European Journal of Pain

ORIGINAL ARTICLE OPEN ACCESS

Deciphering Pain Experience in Adult Patients With Sickle Cell Disease: A Network Analysis of Pain-Related Factors in a Single French Sickle Cell Centre

D. Oudin Doglioni[1] | M. Couette[2] | S. Forté[3] | F. Galacteros[4,5] | M.-C. Gay[6]

[1]Laboratoire Interuniversitaire de Psychologie/Personnalité, Cognition, Changement Social (LIP/PC2S), Université Grenoble Alpes, Université Savoie Mont-Blanc, Grenoble, France | [2]Intensive Care Unit, Teaching Hospital Henri Mondor, Créteil, France | [3]Division of Medical Oncology and Haematology, Department of Medicine, Centre Hospitalier de l'Université de Montréal (CHUM), Montreal, Quebec, Canada | [4]Red Blood Cell Genetic Diseases Unit (UMGGR), Teaching Hospital Henri Mondor, Créteil, France | [5]French National Referral Centre for Sickle Cell Disease (MCGRE), Créteil, France | [6]EA4430 EvaCliPsy, Paris Nanterre University, Nanterre, France

Correspondence: D. Oudin Doglioni (damien.oudin-doglioni@univ-grenoble-alpes.fr)

Received: 24 January 2025 | **Revised:** 28 May 2025 | **Accepted:** 1 June 2025

Keywords: network analysis | Neuromatrix model | pain management | sickle cell disease

ABSTRACT

Background: Sickle cell disease (SCD) is the most prevalent inherited haemoglobinopathy characterised by chronic pain with acute painful episodes due to vaso-occlusion. The effective management of pain by adults with SCD influences their health outcomes. Opioids remain essential for most pain syndromes, but non-pharmacological interventions are preferred for daily pain due to the risk of addiction. However, their effectiveness is variable. Understanding the underlying processes associated with pain is crucial for developing more effective non-pharmacological strategies. This study aimed to enhance comprehension of the pain mechanisms in SCD to identify potential areas of action for effective non-pharmacological interventions.

Method: An evaluation was conducted on the severity and interference of pain, pain-related cognitions and emotions. We used network analysis to simultaneously examine the intricate relationships between these variables.

Results: A pain intensity exceeding 4 at a steady state distinguishes a subgroup at elevated risk of negative pain-related emotions and cognitions. The network analysis revealed intricate interconnections, with three distinct subgroups of variables mimicking the Neuromatrix model (cognitive-evaluative, motivational-affective and sensory-discriminative subgroups). The derived directed acyclic graph suggests potential mechanisms between these three subgroups, with catastrophising having a pivotal role.

Conclusion: This study extends previous research by providing a comprehensive network analysis of pain-related variables in SCD, offering novel insights into the complex interplay between pain experience, cognitions and emotions. These findings have important clinical implications, as they suggest that targeting dysfunctional pain cognitions and/or negative emotions may be beneficial for improving pain management and quality of life in SCD.

Significance Statement: This study was the first to use network analyses to understand simultaneously multiple relationships between variables referring to pain, and pain-related negative emotions and cognitions in adults with SCD. Findings, providing support to the Neuromatrix model, offer novel insight to better understand pain and the associated negative emotions and cognition in SCD. The derived directed acyclic graph explored potential underlying psychological processes associated with pain that could be specifically targeted by future effective psychological interventions.

1 | Background

Sickle cell disease (SCD) is the most prevalent inherited haemoglobinopathy (Piel et al. 2017), characterised by chronic haemolytic anaemia, recurrent vaso-occlusive crises (VOC), progressive organ damage and reduced life expectancy (Houwing et al. 2019). Despite advances in haematopoietic stem cell transplantation and gene therapy (Tanhehco and Bhatia 2019), therapeutic options remain limited. In addition to VOC, other sources of pain impact quality of life, including avascular necrosis, leg ulcers, bone infarcts, chronic osteomyelitis, priapism, and hepatic and splenic sequestration (Ballas and Darbari 2020).

Patients' health status is influenced by their ability to manage their disease, particularly pain (Levenson 2008). Treatment options encompass both long-term strategies (hydroxyurea attenuates VOC; Shah et al. 2019) and acute-phase interventions (Lugthart et al. 2024). Despite other disease-modifying therapies existing, opioids remain central in acute pain management (Booker et al. 2006). Unfortunately, many patients develop addiction and resistance to opioids (Ruta and Ballas 2016), complicating pain management, making pain refractory and requiring other medications (e.g., ketamine, epidural or regional anaesthesia). Non-pharmacological interventions are underexplored (Anie and Green 2015; Chen et al. 2004; Edwards and Edwards 2010; Hildenbrand et al. 2014). A comprehensive review of 28 non-pharmacological interventions (Williams and Tanabe 2016) suggests unsystematic benefits, due to the limited understanding of underlying psychological processes associated. This is an important limitation for developing more effective non-pharmacological strategies.

Kenney and Smith (2022) introduced an explanatory model for SCD pain based on the Neuromatrix framework (Melzack 2001). This neurophysiological model posits that the central nervous system contains a 'body-self Neuromatrix' integrating sensory-discriminative (pain characteristics), cognitive-evaluative (pain experience interpretation; Moseley and Arntz 2007) and motivational-affective (emotional dimension; Price 2000) inputs to generate the subjective experience of pain. Their interaction results in pain perception, motor responses (voluntary or involuntary) and stress responses.

In SCD, studies provide indirect support for the Neuromatrix model which could serve as a foundation for the development of non-pharmacological interventions. For example, although VOC is considered a primary driver of pain (sensory-discriminative input), recent research suggests other physiological and psychological factors also trigger pain (Ballas and Darbari 2020; Edwards et al. 2014): anxiety and/or depression are systematically associated with pain (e.g., Levenson et al. 2008; Master et al. 2016; Schlaeger et al. 2019); pain catastrophising is associated with greater distress and poorer management (e.g., Bakshi et al. 2018; Citero et al. 2007; Schneider et al. 2022); and traumatism associated with pain increases negative emotions and cognition, thus leading to poorer pain management (Childerhose et al. 2023; Hofmann et al. 2007).

Aligning with the Neuromatrix framework, we believe that these elements form an intricate network of interconnected variables, influencing each other. To fully comprehend the complex psychological processes underlying pain in SCD, we should consider these interactions, which are not fully realised by Kenney et al. (2024). Network analysis (NA) provides a suitable framework to better understand the intricate mechanisms that contribute to the pain experience in SCD. To our knowledge, no published study has used NA to gain a deeper understanding of the pain experienced in SCD. Thus, our primary aim was to enhance comprehension of the mechanisms underpinning pain in SCD, thereby identifying potential areas of action for effective non-pharmacological interventions by exploring the relationship between variables referring to the pain experience in adults with SCD using NA.

