



## UvA-DARE (Digital Academic Repository)

### Wired for pain, shaped by the mind

*Interactions between pain and psychopathology in pediatric and adult patient populations*

van der Heijden, H.C.

#### Publication date

2025

[Link to publication](#)

#### Citation for published version (APA):

van der Heijden, H. C. (2025). *Wired for pain, shaped by the mind: Interactions between pain and psychopathology in pediatric and adult patient populations*. [Thesis, fully internal, Universiteit van Amsterdam].

#### General rights

It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

#### Disclaimer/Complaints regulations

If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: <https://uba.uva.nl/en/contact>, or a letter to: Library of the University of Amsterdam, Secretariat, P.O. Box 19185, 1000 GD Amsterdam, The Netherlands. You will be contacted as soon as possible.

# CHAPTER 4

CHARACTERIZATION OF PAIN AND SOMATIZATION AND ITS  
RELATIONSHIP WITH PSYCHOPATHOLOGY IN EARLY ONSET  
PSYCHOSIS

---

---

# CHARACTERIZATION OF PAIN AND SOMATIZATION AND ITS RELATIONSHIP WITH PSYCHOPATHOLOGY IN EARLY ONSET PSYCHOSIS

---

Hanne van der Heijden<sup>a\*</sup>, Maria Goldman<sup>b\*</sup>, Aliza Ray MS<sup>c</sup>, Emma Golden BS<sup>a</sup>,  
Carter R. Petty MA<sup>c</sup>, Emma Deaso BS<sup>d</sup>, Margaret Hojlo BA<sup>b</sup>, Navil Sethna, MD<sup>a</sup>,  
David C. Glahn PhD<sup>b,d,e</sup>, Joseph Gonzalez-Heydrich MD<sup>b,d,e,#</sup>, Jaymin Upadhyay  
PhD<sup>a,f,#</sup>

\*Denotes equal contribution

#Shared senior authorship

<sup>a</sup>Department of Anesthesiology, Critical Care, and Pain Medicine, Boston Children's Hospital, Harvard Medical School, Boston, MA,

<sup>b</sup>Department of Psychiatry and Behavioral Sciences, Boston Children's Hospital, Harvard Medical School, Boston, MA,

<sup>c</sup>Biostatistics and Research Design Center, Boston Children's Hospital, Boston, MA,

<sup>d</sup>Early Psychosis Investigation Center, Boston Children's Hospital, Harvard Medical School, Boston, MA,

<sup>e</sup>Tommy Fuss Center for Neuropsychiatric Disease Research, Boston Children's Hospital, Harvard Medical School, Boston, MA,

<sup>f</sup>Department of Psychiatry, McLean Hospital, Harvard Medical School, Belmont, MA

Published September 7, 2024, PMID: 39260111



## **Abstract**

**Background:** Early onset psychosis (EOP) frequently presents with a severe clinical phenotype and poor long-term prognosis. Clinical experience suggests that individuals with EOP have abnormal pain and somatosensory processing, yet relative to adult-onset psychosis, pain and somatic sensory processing in EOP have rarely been studied.

**Methods:** The history of two characteristic patients is described to illustrate clinical presentations of pain in EOP patients. Furthermore, 31 patients with EOP were studied with self-reported questionnaires informing on pain severity, pain catastrophizing, central sensitization, and somatization. Structured clinical interviews were administered to confirm Diagnostic and Statistical Manual of Mental Disorders-5 EOP diagnosis and the patient's dimensions of psychopathology were measured by the Brief Psychiatric Rating Scale (BPRS).

**Results:** Out of 31 EOP patients, 22 reported distressing pain, where higher pain severity corresponded with greater BPRS total and affectivity and resistance subscale scores. The degree of psychopathology was associated ( $N=31$ ;  $p < 0.05$ , FDR-corrected) with the magnitude of pain catastrophizing, central sensitization, and somatization. Multivariate analysis revealed relationships ( $N=31$ ;  $p < 0.05$ , FDR-corrected) between BPRS subscale (negative symptoms and activation) scores with somatization severity. The observed associations occurred independent of antipsychotic medication usage as quantified by chlorpromazine equivalent doses.

**Conclusions:** Pain and somatosensory symptoms could be a frequent cause of distress in patients with EOP and their severity associated with the degree of psychopathology. Future studies should determine if treating pain and somatic symptoms in EOP patients can lead to better control of psychosis as well as improve quality of life.

## Introduction

Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5) psychotic disorders are characterized by hallucinations, delusions, and thought disorder occurring either mostly during abnormal mood episodes in bipolar and major depressive disorders or also outside of depressive or manic episodes in schizophrenia spectrum disorders including schizoaffective disorder (American Psychiatric Association, 2013). Approximately 20% of individuals with a psychotic disorder experience their initial psychotic episode before 18 years of age (early onset psychosis, EOP). Patients with EOP demonstrate poorer long-term prognosis and higher rates of residual symptoms and disability relative to cases of adult-onset psychosis<sup>1-3</sup>. They also have higher rates of identifiable rare predicted impactful genetic variation<sup>4</sup>. Our experience suggested that patients with EOP often report pain, which is not explained by acute injury or objective findings. In adults, clinical and epidemiological investigations revealed that co-occurring pain syndromes are prevalent in bipolar disorder (BD), where clinical pain is linked to worsened psychiatric symptoms, psychosocial impairment, increased mood episodes, and higher risk of suicidality as<sup>5,6</sup>. Conversely, adults with schizophrenia spectrum disorder (SZ) may exhibit reduced pain sensitivity<sup>7</sup>. Pain and somatosensory symptoms in EOP have rarely been studied. Based on clinical observations, our working hypothesis is that distress from uncomfortable somatic sensations and pain experienced by patients with EOP may exacerbate the severity of other symptoms associated with the illness and, in a cyclical manner, worsen a patient's overall mental and physical health. Herein, we present two cases illustrative of our clinical observations as well as a systematic and prospective assessment of a cohort of individuals with EOP. For the cohort evaluation, we administered questionnaires-based measures of pain and psychopathology first to determine possible associations among these two domains in EOP, which would motivate more intensive laboratory investigation in follow-up studies. We specifically probed pain severity,

