HC		Schizophrenic participants had a much lower electrocutaneous pain threshold than healthy control. Reflex threshold trend demonstrates lower withdrawal for SCH though no sig group differences reported.

		12 SCH			Significant increases in subjective pain sensitization pain ratings as a function of increasing frequency for SCH and HC. Sig group difference with SCH showing less pain sensitization than controls. Withdrawal reflex response/pain sensitivity: Within groups NFR responses increased significantly as a function of increasing stimulation but no sig group differences.
CP	Atik et al (2007)*	27 SCH 30 BP	59 HC	Age Gender Handedness	Cp threshold, tolerance, magnitude and endurance had significant group differences. Post hoc tests revealed that SCH group had higher threshold and lower magnitude than the BP group (who had the lowest), but not to HC. They also had highest tolerance compared to both HC and BP, who again had lowest. They also had the longest endurance times compared to HC, but did not differ to BP.
	Potvin et al (2008)	23 SCH	29 HC	Age Gender Ethnicity	No significant group differences.
Psychometrics	Dworkin et al. (1993)	13 SCH	19 HC	Age	In SCH group sig correlation for lower intensity stimuli and positive symptoms and affective flattening, indicating that higher criteria for reporting painfulness were associated with fewer positive symptoms. Pain threshold was negatively correlated with positive symptoms.
	Levesque et al. (2012)	12 SCH	11 HC		

NOTES: * indicates standardised DFNS QST protocol used. SCH (Schizophrenia), BP (Bi-polar) and HC (Healthy Control). CDT (Cold Detection Threshold), WDT (Warm Detection Threshold), PHS (Paradoxical Heat Sensations), TSL (Thermal Sensory Limen), CPT (Cold Pain Thresholds), HPT (Heat Pain Threshold), MDT (Mechanical Detection Threshold), MPT (Mechanical Pain Threshold), MPS (Mechanical Pain Sensation), DMA (Dynamic Mechanical Allodynia), WUR (Wind-Up Ratio), VDT (Vibration Detection Threshold), PPT (Pressure Pain Threshold), and ELE (Electrical Pain Stimulation).

Table 4: Detailed reported results for each study listed by QST test for personality disorder.

Test	Citation	Sample	Control	Matched	Results
CDT	Ludascher et al. (2009)*	24 BPD (13 SIB 11 non-SIB)	24 HC	Gender	No significant group differences.
	Ludascher et al. (2014)*	20 BPD	20 HC	Age Gender	No significant group differences.

WDT	Ludascher et al. (2009)*	24 BPD (13 SIB 11 non-SIB)	24 HC	Gender	No significant group differences.
	Ludascher et al. (2014)*	20 BPD	20 HC	Age Gender	No significant group differences.
CPT	Ludascher et al. (2009)*	24 BPD (13 SIB 11 non-SIB)	24 HC	Gender	Significant group differences, BPD-SIB had highest thresholds. BPD (including BPD-SIB and BPD-non-SIB) were higher than HC. Correlation showed extreme values for CPT were found in the BPD-SIB group. Sig main effect of group for detection thresholds, pain thresholds and intensity ratings for laser radiant heat stimuli. Post-hoc contrasts were sig for detection thresholds, pain thresholds and heat pain ratings. BPD-SIB showed lowest pain sensitivity. BPD (SIB and non-SIB) were lower than HC.
	Ludascher et al. (2014)*	20 BPD	20 HC	Age Gender	Significant effect for group factor, with BPD showing lower CPT temperatures required for pain.
	Schmahl et al. (2010)*	16 BPD 16 PTSD 20 BN	24 HC	Age Gender	High significant group differences for CPT, with BPD having higher threshold than HC. No sig difference between baseline and after stress pain thresholds.
HPT	**Ludascher et al. (2009)	24 BPD (13 SIB 11 non-SIB)	24 HC	Gender	Significant group differences, BPD-SIB had highest thresholds. BPD (including BPD-SIB and BPD-non-SIB) were higher than HC. Correlation showed extreme values for HPT were found in the BPD-SIB group.
	Ludascher et al. (2014)*	20 BPD	20 HC	Age Gender	Significant effect for group factor, with BPD showing highest HPT.
	Schmahl et al. (2006)	12 BPD	12 HC	Age Gender	BPD had lower pain sensitivity to tonic heat than controls. The mean temperature causing perceived pain intensity of NRS 40 was found to be 46.7 ±0.4°C for patients and 44.2 ±0.6°C for controls and a reduced offset of the stimulus-response function in patients, suggesting there was a downward shift of the stimulus-response function in patients by approximately 30 points on the NRS.
	Schmahl et al. (2010)*	16 BPD 16 PTSD 20 BN	24 HC	Age Gender	Trend towards BPD having higher thresholds than HC, no significant main effect. Sig interaction group*condition for WPT, indicating an accentuation of possible hypoalgesia in BPD patients under stress.
	Schmahl et al. (2004)	10 BPD	14 HC	Gender	Laser detection and pain thresholds were elevated in BPD patients compared to HC.
MPS	Magerl et al. (2012)	22 BPD	22 HC	Age Gender	BPD pain threshold sig higher than HC for individual threshold estimation. Pain threshold at 50% incidence was 74% higher in BPD than HC. Pain reports in BPD were sig lower at any force. SIB and pinprick threshold sig correlated, suprathreshold and SIB sig group effect, no difference in pain measures and intensity. Pain sent stratified by SIB severity, frequent SIB less sensitive to pain.