2 | Method

A cross-sectional study was conducted between 22 January and 19 July 2020 at the Red Blood Cell Genetic Disease Unit of Henri Mondor Teaching Hospital (UMGGR). The study received ethical approval from the French Ethics Committee (CPP Sud-Est 2; reference: 2018-A01662-53). Data were collected anonymously via surveys, adhering to national and international ethical guidelines (French law, Helsinki Declaration) and data protection regulations (GRPD).

2.1 | Patients' Recruitment and Selection

Patients eligible for the study were pre-selected by the clinicians from the lists of appointments for normally scheduled medical consultations according to inclusion, non-inclusion and exclusion criteria, with the aim of having patients in a steady state. Potential participants were approached in the waiting room, before their normally scheduled medical appointment at the UMGGR, by the principal investigator or a trained research nurse assistant. After a detailed explanation of the study and provision of a written information notice, those who consented signed an informed consent form after their medical appointment (As all subjects included in this study were adults under French law, i.e., aged 18 and over, and not under legal guardianship, no additional authorisation was required from the patients). Eligible participants were then administered questionnaires.

Were included adult volunteers (aged 18 or older) with SCD who had a medical follow-up by a physician of the UMGGR. Non-inclusion criteria were the following: individuals with severe difficulties in understanding French that would hinder their ability to complete the questionnaires or respond orally to questions. Exclusion criteria targeted patients in hospitalisation or hospitalised in the month (30 days) for pain (VOC or acute chest syndrome), as we focused on steady-state respondents; patients enrolled in a blood transfusion programme (e.g., erythropheresis), as they do not have acute pain episodes. Patients hospitalised in the previous month for programmed normal care were considered for inclusion. Adults with SCD and another unrelated chronic disease that could potentially influence their pain experience, as determined by clinicians at inclusion, were excluded.

2.2 | Explored Variables

2.2.1 | Descriptive Data

Sociodemographic (gender, age, education level and place of birth) and medical data (genotype, foetal haemoglobin level [HbF], mean corpuscular volume [MCV] and data on hydroxyurea [HU] prescription) were extracted from electronic medical records by clinicians at the time of enrolment.

2.2.2 | Psychometric Assessment of Pain Experience

2.2.2.1 | Pain Experience: Brief Pain Inventory (BPI). The BPI (Cleeland and Ryan 1994) is a bi-factor instrument designed to assess pain severity and pain interference (validation of the French version: Poundja et al. 2007).

The pain severity factor comprises four items, each rated on a 0–10 intensity scale, with 0 representing 'No pain' and 10 indicating, 'Pain as bad as you can imagine'. Participants are asked to rate their worst, least, average and current pain levels within the past 7 days. The pain interference factor consists of seven items, rated on a 0–10 intensity scale, that measure the impact of pain on general activity, mood, walking ability, normal work, relationships, sleep and enjoyment of life within the past 7 days.

For this study, we employed the aggregate scores of each factor, calculated by averaging the scores of the constituent items. Thus, the pain severity factor score was the mean of the four items, and the pain interference factor score was the mean of the seven items. No cut-off or threshold was defined.

Two studies, employing modest sample sizes ($n = 69$, Driscoll et al. 2017; $n = 71$, O'Brien et al. 2025), have reported on the challenges experienced by adults with SCD when completing the BPI within a US context. In France, its psychometric properties was validated among adults with SCD, exhibiting satisfactory performance (Oudin Doglioni 2021). In our sample, the BPI demonstrated very high internal consistency, as measured by McDonald's omega ($\omega = 0.93$).

2.2.2.2 | Pain-Related Beliefs: Pain Beliefs and Perceptions Inventory (PBPI). The PBPI (Williams and Thorn 1989) is a 16-item questionnaire evaluating patients' own conceptualisations of what pain is and what pain means to them (validation of the French version: Dany et al. 2009). PBPI is a four-factor instrument that measures pain as a mystery (pain is perceived as unexplainable), pain as permanent (pain is perceived as possibly long-lasting or as potentially chronic), pain as constant (temporal aspect of pain perceived as intermittent vs. constant) and self-blame reflecting a feeling of responsibility.

The assessment of all items is conducted on a Likert scale that ranges from −2 ('strongly disagree') to 2 ('strongly agree'), with no central modality. The score for each factor is obtained by averaging the scores of the items that comprise it. No cut-off or threshold was defined in the original version. A French calibration of scores exists based on an equal five classes distribution (quintile), with each class comprising 20% of the subjects included (Roussel et al. 2010). However, this was not utilised in the present study. The interpretation of the scores follows that of the original version: the higher the score, the more respondents accept the belief.

To the best of our knowledge, the PBPI has only been utilised in one other study, which focused on adolescents suffering from SCD (Fletcher 2000). In France, the psychometric properties of the PBPI were validated among adults with SCD, exhibiting satisfactory performance (Oudin Doglioni 2021). In our sample, internal consistency was high ($\acute{\omega} = 0.76$).

2.2.2.3 | Pain-Related Cognitive Mechanisms of Coping: Pain Catastrophising Scale (PCS). Catastrophising is a cognitive mechanism of negative coping with pain experience (Sullivan et al. 1995). The PCS (validation of the French version: French et al. 2005) is a 13-item instrument evaluating catastrophising as a three-dimensional construct: magnification reflects the cognitive exaggeration of perceived pain stimuli, rumination is a cognitive focalisation on pain, and helplessness emphasises the negative appraisal in pain situations.

The 13 items under consideration are evaluated using a 5-point frequency scale, ranging from 'not at all' to 'all the time', with a scale value of zero to four. Four scores can be calculated: a total score and scores for each dimension. These scores are obtained by summing up the items. French et al. (2005) indicated a threshold of 22 to distinguish 'catastrophiser' from 'non-catastrophiser'.

The PCS was extensively utilised in the context of SCD, encompassing both paediatric and adult patients. In our sample, internal consistency was high ($\acute{\omega} = 0.93$).

2.2.2.4 | Pain as Trigger of Traumatism Mechanisms: Sensitivity to Pain Traumatisation Scale (SPTS-12). Sensitivity to pain traumatisation is defined as the propensity to develop cognitive, affective and behavioural responses to pain that resemble a traumatic stress reaction (Katz et al. 2017). The concept of pain traumatisation seeks to explain the crucial part played by anxiety in the experience of pain, with reference to the strong inter-relationship between the three most commonly used constructs of pain-related anxiety, namely pain anxiety, dramatisation and anxiety sensitivity.