pain-related constructs (e.g., pain catastrophizing), central sensitization, somatization and psychopathology in children with EOP.

## **Materials and Methods**

This study was approved by the Boston Children's Hospital (BCH) Institutional Review Board. Patients were recruited as part of the Early Psychosis Investigation Center and Developmental Neuropsychiatry Clinic at BCH. Patients and their legal guardian provided informed written assent and consent, respectively. To illustrate clinical observations, medical histories derived from chart reviews of the electronic medical record are presented for two patients with EOP and pain and somatosensory symptoms. To further elucidate the relation between pain and psychopathological symptoms, 31 EOP participants aged 7 to 17 years were prospectively enrolled (mean age [standard deviation]: 13.5 [2.8]). EOP diagnosis was confirmed through a combination of the Structured Clinical Interview for DSM-5 Axis I diagnosis (SCID-5) supplemented by portions of the Kiddie-SADS-Present and Lifetime Version<sup>8</sup> and review of previous psychiatric evaluations. Individuals that reported recent acute injury were excluded. The Brief Psychiatric Rating Scale (BPRS, 18-item), with subscales of positive symptoms, negative symptoms, affectivity, activation and resistance, was used to quantify psychopathology<sup>9</sup>. Lastly, the following questionnaire battery was administered to assess the presentation of pain-related symptoms, based on self-reports with assistance by study personnel if needed: Pain-Frequency-Severity-Duration (PFSD) Scale, an assessment of a pain amplification state over 2 weeks<sup>10</sup>; Pain Catastrophizing Scale (PCS, Child), a 13-item scale informing on the patient's magnification, helplessness and renumeration with regards to their pain<sup>11</sup>; Central Sensitization Inventory (CSI), a 25-item scale used to determine severity of centralized pain<sup>12</sup>; Children's Somatization Inventory (CSI-24, Child), a self-report of somatic

symptoms over 2 weeks<sup>13</sup>. Given the sample size of 31, we have 80% power to detect correlations of 0.48 (assuming unadjusted alpha=0.05). Pearson correlation coefficients and multivariate linear regressions were calculated to determine associations among study measures. Because the CSI and CSI-24 measure similar constructs and were highly correlated (R=0.89), only the CSI-24 was used in multivariate analyses. To correct for multiple comparisons, adjusted p-values were calculated using the Benjamini & Hochberg linear step-up procedure (false discovery rate (FDR;  $\alpha=0.05$ )). Medications for each participant at the time of questionnaire completion were noted and antipsychotic dosages were converted to Chlorpromazine (CPZ) equivalents. Statistical analysis was performed with SAS software, version 9.4 (SAS Institute Inc).