ELE	Fedora, & Reddon (1993)	28 BPD	28 HC	Age Gender	BPD groups were significantly higher than HC for pain thresholds. Negative correlation between pain thresholds and degree of monotony avoidance in psychopathic patients, with the highest thresholds recorded in those who were the lowest thrill seekers.
	Ludascher et al. (2007)*	12 BPD	12 HC	Age Gender	No sig group differences for electrical detection thresholds. BPD had sig higher pain threshold than HC.
TPD	Pavony & Lenzenweger (2014)*	27 BDP 20 MDD	44 HC		No significant group differences.
CP	Bohus et al. (2000)	12 BPD	19 HC	Age Gender	HC vs BPD-C and D sig main effect of group on intensity and unpleasantness. Sig effects of time on intensity and unpleasantness ratings.
	McCown et al (1993)*	20 BPD 20 OPD	20 HC	Age Gender	No sig difference between group initial tolerances. Sig group differences, where BPD had longest post immersion voluntary exposure compared to OPD and HC.
	Pavony & Lenzenweger (2014)*	27 BPD 20 MDD	44 HC		No sig group differences for threshold. Sig group differences, BPD had higher tolerance and endurance compared to HC and MDD.
Psychometrics	Ludascher et al. (2009)	24 BPD (13 SIB 11 non-SIB)	24 HC	Gender	Sig positive correlation with pain intensity ratings and symptom severity.
	Ludascher et al. (2007)	12 BPD	12 HC	Age Gender	Pain threshold sig correlated to trait dissociation, state dissociation and aversive arousal in patients but not HC.

NOTES: * indicates standardised DFNS QST protocol used. **used both standard and comparable pain induction methods. BPD (Borderline Personality Disorder), PTSD (Post-Traumatic Stress Disorder), SIB (Self-Injurious Behaviour), BN (Bulimia Nervosa), MDD (Major Depressive Disorder), OPD (Other Personality Disorder) and HC (Healthy Control). CDT (Cold Detection Threshold), WDT (Warm Detection Threshold), PHS (Paradoxical Heat Sensations), TSL (Thermal Sensory Limen), CPT (Cold Pain Thresholds), HPT (Heat Pain Threshold), MDT (Mechanical Detection Threshold), MPT (Mechanical Pain Threshold), MPS (Mechanical Pain Sensation), DMA (Dynamic Mechanical Allodynia), WUR (Wind-Up Ratio), VDT (Vibration Detection Threshold), PPT (Pressure Pain Threshold), and ELE (Electrical Pain Stimulation).

Table 5: Detailed reported results for each study listed by QST test for eating disorders.

Test	Citation	Sample	Control	Matched	Results
CDT	Pauls et al. (1991)	9 AN 10 BN	10 HC	Gender	No significant group differences.
WDT	Pauls et al. (1991)	9 AN 10 BN	10 HC	Gender	No significant group differences.
HPT	Bar et al. (2006)*	14 AN	15 HC	Gender	Sig group main effect, sig group*time interaction for heat pain threshold, where patients had higher thresholds than HC, with results remaining significant even after controlling for skin temperature.
	Bar et al. (2013)*	19 AN	19 HC	Age Gender Smoking	Overall significant group differences for thermal pain on both forearms, with sig diff between patients and HC for WPT on the right and left, with patients averaging 2 degrees higher than HC.