SPTS-12 comprises 12 items that are evaluated using a 5-point Likert scale, ranging from 0 'strongly disagree' to 4, 'strongly agree'. The total score is derived by summing up the item scores. No threshold or cut-off is proposed by the authors.

SPTS-12 is a recently developed instrument for which formal validation in France has not yet been conducted. This scale had not yet been employed in a study on individuals living with SCD. However, the psychometric properties of the scale were evaluated in a French context, and satisfactory performance was exhibited (Oudin Doglioni 2021). In our sample, SPTS-12 internal consistency was high ($\acute{\omega} = 0.88$).

2.2.3 | Psychometric Evaluation of Emotional Covariates of the Pain Experience

2.2.3.1 | Anxiety and Depression: Hospital Anxiety and Depression Scale (HADS). Depression and anxiety are well-established comorbidities of acute and chronic pain conditions (Asmundson and Katz 2009). Research indicates a higher prevalence of pain among individuals with depression or anxiety, and conversely, a higher prevalence of depression or anxiety among individuals experiencing pain compared to the general population (Lerman et al. 2015). To assess these psychological factors, we employed the 14-item HADS (Zigmond and Snaith 1983), as recommended by Oudin Doglioni et al. (2021), which excludes items that overlap with the neurovegetative symptoms characteristic of SCD. In our sample, HADS internal consistency was good ($\acute{\omega} = 0.75$).

2.2.3.2 | Alexithymia: Toronto Alexithymia Scale (TAS-20). Alexithymia, characterised by difficulties in identifying and describing self-emotions and a tendency to focus on external events rather than internal feelings (Bagby et al. 1994), is a multidimensional construct that may contribute to the development and exacerbation of pain symptoms. By impairing emotion processing and regulation, alexithymia can lead patients to misinterpret emotional arousal as physical symptoms, resulting in unnecessary medical attention (Di Tella and Castelli 2016). To assess alexithymia within our population, we used the well-validated 20-item TAS-20 (Bagby et al. 1994), which demonstrated strong internal consistency in our sample ($\acute{\omega} = 0.80$). In this study, we used the total TAS-20 score, as we were interested in the general level of alexithymia rather than the specific underlying processes.

2.2.3.3 | Cognitive-Emotional Processing: Emotional Processing Scale (EPS-25). Rachman (1980) initially proposed the concept of emotional processing. He described it as a mechanism whereby emotional distress is gradually resolved, enabling uninterrupted engagement in other activities and behaviours. Incomplete emotional processing can manifest in various psychological and physical symptoms (Baker et al. 2007). EPS-25 is a self-report measure designed to assess individual differences in emotional processing styles and potential deficits (Baker et al. 2007). It consists of five subscales: suppression, signs of unprocessed emotion, unregulated emotion, avoidance and impoverished emotional experience (Gay et al. 2019). For this study, we utilised the total EPS-25 score, as we were primarily interested in overall emotional processing difficulties rather than specific subscale profiles. The internal consistency of the EPS-25 in our sample was high ($\acute{\omega} = 0.94$).

2.3 | Statistical Procedure

2.3.1 | Descriptive and Bivariate Analysis

Standard descriptive and bivariate statistical analyses were employed. Descriptive statistics included measures of central tendency (mean and median) and dispersion (percentage). Bivariate analyses comprised mean comparisons (Student's *t*-test, ANOVA or nonparametric equivalents, as appropriate) and correlation analysis (Pearson's r correlation coefficient). All descriptive and bivariate analyses were conducted using Jamovi (The Jamovi Project 2020).

The potentially existing relationships (correlation) or differences (mean comparison) between, on the one hand, the variables referring to the evaluation of the experience of pain and, on the other hand, the sociodemographic and medical variables were systematically evaluated. Only statistically significant relationships or differences were reported. Exceptionally, we reported non-significant relationships or differences to confirm the existence of no difference (particularly for genotypes). In addition, we assessed the relationship in-between all the variables referring to the experience of pain. Statistically significant relationships were systematically reported. When no relationship was reported, it should be understood as statistically non-significant. Regarding the sociodemographic and medical data, we refrained from reporting all statistically significant differences or relationships. We have endeavoured to provide the most relevant information for healthcare professionals and clinicians to picture the population covered by the network analyses.

2.3.2 | Network Analysis (NA) in Psychology

Unlike structural equation modelling, which relies on a predetermined cause-effect structure, NA provides an exploratory data-driven framework to investigate how variables intertwine, highlighting those with the most significant influence (Borsboom and Cramer 2013). A key advantage of NA lies in its utilisation of partial correlations or predictive values to assess associations between variables (Epskamp, Borsboom, et al. 2018). These measures quantify the strength of a relationship while accounting for the effects of other variables in the network model, akin to multiple regression coefficients. This approach lends support for conditional processes, demonstrating how variables interact in the presence of other factors, which could be depicted by a directed acyclic graph (DAG), derived from the NA, suggesting a potential psychological mechanism (Borsboom and Cramer 2013). Cross-sectional networks provide insights into variable covariation and the network typology they form or psychological processes they suggest. This method explores how variables interact and identifies those with greater centrality in the network (Borsboom and Cramer 2013). By doing so, they inform on the potential role of triggering and maintaining factors, which could therefore be targets of interventions (Bringmann et al. 2019). By focusing on central nodes or traits, such intervention would affect other nearby nodes and therefore the entire network. Although cross-sectional networks provide insights into potential processes or mechanisms, they do not imply demonstrated causality.

Data analyses were performed using the R software (Version 4.3.2) (R Core Team 2023). The NA methodology adopted in this study adheres to established network research protocols (Bernstein et al. 2019; Burger et al. 2020; Isvoranu et al. 2021; Van Zyl 2021) and largely draws from the approach developed by Epskamp, Borsboom, et al. (2018). NA encompasses three principal phases (Epskamp, Borsboom, et al. 2018): (1) estimation of the statistical model underlying the data used to construct the network, (2) analysis of the weighted network structure utilising

graph theory (e.g., to examine node centrality) and (3) evaluation of the accuracy of the network parameters and measures.

One of the fundamental premises of NA is that the data must exhibit a multivariate normal distribution for psychological NA on continuous data to be conducted (Epskamp, Borsboom, et al. 2018). To address this issue, following established guidelines in the field (Epskamp, Borsboom, et al. 2018), we employed the non-paranormal transformation, using the *Huge* R package (Jiang et al. 2022) to normalise the data before estimating the Gaussian Graphical Model (GGM).