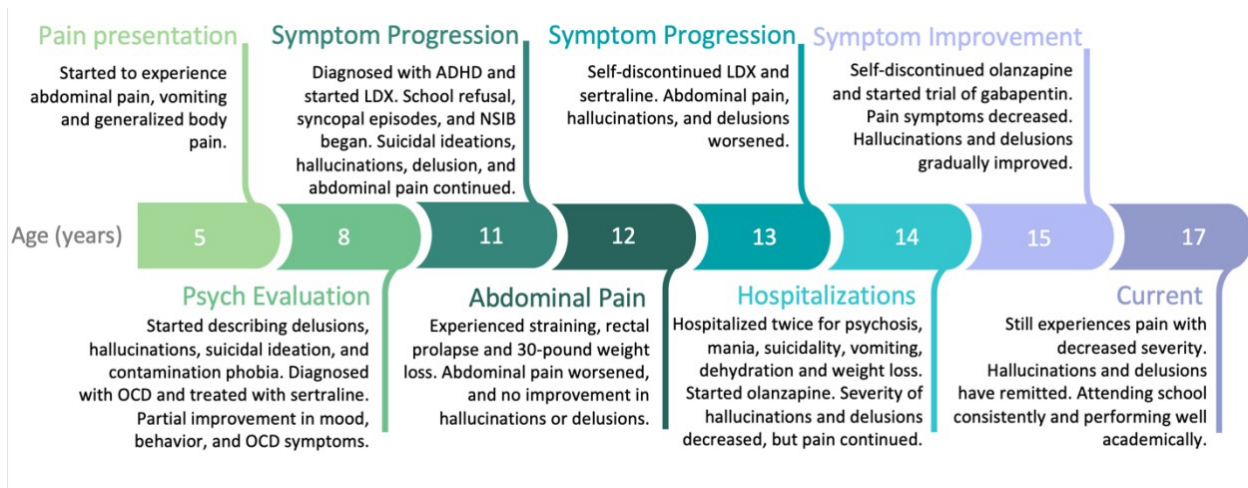
## Results

### Clinical Vignettes

**EOP Patient 1:** Patient 1 is a 17-year-old white non-Hispanic cisgender male with no known history of maltreatment or trauma who complained of persecutory hallucinations from age 8 until 15. Birth and development to age 5 was normal. At age 5, he complained weekly about abdominal pain, vomiting, and generalized body pain (**Figure 1**). At age 8, he developed a contamination phobia with excessive handwashing, suicidal ideation, paranoid delusions, and persecutory hallucinations not consistent with cultural or familial beliefs. He was diagnosed with obsessive compulsive disorder (OCD) and treated with sertraline 150 mg/day. Mood, behavior, and OCD symptoms ameliorated. However, paranoid delusions, hallucinations, and pain continued.

Subsequent diagnoses, treatments, and the results preceded as follows: at age 11 diagnosed attention-deficit hyperactivity disorder (ADHD) and given lisdexamfetamine (LDX) 30 mg/day during which

symptoms worsened coinciding with school refusal, non-suicidal self-injurious behavior, and monthly syncopal episodes. At age 12, he experienced more severe abdominal pain, straining, rectal prolapse, a 30-pound weight loss, and continued precursory hallucinations and delusions. At age 13, patient self-discontinued LDX and sertraline which was followed by worsened abdominal pain, hallucinations, and delusions. Age 14, he was hospitalized twice for psychosis, mania, suicidality, vomiting, dehydration and weight loss. He initially refused psychotropic medications except for cannabidiol oil, which had no effect on pain, but improved his anxiety. He took olanzapine 5 mg/day for 8 months. This decreased severity of hallucinations, delusions and aggression, but pain continued with a self-reported pain level of 8-9 on a 0- 10 rating scale. At age 15, he refused further antipsychotic treatment, but agreed to a trial of gabapentin 1200 mg/day with pain decreased and hallucination abated. He has maintained this remission for 2 years. Having had persistent school refusal since the age of 11, now at age 17, he is attending school consistently and performing well academically and socially.

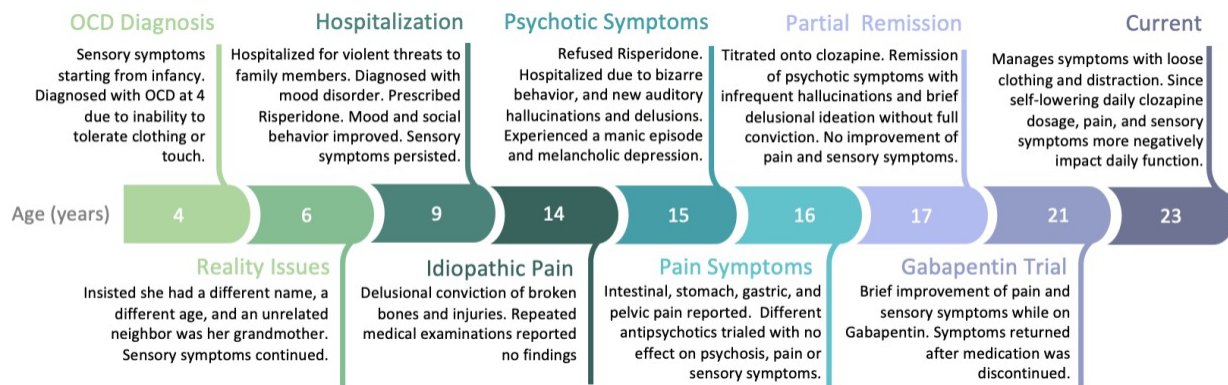


**Figure 1. Clinical history and timeline of EOP Patient 1.** Patient 1 started to experience pain at the age of 5, and psychiatric symptoms were first diagnosed at the age of 8. The trajectory of psychiatric and somatosensory symptoms over the next years are summarized, up to the patient’s current age of 16 years. OCD: Obsessive compulsive disorder, LDX: Lisdexamfetamine, ADHD: Attention-deficit hyperactivity disorder, NSIB: Non-suicidal self-injurious behavior.

**EOP Patient 2:** Patient 2 is a 23-year-old white non-Hispanic cis-gendered female with aversive somatosensory symptoms since infancy (**Figure 2**) manifested as an inability to tolerate normal clothing or touch. At age 4, this was interpreted as potential OCD and treated with sertraline (dose unknown) which was discontinued due to increased irritability, hyperactivity, and impulsiveness. From age 6-to-9 years old, she insisted she had a different name, a different age, and that an unrelated neighbor was her grandmother. The vehemence and persistence of these claims seemed outside the range of normal childhood play and were of great concern to her parents. At age 9, she was hospitalized for violent threats to family members and diagnosed with a mood disorder. Mood and social behavior improved on 1 mg/day of risperidone, but somatosensory symptoms did not. From ages 14 onward, she had delusional conviction about broken bones and other injuries with extreme pain despite repeated medical examinations demonstrating no findings.