				Coffee Education	
	De Zwaan et al. (1996)	40 ED	32 HC		Patients had significantly higher threshold for thermal pain compared to HC. M threshold for pressure sig related to M threshold to thermally induced pain.
	Krieg et al. (1993)	23 AN	41 HC	Gender	No group differences for warm pain threshold. All groups had clearly lower mean pain thresholds than the patients with acute anorexia nervosa and bulimia nervosa from their previous study. Pain threshold sig correlated to skin temp in recovered anorexics with intermediate recovery outcome.
	Lautenbacher et al. (1990)	10 AN 10 BN	10 HC	Gender	Sig group diff for phasic pain thresholds but not tonic. Warm pain threshold for anorexic and bulimic patients was sig higher under phasic and tonic compared to healthy controls. No other group comparison was sig.
	Lautenbacher et al (1991)	19 AN 20 BN	21 HC	Gender	Sig group differences in pain thresholds, with both Anorectic and bulimic patients having higher warm pain thresholds than HC.
	Papezova et al. (2005)	39 ED	17 HC	Gender	PT detection latencies were highly correlated within subjects. Sig group differences where eating disorders had higher pain thresholds than HC, specifically Bulimia nervosa and binge-purge anorexia, restrictive anorexia did not differ. Sig linear trend with progression from HC to restrictors to bulimics to binge purge.
	Yamamotova et al. (2009)	21 BN	21 HC	Gender BMI	Sig main effect of group, a significant main effect of condition and a significant condition*group interaction. The main effect of group was due to higher pain thresholds in BN than HC on all six measurements.
	Schmahl et al. (2010)	20BN 16BPD 16PTSD	24 HC	Age Gender	No significant group differences
	Pauls et al. (1991)	9 AN 10BN	10 HC	Gender	Significant group differences where both patient groups had higher thresholds, no significant group*site interaction.
	De Zwaan et al. (1996)	22AN 18BN	32 HC	Gender	Significant group differences for thermal pain thresholds where AN and BN patients had higher thresholds than HC.
PPT	De Zwaan et al. (1996)*	40 ED	32 HC		Patients had significantly higher threshold for pressure pain compared to HC. M threshold for pressure sig related to M threshold to thermally induced pain.
	Raymond et al. (1999)*	43 AN	65 HC	Gender	AN group had higher baseline PDT than controls, with age acting as the covariate.
	De Zwaan et al. (1996)	22AN 18BN	32 HC	Gender	Mechanical pain thresholds were significantly higher in patients than HC.
	Faris et al. (1992)	27BN	31 HC	Gender	Both pressure detection and pain thresholds were significantly higher in in BN than HC.

	Raymond et al. (1995)	27BED 33 Ob	44 HC	Gender	Significantly higher detection thresholds in patients than HC, but no significant difference for pain threshold.
VDT	Pauls et al. (1991)	9 AN 10 BN	10 HC	Gender	No significant group differences.
TPD	**Keizer et al. (2012)	25 AN	28 HC	Gender Age	For Tactile Estimation there was a sig main group effect, body part effect and a body part*group interaction. Post hoc showed distance estimation for arm and abdomen were larger in patients than controls. Patients had sig higher TPD than controls. There was no sig main group effect for detection and a significant body part*group interaction. Post hoc test showed patients had sig diff PDT for the abdomen but not arm compared to HC. PDT for arm and abdomen diff sig in patients.
Psychometrics	Bar et al. (2013)	19 AN	19 HC	Age Gender Smoking Coffee Education	Significant negative correlation for pain ratings and symptom severity.

NOTES: * indicates standardised QST protocol used. **used both standard and comparable pain induction. AN (Anorexia Nervosa), BN (Bulimia Nervosa), ED (Eating Disorder), BPD (Borderline Personality Disorder), PTSD (Post-Traumatic Stress Disorder), BED (Binge Eating Disorder), Ob (Obese) and HC (Healthy Control). CDT (Cold Detection Threshold), WDT (Warm Detection Threshold), PHS (Paradoxical Heat Sensations), TSL (Thermal Sensory Limen), CPT (Cold Pain Thresholds), HPT (Heat Pain Threshold), MDT (Mechanical Detection Threshold), MPT (Mechanical Pain Threshold), MPS (Mechanical Pain Sensation), DMA (Dynamic Mechanical Allodynia), WUR (Wind-Up Ratio), VDT (Vibration Detection Threshold), PPT (Pressure Pain Threshold), and ELE (Electrical Pain Stimulation).