2.3.2.1 | Step 1: Estimation of the Network Model. This study primarily employed undirected networks, where nodes represent variables connected through non-directional edges (Hevey 2018). Pairwise Markov Random Fields (PMRFs) (Costantini et al. 2015) were utilised to estimate psychological networks through GGMs of partial correlation coefficients between pairs of variables after conditioning on the remaining variables in the dataset (i.e., the relationship between the two variables cannot be solely attributed to any other variable/node in the model) (Epskamp, Waldorp, et al. 2018).

A frequently employed method for estimating GGM structures in prior studies is the *EBICglasso* algorithm (Epskamp and Fried 2018), which utilises the graphical *LASSO* algorithm (glasso) (Friedman et al. 2008) in conjunction with the extended Bayesian information criterion (EBIC) (Chen and Chen 2008) for tuning parameter selection to determine a regularised GGM based on a correlation matrix as input.

For network visualisation, the *qgraph* R package was employed. The network layout is based on the Fruchterman–Reingold algorithm representation (Fruchterman and Reingold 1991), which optimises the layout such that nodes with weaker connections and fewer edges are positioned further apart, while nodes with stronger connections and more edges are placed closer together (Epskamp, Borsboom, et al. 2018).

2.3.2.2 | Step 2: Analysis of the Weighted Network Structure and Centrality Indices. The second step involved examining not only the structure of the network but also the strength of the connections between pairs of nodes (Epskamp, Borsboom, et al. 2018). This was achieved by evaluating the edge weight, which can be either positive or negative (sign) and vary in strength (strength) (Newman 2010).

The relative importance of individual nodes was assessed by measuring node strength, which reflects the magnitude of direct associations with other nodes (the sum of the strengths of all edges connected to a given node) (Costantini et al. 2015). Other strength indicators (e.g., closeness and betweenness) were not considered in this study due to conceptual concerns regarding their applicability to psychological networks (Bringmann et al. 2019).

In line with previous studies (Bernstein et al. 2019; Burger et al. 2020; Isvoranu et al. 2021; Van Zyl 2021), a community analysis was conducted to explore the presence of subnetworks within the network structure (Traag and Bruggeman 2009). This analysis was performed using the Exploratory Graph Analysis (EGA), which utilises the *Walktrap* algorithm to identify clusters of densely connected nodes, also known as communities (Golino and Epskamp 2017). If communities were identified within the main network, subsequent analyses would not be conducted, consistent with the exploratory nature of this study. EGA was applied using the *EGAnet* package for R (Golino et al. 2023).

2.3.2.3 | Step 3: Evaluation of the Accuracy of the Network Parameters and Measures. To evaluate the accuracy of the network and estimators, additional analyses were conducted. For edge-weight accuracy, 95% confidence intervals containing the true parameter value were estimated using bootstrapping (Epskamp, Borsboom, et al. 2018). In this study, nonparametric bootstrapping was employed (Epskamp, Borsboom, et al. 2018). To assess centrality, stability and accuracy, a case-dropping subset bootstrapping approach was utilised (Epskamp, Borsboom, et al. 2018). Stability was measured using the correlation stability coefficient (CSC), which represents the maximum proportion of cases that can be discarded while maintaining a 95% probability that the correlation between the original centrality indices and the centrality of networks derived from subsets remains higher than a predefined threshold (typically cor = 0.70). CSC values should exceed 0.25 and ideally surpass 0.50. The *bootnet* package for R was employed to execute both the nonparametric and case-dropping bootstrapping procedures, with 1000 bootstrap samples (Epskamp and Fried 2023).

2.3.3 | Directed Acyclic Graphs

Directed networks were explored through Bayesian Networks, represented in a DAG framework (Epskamp, Waldorp, et al. 2018). The *bnlearn* package for R was utilised to achieve this (Scutari et al. 2023), employing the *Inductive Causation PC-stable* algorithm. No arrows were 'blacklisted' (excluded). The algorithm generates an initially directed model that is not uniquely identified, implying that multiple edges could be reversed without altering the conditional independence (Briganti et al. 2023). To enhance the robustness of the findings, the model was bootstrapped 1000 times to unveil a stable network exhibiting the most prevalent directed arrows (Briganti et al. 2023). Arrows present in more than half ($\geq 50\%$) of bootstrapped networks were retained in the final model.

2.3.4 | Missing Data Management

For the descriptive and bivariate analyses, a complete case analysis approach was adopted, including $n = 517$ respondents, meaning that no respondents with missing data were excluded, and no imputation techniques were used. This approach was chosen to maximise sample size and minimise potential bias. Total sample sizes for each variable were indicated in Table 1 and Table 2.

However, due to the sensitivity of NA to missing data, a more conservative approach was necessary. Respondents with missing data on any of the variables included in the NA (pain experience, pain-related covariates and emotional covariates to pain) were excluded, leaving $n = 367$ respondents (Figure S1). This

TABLE 1 | Sociodemographic and medical characteristics of the total sample ($n = 517$) and network analysis subsample ($n = 367$) French adults with sickle cell disease.

		Total sample					Sample included in NA ($n = 367$)			
Variables	**Subcategories**	N_{total}	**M/*n* (%)**	**SD**	**Min**	**Max**	**M/*n* (%)**	**SD**	**Min**	**Max**
Age		516	40.11	11.48	19	73	39.69	11.15	19	73
Gender	Female	515	319 (61.9%)				233 (63.5%)			
Study level[a]	< Bac	506	158 (31.2%)				105 (28.9%)			
	Without diploma		60 (11.9%)				41 (11.3%)			
	BEPC/Brevet/CAP		98 (19.4%)				64 (17.6%)			
	Bac		80 (15.8%)				48 (13.2%)			
	> Bac		268 (53.0%)				210 (57.8%)			
Place of birth	France	514	229 (44.6%)				354 (98.9%)			
	Africa		269 (52.3%)				3 (0.8%)			
	Other countries		16 (3.1%)				1 (0.3%)			
Genotype	SS	514	394 (76.7%)				281 (77.0%)			
	SC		88 (17.1%)				60 (16.4%)			
	$S\beta^0$		12 (2.3%)				10 (2.7%)			
	$S\beta^+$		15 (2.9%)				10 (2.7%)			
MCV		506	90.62	16.70	53	141	90.83	16.22	57	133
Categories	MCV < 80 fl		143 (27.7%)				97 (26.4%)			
	MCV 80 fl-95 fl		196 (39.9%)				144 (39.2%)			
	MCV > 95 fl		178 (34.4%)				126 (34.3%)			
HbF		489	10.19	8.65	0.40	34.40	10.19	8.63	0.40	33.70
Categories	HbF < 10%		282 (54.6%)				203 (55.3%)			
	HbF 10%–20%		127 (24.6%)				90 (24.5%)			
	HbF > 20%		108 (20.9%)				74 (20.2%)			
HU	HU prescribed[b]	517	259 (50.1%)				231 (62.9%)			
	Dosage (g)	238	1021	367	250	3000	1032	367	250	3000
	Duration of prescription (years)	243	6.92	4.67	0	31	6.82	4.65	0	31

Abbreviations: %, percentage; Bac, 'Baccalauréat' (French high school terminal diploma equivalent to 12 years of schooling); BEPC/Brevet/CAP, French types of diplomas obtain at the end of secondary school; HbF, foetal haemoglobin level; HU, hydroxyurea; M, mean; MCV, mean corpuscular volume; Min/Max, minimum and maximum values; *n*, number of individuals in a specific condition; N_{total}, Number of respondents for the specific variable; SD, standard deviation.