At age 15 while refusing risperidone, she was hospitalized due to auditory hallucinations, new delusions, bizarre behavior not consistent with familial or cultural beliefs and extreme mood instability including a manic episode followed by melancholic depression. At age 16, her aversive somatic symptoms continued; any clothing that even lightly touched her genital region caused her intolerable pain and discomfort. She experienced intestinal, stomach, gastric, and pelvic pain. At this time, she reported that her father sexually abused her at age 3. This was investigated, thought to be delusional, and allegations went away upon antipsychotic treatment. She has no known history of child maltreatment or abuse. She was trialed with olanzapine, aripiprazole, paliperidone and risperidone with little improvement in hallucinations, delusions, pain, or sensory symptoms. At age 17, she was titrated onto clozapine at 537.5mg/day, along with aripiprazole 1 mg/day, and escitalopram 5mg/day. On this regime, she has experienced 5 years of infrequent hallucinations, brief delusional ideation for which she does not have full conviction, and which minimally impacts her behavior, although her pain and sensory symptoms have continued. At age 21,

these decreased on gabapentin 200 mg/day, which was discontinued due to excessive tiredness. She was managing her pain and sensory symptoms well by wearing loose clothing and using distraction. Recently at age 23, she insisted on lowering her daily clozapine dose by 12.5mg. Subsequently, her pain and sensory symptoms have more negatively impacted her behavior. Despite loose clothing and attempts at distraction, these symptoms have caused her to leave work.

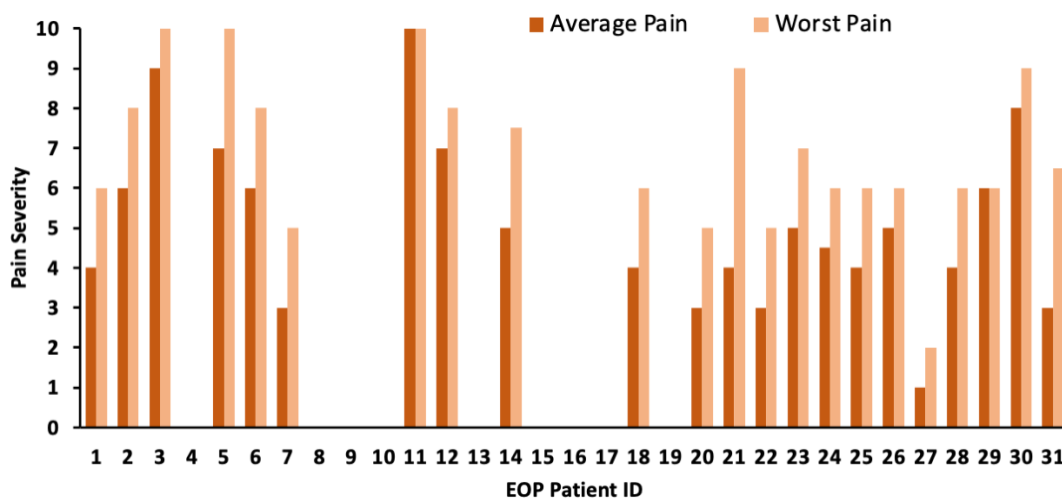


**Figure 2. Clinical history and timeline of EOP Patient 2.** Patient 2 was first diagnosed with OCD at the age of 4, and in the following years, additional psychiatric and somatosensory signs and symptoms arose. The patient is currently 22 years old and continues to experience somatosensory sensitivity, while medications have improved the psychiatric symptoms. OCD: Obsessive compulsive disorder.

### EOP Cohort Study Results

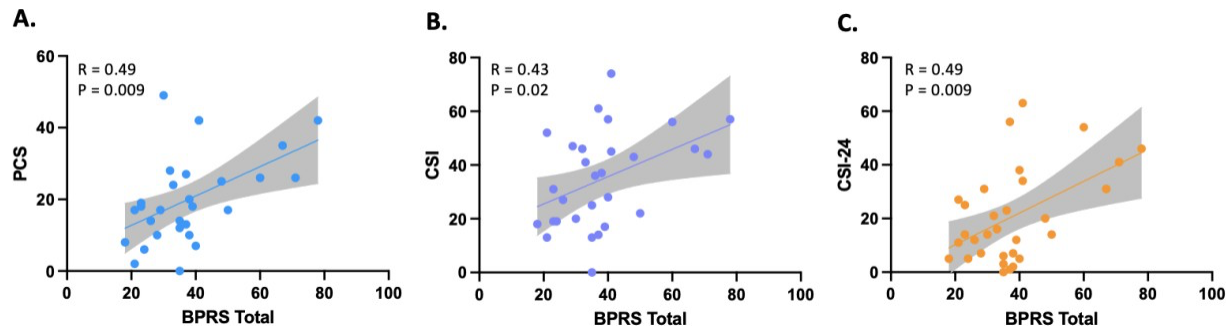
Of the 31 participants enrolled, 22 individuals reported experiencing pain in the last 14 days (**Figure 3**). Pain severity reported on a 0-10 numerical pain rating scale was not associated with age, gender, or CPZ-equivalent dose (all  $p > 0.3$ ). Of these 22 patients, 20 reported a 'worst pain' level of 4 or more (0-10 numerical rating scale), indicating the presence of moderate to severe pain. The 'average pain' level (0-10 numerical rating scale) reported by these patients was mean 3.6 (standard deviation (SD)=2.96), while the 'worst pain' rating was 4.9 (SD=3.59). In comparison, in a cohort of pediatric complex regional pain syndrome (CRPS) patients (N=15), the average pain levels before treatment admission were 6.6 (SD=2.02), while in juvenile idiopathic arthritis (JIA) patients an average pain rating of 3.2 (SD=2.59) was

observed <sup>14</sup>. In EOP patients who reported experiencing moderate to severe pain (N=22), there was a significant positive correlation between self-reported worst pain levels and severity of psychopathology, as assessed by the BPRS total score (**Table 1**, see **Supplemental Table 1**). Further analyses revealed that the worst pain levels were associated with scores on the BPRS affectivity and BPRS resistance subscales (**Supplemental Figure 1**). Other BPRS subscales were not significantly associated with the worst pain levels. **Supplemental Table 2** displays the correlation matrix of the main study variables.