[a]A greater proportion ($\chi^2(3) = 13.4$, $p = 0.004$) of adults who were included in the network analysis ($n = 367$, 71%) reported a level of education that exceeded the Baccalauréat than those who were not included in the analysis ($n = 150$, 29%).

[b]Adults who were included in the network analysis reported a higher frequency of taking HU (i.e., having a prescription) in comparison with those who were not included ($\chi^2(1) = 83.5$, $p < 0.001$, RR = 2.19).

ensured the accuracy and reliability of the NA results. As there was no existing minimum sample size recommendation for the application of NA in the domain of psychology, we adopted the approach proposed by Epskamp, Borsboom, et al. (2018). This entailed the assessment of both network parameters and measures accuracy using the parametric bootstrap method, which was implemented in the *Bootnet* package (refer to the third step in the NA section above).

3 | Results

3.1 | Participants' Characteristics

Table 1 summarises the sociodemographic and medical characteristics of our population, whereas Table 2 groups data of their pain experience, pain-related covariates and emotions associated with pain.

TABLE 2 | Summary of the pain experience, pain-related covariates (cognition, emotion and behaviour) and emotional covariates of pain of the total sample ($n = 517$) and network analysis subsample ($n = 367$) French adults with sickle cell disease.

		Total sample					Sample included in NA ($n = 367$)			
Variables	**Subcategories**	N_{total}	**M/*n* (%)**	**SD**	**Min**	**Max**	**M/*n* (%)**	**SD**	**Min**	**Max**
Pain experience (BPI)										
Intensity	Pain severity	416	3.51	1.99	0	9.50	3.45	1.96	0	9.50
	Worst pain	415	5.24	3.47	0	10	5.18	3.47	0	10
	Least pain[a]	414	2.07	1.86	0	9	1.95	1.79	0	9
	Pain in general	412	4.71	2.79	0	10	4.71	2.75	0	10
	Pain now	412	2.00	2.28	0	10	1.98	2.26	0	10
	Presence of pain (M > 4)		191 (45.9%)				164 (44.7%)			
	No pain (M < 1)		52 (12.5%)				25 (6.8%)			
Interferences	Pain interference	413	3.11	2.59	0	10	3.06	2.60	0	10
	General activities	411	3.31	3.03	0	10	3.26	3.00	0	10
	Walking	410	3.17	3.09	0	10	3.13	2.89	0	10
	Working	407	3.58	3.20	0	10	3.08	3.04	0	10
	Mood	400	3.15	2.91	0	10	3.55	3.21	0	10
	Relationship with others	411	2.63	2.82	0	10	2.58	2.80	0	10
	Sleep	413	3.47	3.15	0	10	3.37	3.17	0	10
	Enjoyment of life	386	2.46	2.97	0	10	2.44	2.95	0	10
	No interference (M < 1)		120 (29.1%)				116 (31.6%)			
Pain-related beliefs (PBPI)	Mystery	517	−2.92	4.26	−10	10	−3.13	4.70	−10	10
	Time: persistence	517	−0.33	2.87	−6	6	−0.35	3.24	−6	6
	Time: constant	517	−2.28	3.80	−8	8	−2.43	4.17	−8	8
	Self-blame	517	−3.56	2.20	−6	6	−3.55	2.42	−6	6
Catastrophising (PCS)	Total score	405	24.60	12.88	0	52	24.45	12.80	0	52
	(over the threshold: > 22)	405	249 (61.5%)				225 (61.3%)			
	Helplessness	408	9.95	6.26	0	24	9.86	6.23	0	24
	(over the threshold: > 13)	408	131 (32.1%)				114 (31.1%)			
	Magnification	408	5.42	3.51	0	12	5.43	3.51	0	12
	(over the threshold: > 5)	408	231 (56.6%)				210 (57.2%)			
	Rumination	409	9.15	4.59	0	16	9.16	4.51	0	16
	(over the threshold: > 11)	409	182 (44.5%)				161 (43.9%)			

(Continues)

TABLE 2 | (Continued)

Variables	Subcategories	Total sample					Sample included in NA ($n = 367$)			
		N_{total}	M/*n* (%)	SD	Min	Max	M/*n* (%)	SD	Min	Max
Sensitivity to pain traumatisation (SPTS-12)	Total score	407	23.74	10.68	0	48	23.7	10.6	0	48
	Low sensitivity (M < 13.06 [M − 1SD])		78 (27.1%)				70 (27.1%)			
	High sensitivity (M > 34.42 [M + 1SD])		65 (22.6%)				56 (21.7%)			
Anxiety (HADS)	Total score	502	8.18	3.87	0	18	8.05	3.90	0	18
	(over the threshold: > 11)		137 (27.3%)				95 (25.9%)			
Depression (HADS)	Total score	497	5.61	3.63	0	25	5.55	3.73	0	25
	(over the threshold: > 11)		49 (9.9%)				38 (10.4%)			
Alexithymia (TAS-20)	Total score	386	52.34	11.40	24	80	51.18	11.53	24	80
	(over the threshold: > 61)	386	104 (26.9%)				160 (43.6%)			
	DIF	388	18.21	5.84	7	33	18.14	5.89	7	33
	DDF	392	14.39	4.17	5	25	14.37	4.23	5	25
	EOT[b]	388	19.82	4.21	8	30	19.66	4.12	8	29.3
Cognitive-emotional processing (EPS-25)	Total score	394	3.52	1.72	0	9	3.52	1.73	0	9
	Low (M < 1.80 [M-1SD])		60 (21.1%)				57 (21.4%)			
	High (M > 5.24 [M + 1SD])		67 (23.6%)				64 (24.1%)			
	Suppression	394	3.95	2.34	0	9	3.98	2.35	0	9
	Unprocessed emotions	393	4.10	2.26	0	9	4.13	2.29	0	9
	Unregulated emotions	394	2.64	1.93	0	9	2.63	1.93	0	9
	Avoidance	395	4.02	1.78	0	9	4	1.78	0	9
	Impoverished emotional experience	393	2.87	1.85	0	9	2.86	1.83	0	9

Abbreviations: %, percentage; BPI, Brief Pain Inventory; DDF, difficulties in describing feelings; DIF, difficulties in identifying feelings; EOT, Externally oriented thoughts; EPS-25, Emotional Processing Scale; HADS, Hospital Anxiety and Depression Scale; M, mean; Min/Max, minimum and maximum values; *n*, number of individuals in a specific condition; N_{total}, number of respondents for the specific variable; PBPI, Pain Beliefs and Perception Inventory; PCS, Pain Catastrophizing Scale; SD, standard deviation; SPTS-12, Sensitivity to Pain Traumatisation Scale; TAS-20, Toronto Alexithymia Scale.

[a]Adults who were included in the network analysis reported a lower 'least pain' during the past 7 days in comparison with those who were not included (Welch's $t(56.3) = 3.24$, $p = 0.002$).

[b]Adults who were included in the network analysis reported a lower level of externally oriented thoughts in comparison with those who were not included (Welch's $t(24.1) = 3.88$, $p < 0.001$).

3.1.1 | Sociodemographic and Medical Characteristics

The study population consisted of 517 adults with SCD, primarily female (61.94%), with a mean age of approximately 40 years (median 38 years). The participants were born in Africa and France in almost equal numbers. Most participants had attained a higher level of education than the French high school terminal diploma 'Baccalauréat' (equivalent to 12 years of schooling). Notably, individuals born in Africa were more likely to have a lower educational level ('Baccalauréat' or less), whereas those born in France tended to have a higher educational level ('Licence' [university undergraduate level corresponding to 3 years of studies] or more; $\chi^2(9) = 28.10$, $p < 0.001$).

Two thirds of the sample were homozygous SS, whereas the remaining third were composite heterozygotes, including 17.1% SC and 5.3% with combined S-β-thalassaemia. Consequently, over two thirds of the participants had a severe form of SCD (SS or Sβ0). No difference appeared in the genotype distribution according to the place of birth. Half of our population were under

HU, with a mean reported dose of 1021 mg. Respondents declared being under HU for almost 7 years. The data on MCV and HbF were provided as supplementary information (see Table 1) for clinicians, offering additional insights into the medical characteristics of our study population. These medical data were not incorporated into the NA.

3.1.2 | Pain Experience and Pain-Related Covariates

3.1.2.1 | Pain Severity (BPI). Data revealed a low average pain intensity across the past week, with 29 (7%) respondents reporting no pain. However, this seemingly mild average belies a more nuanced picture. Ninety-three per cent of participants ($n = 387$) reported experiencing pain with an intensity exceeding zero. Nearly half (45.9%, $n = 191$) required medication to manage their pain, exceeding the threshold of $M > 4$ as defined by the Haute Autorité de Santé (HAS; French National Authority for Health) (2020). Notably, 12.0% ($n = 50$) reported severe to unbearable pain ($M > 6$).

A significant proportion (65.5%, $n = 270$) of patients indicated their pain 'in general' (BPI, item 3) required medication during the past week ($M > 4$). This finding aligns with potential chronic pain presentations. Additionally, a substantial majority (73.6%) reported an average increase of 2.7 points in pain intensity between 'in general' and 'now' (BPI, item 4). This suggests a potential cognitive reappraisal of pain perception during the assessment itself.

Importantly, neither pain intensity nor its categorical distribution, as defined by the HAS recommendations in 2020 (2020), demonstrated statistically significant differences based on patient genotypes ($F(1, 412) = 0.14$, $p = 0.710$; $\chi^2(16) = 22.97$, $p = 0.115$). However, respondents born in Africa reported a higher severity of pain than those born in France (ANOVA—post hoc comparisons with Bonferroni correction: $t(412) = -3.35$, $p = 0.003$).

3.1.2.2 | Pain Interference (BPI). Pain interference with daily activities was minimal, aligning with the reported low average pain intensity (see supra). A strong dependency was observed between the HAS-defined categories (2020) of pain intensity and interference ($\chi^2(16) = 198$, $p < 0.001$). This association is further corroborated by the significant positive correlation between pain intensity and interference with daily life ($r = 0.64$, $p < 0.001$).

Neither genotypes nor the severity of SCD significantly impacted overall interference or its seven constituent dimensions. However, female and older patients experienced significantly higher levels of interference (respectively, Mann–Whitney $U = 16{,}592$, $p = 0.004$; $r = 0.138$, $p = 0.005$). Additionally, women exhibited higher levels of interference across all seven assessed dimensions of pain interference (Mann–Whitney U, $p < 0.05$). African respondents reported a higher level of interference than French respondents (ANOVA—post hoc comparisons with Bonferroni correction: $t(409) = -3.15$, $p = 0.005$).

3.1.2.3 | Pain-Related Beliefs (PBPI). Approximately 90% of patients reported understanding the nature and origin of their pain (dimension: mystery). Regarding pain temporality, nearly 90% perceived their pain as intermittent rather than constant (dimension: constancy), and approximately two thirds viewed their pain as acute rather than chronic (dimension: permanence). Notably, nearly one third of patients expressed feelings of responsibility for the onset and persistence of their pain (dimension: self-blame), with almost 35% attributing blame to themselves during a pain crisis.

Regarding the constancy dimension, patients with a more severe genotype (SS or Sβ0) perceived their pain experience as more intermittent than those with a less severe genotype (Mann–Whitney $U = 18{,}380$, $p = 0.026$).

3.1.2.4 | Pain-Related Cognitive Mechanisms of Coping (PCS). Over 60% of our study population exceeded the clinical threshold for catastrophising (> 22), indicating a tendency to respond to painful stimuli with negative cognitive patterns that occur before, during or after pain episodes. These cognitive distortions are primarily characterised by:

- Magnification: Nearly 60% of participants had a score above the clinical threshold of 5, thus exhibiting a heightened perception of the threat posed by painful stimuli. This amplification correlated positively with unprocessed emotions (EPS-25; $r = 0.38$, $p < 0.001$) and anxiety (HADS; $r = 0.49$, $p < 0.001$).
- Rumination: Almost 45% of participants reported ruminating on past painful experiences. This repetitive negative thinking tendency was linked to anxiety levels (HADS; $r = 0.47$, $p < 0.001$) and unprocessed emotions (EPS-25; $r = 0.36$, $p < 0.001$).
- Helplessness: Nearly a third of respondents expressed feelings of helplessness in the face of pain. These feelings correlated positively with unprocessed emotions (EPS-25; $r = 0.36$, $p < 0.001$) and anxiety (HADS; $r = 0.50$, $p < 0.001$).