**Figure 3. Single-subject pain severities over the last 14 days across all 31 children with EOP.** Average pain is depicted in brown, Worst pain is shown in beige. At the time of study evaluation, pain was not reported by 9 patients with EOP in the previous 14 days.

Across all 31 children with EOP, higher PCS, CSI, and CSI-24 total scores corresponded with higher BPRS total scores (R=0.43 to 0.49), remaining significant after multiple comparison corrections (**Figure 4**). Here, BRPS subscale scores for negative symptoms and activation were significantly correlated with the CSI-24 total score following an FDR correction (**Table 2**). There was no effect of CPZ equivalence on BPRS total and subscores in univariate nor multivariate analysis (all p-values>0.2).



**Figure 4. Psychopathology, pain catastrophizing, sensitization, and somatization in EOP.** In a cohort of 31 patients with EOP, significant associations were observed between BPRS total scores with **(A)** pain catastrophizing, **(B)** central sensitization, and **(C)** somatization. FDR adjusted p-values are reported. The 95% confidence interval is depicted. BPRS: Brief Psychiatric Rating Scale.

## Discussion

In this preliminary analysis of a sample of patients with EOP, we identified that many children with classical hallmarks of psychosis struggle with pain and somatization symptoms which can precede the onset of frank psychosis. In the two illustrated EOP cases, pain and somatosensory abnormalities contributed to significant functional impairment and hindered basic activities of daily life, as apparent from school refusal in Patient 1 and poor work attendance in Patient 2. Therefore, understanding and effectively treating pain and somatic symptoms in EOP may ultimately improve quality of life and daily functioning in this clinical population.

Pain and pain-related distress (particularly anxiety and depression) in EOP patients may mutually exacerbate the severity of symptoms in both conditions, and in each condition when the symptoms are severe and result in disability. Therefore, treating pain could potentially reduce the severity of psychotic disability and vice versa. For example, for Patient 1, treatment of pain with gabapentin coincided with remission of hallucinations and delusions, while for Patient 2 an adjustment of clozapine dose reduced pain and sensory symptoms. Unfortunately, Patient 2's subsequent choice to reduce clozapine dose

reintroduced her symptom presentation, which had a negative impact on daily function. Whether treatment of pain can alleviate psychotic symptoms must be corroborated in a larger cohort of patients and it is possible that pain and EOP may have an interactive effect.

Before receiving a psychotic diagnosis, patients are frequently diagnosed with other mental health conditions. Both cases of EOP patients that are described herein initially received an OCD diagnosis before developing psychotic symptoms, while one patient in our EOP cohort also had a secondary diagnosis of OCD. This observation is in accord with prior studies in adults with psychosis, where comorbidity (i.e., OCD) has been described<sup>15, 16</sup>. Whether the association between OCD and psychosis stems from shared psychopathological features remains to be clarified.

Of the 31 patients with EOP who were evaluated, a subset of 22 individuals presented with significant levels of pain, and therefore this subsample could provide more insight into the relation between pain and psychopathology. In this subgroup, the worst pain ratings were associated with the degree of psychopathology as assessed by the BPRS Total score and with BPRS measures of affectivity and resistance. Only the worst pain rating surpassed a threshold of significance although the direction of the relation was similar in other pain measures (e.g. average pain and PFSD composite score), and one could speculate about why a more episodic measure like worst pain may be more highly correlated with psychopathology. The emotional impact of the more extreme pain experienced may be more pronounced but would need further investigation in a larger cohort to elucidate this relation. Moreover, the BPRS affectivity subscale consists of anxiety, guilt, depression, and somatic concern items, whilst the resistance subscale includes hostility, uncooperativeness, and suspiciousness. High scores on the BRPS affectivity subscale indicate a heightened intensity of emotional responses experienced by individuals. This intensity, coupled with the integration of somatic concern, may correlate with somatic symptoms,

thereby potentially reinforcing the identified associations. In general, individuals who experience pain often report feelings of anxiety and depression and show other signs of emotional dysregulation<sup>17</sup>. Therefore, pain severity, psychological aspects of pain, and psychopathology can interact with each other. Further investigation into the cooccurrence of pain phenotypes and their global response to analgesic treatment that might impact psychosis is warranted. Findings from this subset should be considered preliminary, particularly given the skewed distribution of PFSD that provides little information at higher scores.