The severity of catastrophising increased with escalating pain intensity categories, as defined by the French National Authority for Health ($F(4, 398) = 12.06$, $p < 0.001$). A pain intensity threshold of four, indicating the need for treatment (Haute Autorité de Santé 2020), differentiated two groups: as pain intensity increased, participants were more likely to exceed the clinical threshold for catastrophising and its component dimensions (respectively, $\chi^2(4) = 24.55, 23.65, 37.16, 34.09$; all p values < 0.001).

3.1.2.5 | Pain as Trigger of Traumatism Mechanisms (SPTS-12). Over half of our study population exhibited above-average scores, suggesting a predisposition to developing a pain response akin to post-traumatic stress disorder (PTSD). Notably, nearly a quarter reported exceptionally high sensitivity to trauma (a standard and a half deviation above mean).

Strong positive correlations were observed between trauma sensitivity and rumination (PCS; $r = 0.75$, $p < 0.001$), magnification (PCS; $r = 0.69$, $p < 0.001$) and feelings of helplessness (PCS; $r = 0.67$, $p < 0.001$). Additionally, moderate positive correlations were found between trauma sensitivity and unprocessed emotions (EPS-25; $r = 0.40$, $p < 0.001$) and anxiety levels (HADS; $r = 0.47$, $p < 0.001$).

Our analysis revealed a significant difference in trauma sensitivity based on pain intensity thresholds, as defined by the French National Authority for Health (HAS) (2020). Participants reporting no pain or low pain intensity (<4) exhibited lower levels of trauma sensitivity compared to those with moderate to unbearable pain intensity (>4; Student's $t(403) = -6.17$, $p < 0.001$).

3.1.3 | Emotional Covariates of the Pain Experience

3.1.3.1 | Anxiety and Depression (HADS). The experience of SCD in France is characterised by elevated levels of anxiety. Over 27% of our study population exceeded the clinical threshold for anxiety, significantly surpassing the prevalence observed in other SCD studies (Franco et al. 2022; Jonassaint et al. 2024; Levenson et al. 2008), which typically report a prevalence of less than 10%.

Approximately 10% of our population met the pathological threshold for depression. This finding is lower than the prevalence reported in other countries for SCD. Literature reviews suggest that between 29% and 36% of adult SCD patients experience depression (Oudin Doglioni et al. 2021).

In our sample, individuals of African origin were more likely to exhibit both anxiety and depression compared to adults born in France (ANOVA, $p < 0.05$). Although gender did not influence depression levels, women tended to experience a higher level of anxiety compared to men (Mann–Whitney $U = 26{,}839$, $p = 0.027$).

3.1.3.2 | Alexithymia (TAS-20). Approximately 27% of our study population met the clinical threshold for alexithymia (>61), indicating difficulties in identifying and expressing self-feelings and engaging in externalised thinking.

Alexithymia scores were not significantly influenced by sociodemographic factors, except for the educational level. As educational attainment increased, total alexithymia scores decreased ($F(3, 376) = 4.36$, $p = 0.005$). This reduction was primarily driven by improvements in emotion identification ($F(3, 377) = 3.14$, $p = 0.025$) and decreased external-oriented thinking ($F(3, 378) = 8.17$, $p < 0.001$).

3.1.3.3 | Cognitive-Emotional Processing (EPS-25). Our study population exhibited high scores across all dimensions and the total score of the scale. Patients who met the clinical threshold for alexithymia (>61) reported higher levels of dysfunctional emotional processing across all dimensions and the total score compared to those below the threshold (Student's *t*-test, all *p* values <0.001). Additionally, women exhibited higher levels of dysfunctional processing than men (Student's $t(392) = 1.79$, $p = 0.037$), characterised by increased unprocessed or unregulated emotions, avoidance behaviours and impoverished emotional experiences.

3.2 | Network Analysis (NA) of Pain Experience, Pain-Related Covariates and Emotional Covariates Associated With Pain Experience

Pearson's correlation matrix is available as Table S1.

3.2.1 | Estimation of the 'Pain in SCD' Network Model and Centrality Indices

The network derived from the analysis is depicted in Figure 1A. The edges represent unregularised (undirected) partial correlations between nodes. Blue edges signify positive associations, whereas red edges indicate negative associations. The thicker and darker edges indicate stronger partial correlations between nodes. The visual representation of the network (based on the Fruchterman–Reingold algorithm representation) emphasises the clustering of nodes with strong connections and the separation of nodes with weak connections.

Table S2 summarises the strength of associations between pairs of nodes in the network. The strongest associations were between pain severity and interference (BPI; $\gamma = 0.414$), the SPTS total score and the catastrophising subdimension rumination (SPTS—PCS-Rumination; $\gamma = 0.400$), the catastrophising subdimensions magnification and helplessness (PCS; $\gamma = 0.370$), the emotional processing scale total score and the alexithymia total score (EPS-25—TAS-20; $\gamma = 0.309$), and the alexithymia total score and the pain belief subdimension mystery (TAS-20—PBPI-Mystery; $\gamma = 0.255$).

Centrality indices (Figure 1B and Table S3), which measure the influence of each node in the network, revealed that the catastrophising subdimension helplessness (PCS; $s = 1.130$), the sensitivity to pain traumatisation (SPTS-12; $s = 1.049$) and the catastrophising subdimension magnification (PCS; $s = 1.025$) were the most influential nodes in the network. Conversely, the perception of pain as permanent (PBPI, $s = 0.395$), the self-blame associated with pain experience (PBPI, $s = 0.450$) and the perception of pain experience as a mystery (PBPI, $s = 0.719$) were the less influential nodes.

3.2.2 | 'Pain in SCD' Network Community Analysis

Community analysis was conducted to examine the network structure, specifically whether nodes function as a unified network or form distinct communities of covering nodes. The analysis revealed the presence of three primary communities (visualised by coloured nodes in Figure 1A). The first community comprised cognitive-evaluative processes associated with pain experience (coloured in green; SPTS-12 and all PCS subdimensions: Rumination, Helplessness, Magnification). The second community focused on motivational-affective input triggered by pain (coloured in blue; PBPI subdimensions Self-blame and Mystery, TAS-20, EPS-25 and HADS-Anxiety). The third community characterised the pain experience of French adults with SCD (Sensory-discriminative; coloured in yellow; PBPI subdimensions Permanent and Constancy, BPI subdimensions Pain Severity and Pain Interference, and HADS-Depression).