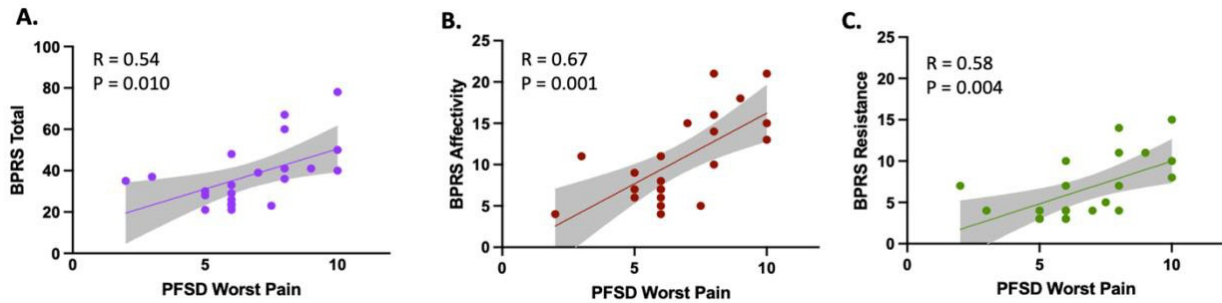
In accord with the two case studies that are presented, the investigation of 31 EOP patients further revealed that pain presentation, pain catastrophizing, central sensitization, and somatization bear on the degree of psychopathology. Central sensitization and somatization scores were highly correlated, perhaps owing to both measures similarly probing signs and symptoms such as bodily pain, physiological dysregulation, and gastrointestinal disorders. A more robust correlation of CSI-24 to BPRS relative to CSI may reflect that the CSI-24 is better suited for probing pain and somatic symptoms in pediatric populations as it is developed specifically for children. The current observations made at the single patient or cohort level suggest that bodily pain and involvement of somatic (e.g., muscle/joint) or visceral (e.g., gastrointestinal) signs and symptoms can occur in conjunction with psychotic features and may worsen the overall well-being of EOP patients. However, these preliminary observations should be corroborated in a larger cohort of EOP patients including assessment of clinical, laboratory and neurobiological underpinnings. In our sample, we included patients aged 7 to 17, which provided insight into pain phenotypes across ages and showed that even in the younger children there was significant pain experienced. Yet, to date, the presentation of pain or pain phenotypes in EOP has received very little attention from both clinical and research standpoints.

Mechanistic insights on pain and psychosis can be drawn from studies performed in adults with SZ or BD <sup>5</sup>, <sup>18, 19</sup>, but assessment of pain in individuals with EOP is critical, as the experience or processing of pain can differ between pediatric and adult populations <sup>20</sup>. In the current investigation, we report high rates of pain and somatosensory symptoms in EOP patients, which is similar to what is reported in adult BD patients while adult SZ patients appear to have a decreased sensitivity to pain <sup>5-7</sup>. Pain and related constructs (i.e., central sensitization, and somatization) in EOP may provide insight into earlier stages of the illness.

The relationship between psychosis and pain is likely multifactorial, potentially involving mood disorders such as anxiety and depression, heightened pain sensitivity, and associated distress. However, the precise mechanisms remain to be elucidated. The NMDA hypofunction theory of psychosis provides one potential link between psychosis and amplified pain sensitivity in EOP <sup>21</sup>. This theory posits that hypo-functioning of NMDA receptors on fast spiking inhibitory GABA-interneurons leads to glutamatergic hyperstimulation of mesolimbic dopamine neurons, which may underpin the characteristic hallucinations and delusions of psychosis. Similarly reduced GABA-inhibition of sensory and pain pathways could lead to the central sensitization <sup>22</sup>. Furthermore, psychosis is thought to be a complex neurodevelopmental disorder whose neurobiological underpinnings are not yet fully understood. It has been conceptualized as arising from the interaction between genetic predisposition and psychosocial factors <sup>23</sup>. The occurrence of pain and other somatic symptoms in EOP could perhaps partly be explained by the neurodevelopmental trajectories of various central nervous system (CNS) structures or circuits. We propose that in individuals with EOP, neuroanatomical abnormalities or disruptions in myelination, could ultimately interfere with pain regulation and somatosensory processing early in life, potentially impacting critical CNS areas such as the prefrontal and sensorimotor cortices <sup>24, 25</sup>. However, this mechanistic hypothesis is currently untested. Further research is essential to clarify how chronic pain, psychosocial factors, and childhood psychosis risk interconnect.

This work underscores the need for further investigation into the pathogenesis, clinical trajectories, and impact of pain and somatic symptoms in EOP. Given the overlapping EOP and chronic pain or somatosensory symptoms, it is essential to understand the coexistence of these two conditions. Practitioners faced with treatment-resistant severe pain, may consider the interconnected EOP presentation and referral to mental health providers for early diagnosis and treatment.

**Supplemental Figure 1. Pain severity vs. psychopathology in EOP patients reporting pain.** In 22 patients with EOP who reported pain, worst pain levels as reported in the Pain Frequency-Severity-Duration Scale were significantly correlated with the BPRS (A) total score as well as the BPRS (B) Affectivity, and (C) Resistance subscale scores. Pearson correlation coefficient test was conducted to assess the correlation between BPRS subscales and pain levels. The 95% confidence interval is depicted. BPRS: Brief Psychiatric Rating Scale.



**Table 1. Pain vs. psychopathology in patient with EOP.** 22 patients with EOP reported pain on the Pain-Frequency-Severity-Duration (PFSD) scale. Relationships were evaluated among PFDS composite scores, average pain (0-10 pain scale, in last 14 days), worst pain (0-10 pain scale, in last 14 days), and number of days with pain (in last 14 days) with brief psychiatric rating scale (BPRS) total scores. Self-reported worst pain severity associated positively with BPRS total scores.

Independent Variable	Dependent Variable	Correlation (R)	P-value	Adjusted p-values (FDR)
PFSD Composite Score	BPRS Total	0.32553	0.1393	0.1857
Average Pain		0.35220	0.1079	0.1857
Worst Pain		<b>0.53808</b>	<b>0.0098</b>	<b>0.0392</b>
# of Days with Pain		-0.02795	0.9017	0.9017

**Table 2. Multivariate analysis of psychopathology, pain, pain catastrophizing, and somatization in 31 patients with EOP.** The multivariate model included the degree of psychopathology as defined by brief psychiatric rating scale (BPRS) total and sub-scale scores, presence of pain, pain catastrophizing scale (PCS) total score, and child somatization inventory total score (CSI-24). BPRS Negative and BPRS Activation were both associated with the severity of somatizations following FDR corrections.

Outcome	Parameters	Multivariate Analysis Parameter Estimate	Multivariate Analysis p-values	Adjusted p-values (FDR)
<b>BPRS Total</b>	Pain (absent)	-8.29	0.150	0.208
	PCS	0.37	0.122	0.189
	CSI24	0.35	<b>0.049</b>	0.111
<b>BPRS Positive</b>	Pain (absent)	-0.57	0.719	0.762
	PCS	0.12	0.073	0.146
	CSI24	0.03	0.591	0.664
<b>BPRS Negative</b>	Pain (absent)	-3.10	<b>0.019</b>	0.070
	PCS	0.001	0.979	0.979
	CSI24	0.14	<b>0.001</b>	<b>0.022</b>
<b>BPRS Affectivity</b>	Pain (absent)	-3.03	0.126	0.189
	PCS	0.14	0.102	0.183
	CSI24	0.16	<b>0.012</b>	0.070
<b>BPRS Activation</b>	Pain (absent)	-2.25	<b>0.018</b>	0.070
	PCS	0.08	<b>0.035</b>	0.098
	CSI24	0.09	<b>0.004</b>	<b>0.032</b>
<b>BPRS Resistance</b>	Pain (absent)	-1.90	0.209	0.269
	PCS	0.04	0.559	0.664
	CSI24	0.10	<b>0.038</b>	0.098

## References

1. Grover, S.; Sahoo, S.; Nehra, R., A comparative study of childhood/adolescent and adult onset schizophrenia: does the neurocognitive and psychosocial outcome differ? *Asian J Psychiatr* **2019**, *43*, 160-169.
2. Immonen, J.; Jaaskelainen, E.; Korpela, H.; Miettunen, J., Age at onset and the outcomes of schizophrenia: A systematic review and meta-analysis. *Early Interv Psychiatry* **2017**, *11* (6), 453-460.
3. Driver, D. I.; Thomas, S.; Gogtay, N.; Rapoport, J. L., Childhood-Onset Schizophrenia and Early-onset Schizophrenia Spectrum Disorders: An Update. *Child Adolesc Psychiatr Clin N Am* **2020**, *29* (1), 71-90.
4. Brownstein, C. A.; Douard, E.; Mollon, J.; Smith, R.; Hojlo, M. A.; Das, A.; Goldman, M.; Garvey, E.; Cabral, K.; Li, J.; Bowen, J.; Rao, A. S.; Genetti, C.; Carroll, D.; Knowles, E. E. M.; Deaso, E.; Agrawal, P. B.; Beggs, A. H.; D'Angelo, E.; Almasy, L.; Alexander-Bloch, A.; Saci, Z.; Moreau, C. A.; Huguet, G.; Deo, A. J.; Jacquemont, S.; Glahn, D. C.; Gonzalez-Heydrich, J., Similar Rates of Deleterious Copy Number Variants in Early-Onset Psychosis and Autism Spectrum Disorder. *Am J Psychiatry* **2022**, *179* (11), 853-861.
5. Leo, R. J.; Singh, J., Migraine headache and bipolar disorder comorbidity: A systematic review of the literature and clinical implications. *Scand J Pain* **2016**, *11*, 136-145.
6. Stubbs, B.; Eggermont, L.; Mitchell, A. J.; De Hert, M.; Correll, C. U.; Soundy, A.; Rosenbaum, S.; Vancampfort, D., The prevalence of pain in bipolar disorder: a systematic review and large-scale meta-analysis. *Acta Psychiatr Scand* **2015**, *131* (2), 75-88.
7. Stubbs, B.; Thompson, T.; Acaster, S.; Vancampfort, D.; Gaughran, F.; Correll, C. U., Decreased pain sensitivity among people with schizophrenia: a meta-analysis of experimental pain induction studies. *Pain* **2015**, *156* (11), 2121-2131.
8. Geller, B.; Zimmerman, B.; Williams, M.; Bolhofner, K.; Craney, J. L.; DelBello, M. P.; Soutullo, C., Reliability of the Washington University in St. Louis Kiddie Schedule for Affective Disorders and Schizophrenia (WASH-U-KSADS) mania and rapid cycling sections. *J Am Acad Child Adolesc Psychiatry* **2001**, *40* (4), 450-5.
9. Lukoff, D.; Nuechterlein, K.; Ventura, J., Manual for the expanded brief psychiatric rating scale. *Schizophr Bull* **1986**, *12*, 594-602.
10. Salamon, K. S.; Davies, W. H.; Fuentes, M. R.; Weisman, S. J.; Hainsworth, K. R., The pain frequency-severity-duration scale as a measure of pain: preliminary validation in a pediatric chronic pain sample. *Pain Res Treat* **2014**, *2014*, 653592.
11. Sullivan, M.; Bishop, S.; Pivik, J., The Pain Catastrophizing Scale: Development and validation. *Psychological Assessment* **1995**, *7*, 524-532.
12. Shulman, J.; Zurakowski, D.; Keysor, J.; Jervis, K.; Sethna, N. F., Offset analgesia identifies impaired endogenous pain modulation in pediatric chronic pain disorders. *Pain* **2020**, *161* (12), 2852-2859.
13. Walker, L. S.; Beck, J. E.; Garber, J.; Lambert, W., Children's Somatization Inventory: Psychometric Properties of the Revised Form (CSI-24). *Journal of Pediatric Psychology* **2008**, *34* (4), 430-440.
14. Upadhyay, J.; Lemme, J.; Cay, M.; Van Der Heijden, H.; Sibai, D.; Goodlett, B.; Lo, J.; Hoyt, K.; Taylor, M.; Hazen, M. M.; Halyabar, O.; Meidan, E.; Schreiber, R.; Chang, M. H.; Nigrovic, P. A.; Jaimes, C.; Henderson, L. A.; Ecklund, K.; Sundel, R. P., A multidisciplinary assessment of pain in juvenile idiopathic arthritis. *Semin Arthritis Rheum* **2021**, *51* (4), 700-711.
15. Meier, S. M.; Petersen, L.; Pedersen, M. G.; Arendt, M. C.; Nielsen, P. R.; Mattheisen, M.; Mors, O.; Mortensen, P. B., Obsessive-compulsive disorder as a risk factor for schizophrenia: a nationwide study. *JAMA Psychiatry* **2014**, *71* (11), 1215-21.
16. Cheng, Y. F.; Chen, V. C.; Yang, Y. H.; Chen, K. J.; Lee, Y. C.; Lu, M. L., Risk of schizophrenia among people with obsessive-compulsive disorder: A nationwide population-based cohort study. *Schizophr Res* **2019**, *209*, 58-63.
17. IsHak, W. W.; Wen, R. Y.; Naghdechi, L.; Vanle, B.; Dang, J.; Knosp, M.; Dascal, J.; Marcia, L.; Gohar, Y.; Eskander, L.; Yadegar, J.; Hanna, S.; Sadek, A.; Aguilar-Hernandez, L.; Danovitch, I.; Louy, C., Pain and Depression: A Systematic Review. *Harv Rev Psychiatry* **2018**, *26* (6), 352-363.

18. Minichino, A.; Delle Chiaie, R.; Cruccu, G.; Piroso, S.; Di Stefano, G.; Francesconi, M.; Bersani, F. S.; Biondi, M.; Truini, A., Pain-processing abnormalities in bipolar I disorder, bipolar II disorder, and schizophrenia: A novel trait marker for psychosis proneness and functional outcome? *Bipolar Disord* **2016**, *18* (7), 591-601.
19. Stubbs, B.; Mitchell, A. J.; De Hert, M.; Correll, C. U.; 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. *Schizophr Res* **2014**, *160* (1-3), 1-8.
20. Tong, H.; Maloney, T. C.; Payne, M. F.; King, C. D.; Ting, T. V.; Kashikar-Zuck, S.; Coghill, R. C.; Lopez-Sola, M., Processing of pain by the developing brain: evidence of differences between adolescent and adult females. *Pain* **2022**, *163* (9), 1777-1789.
21. Olney, J. W.; Farber, N. B., Glutamate receptor dysfunction and schizophrenia. *Arch Gen Psychiatry* **1995**, *52* (12), 998-1007.
22. Latremoliere, A.; Woolf, C. J., Central sensitization: a generator of pain hypersensitivity by central neural plasticity. *J Pain* **2009**, *10* (9), 895-926.
23. Zwicker, A.; Denovan-Wright, E. M.; Uher, R., Gene-environment interplay in the etiology of psychosis. *Psychol Med* **2018**, *48* (12), 1925-1936.
24. Valdes-Tovar, M.; Rodriguez-Ramirez, A. M.; Rodriguez-Cardenas, L.; Sotelo-Ramirez, C. E.; Camarena, B.; Sanabrais-Jimenez, M. A.; Solis-Chagoyan, H.; Argueta, J.; Lopez-Riquelme, G. O., Insights into myelin dysfunction in schizophrenia and bipolar disorder. *World J Psychiatry* **2022**, *12* (2), 264-285.
25. Vieira, S.; Gong, Q.; Scarpazza, C.; Lui, S.; Huang, X.; Crespo-Facorro, B.; Tordesillas-Gutierrez, D.; de la Foz, V. O.; Setien-Suero, E.; Scheepers, F.; van Haren, N. E. M.; Kahn, R.; Reis Marques, T.; Ciufolini, S.; Di Forti, M.; Murray, R. M.; David, A.; Dazzan, P.; McGuire, P.; Mechelli, A., Neuroanatomical abnormalities in first-episode psychosis across independent samples: a multi-centre mega-analysis. *Psychol Med* **2021**, *51* (2), 340-350.
26. Association, A. P., *Diagnostic and statistical manual of mental disorders*. 5th ed.; 2013.