A bridge strength analysis (Figure S2) identified the most influential nodes connecting different communities. The nodes with the highest influence were, in descending order: Anxiety (community 2: motivational-affective input, $s = 0.69$), Depression (community 3: sensory-discriminative input, $s = 0.43$) and Helplessness (community 1: Cognitive-evaluative input, $s = 0.41$).

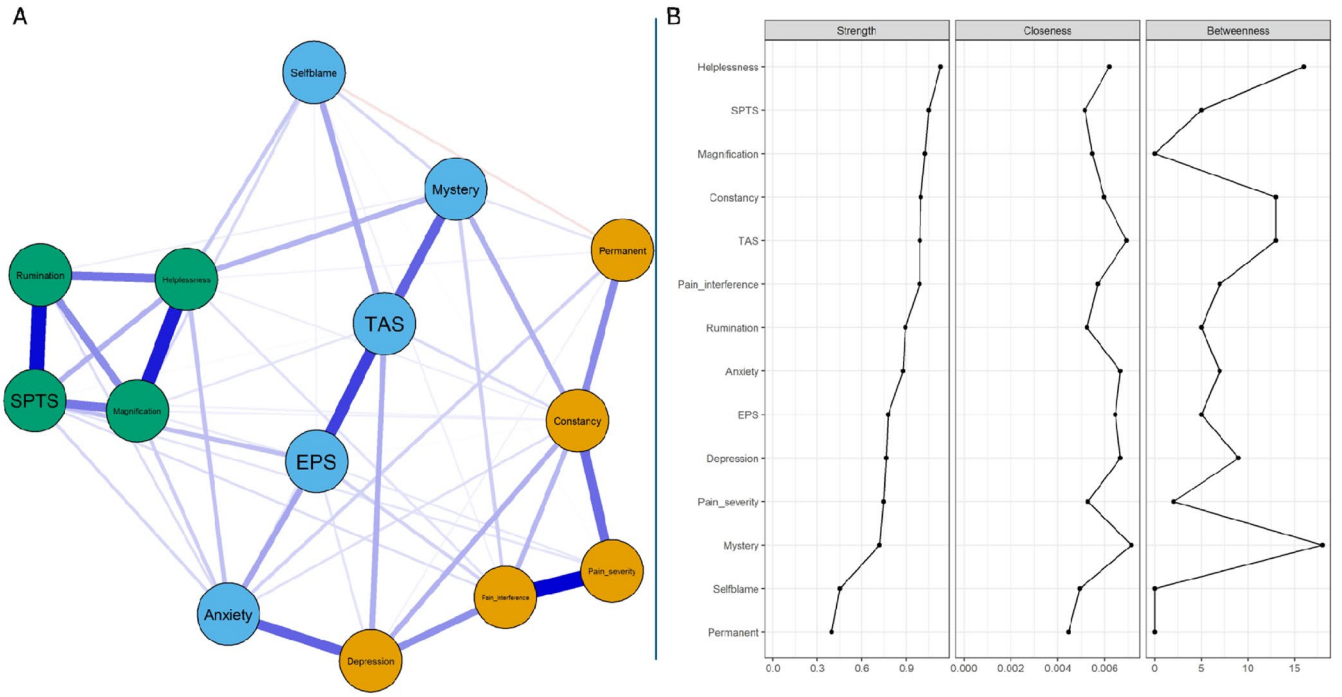

FIGURE 1 | (A) Undirected network (with three communities) of the pain experience, pain-related cognition and emotion in 347 French adults with sickle cell disease. (B) Undirected network three indices of centrality ordered by strength (closeness and betweenness were not considered in this study due to conceptual concerns regarding their applicability to psychological networks (Bringmann et al. 2019). **Communities.** Green (cognitive-evaluative input): Cognitive processes associated with the pain experience (SPTS [Sensitivity to Pain Traumatisation Scale; SPTS-12]—PCS [Pain Catastrophising Scale] Rumination—PCS-Magnification—PCS-Helplessness). Blue (motivational-affective input): Emotional processes triggered by the pain experience (PBPI [Pain Beliefs and Perceptions Inventory] Self-blame—PBPI-Mystery—TAS [Toronto Alexithymia Scale; TAS-20]—EPS [Emotional Processing Scale; EPS-25]—HADS [Hospital Anxiety and Depression Scale] Anxiety). Orange (sensory-discriminative input): Characterisation of the pain experience (PBPI-Permanent—PBPI-Constancy—BPI [Brief Pain Inventory] Pain severity—BPI-Pain interference—HADS-Depression). **Note**. Centrality indices values are reported in Table S3.

3.2.3 | Pain in SCD Network Accuracy

The case-dropping bootstrap helps identify the robustness of the centrality indices used when estimating the model (here, node strength). When performing the analysis, it appeared that the average correlation for strength (CSC = 0.67) was above the 0.25 threshold. The strength indicator can therefore be considered valid.

3.3 | Directed Acyclic Graph of the Pain Experience in SCD

Directed acyclic graphs were employed to represent the Bayesian networks, visualising the directed associations between the included nodes, thus potential psychological processes. A bootstrap procedure was implemented to identify the arrows that consistently appeared across iterations (> 50%), as depicted in Figure 2.

The proposed network demonstrated a lack of substantial interconnections between the three identified communities. Specifically, there was an absence of a direct link between the first community (cognitive-evaluative input) and the third community (sensory-discriminative input), and only one indirect link was identified (Helplessness-Mystery-Constancy). Conversely, the nodes within the three communities exhibited robust interconnectedness. The second community (motivational-affective input) received the most links from the other communities (three from each of the other two communities), while it sent only one link to the third community.

4 | Discussion

The present study's findings align with previous research (Ballas and Darbari 2020; Ballas et al. 2012; Taylor et al. 2010), demonstrating pain as a central feature of SCD. Our results further elucidate that higher pain intensity (BPI > 4) distinguishes a subgroup at an elevated risk of dysfunctional pain cognitions and negative pain-related emotions. NA revealed intricate interconnections between pain experience, cognitions and emotions, forming three distinct communities. This structure mirrors the explanatory model of Kenney and Smith (2022) grounded in the Neuromatrix framework (Melzack 2001). The DAG provides valuable insights into potential psychological processes between these three communities and their constituent variables, which still need to be demonstrated.

The first community (cognitive-evaluative input) exhibited a high degree of interconnectedness. Notably, the nodes of

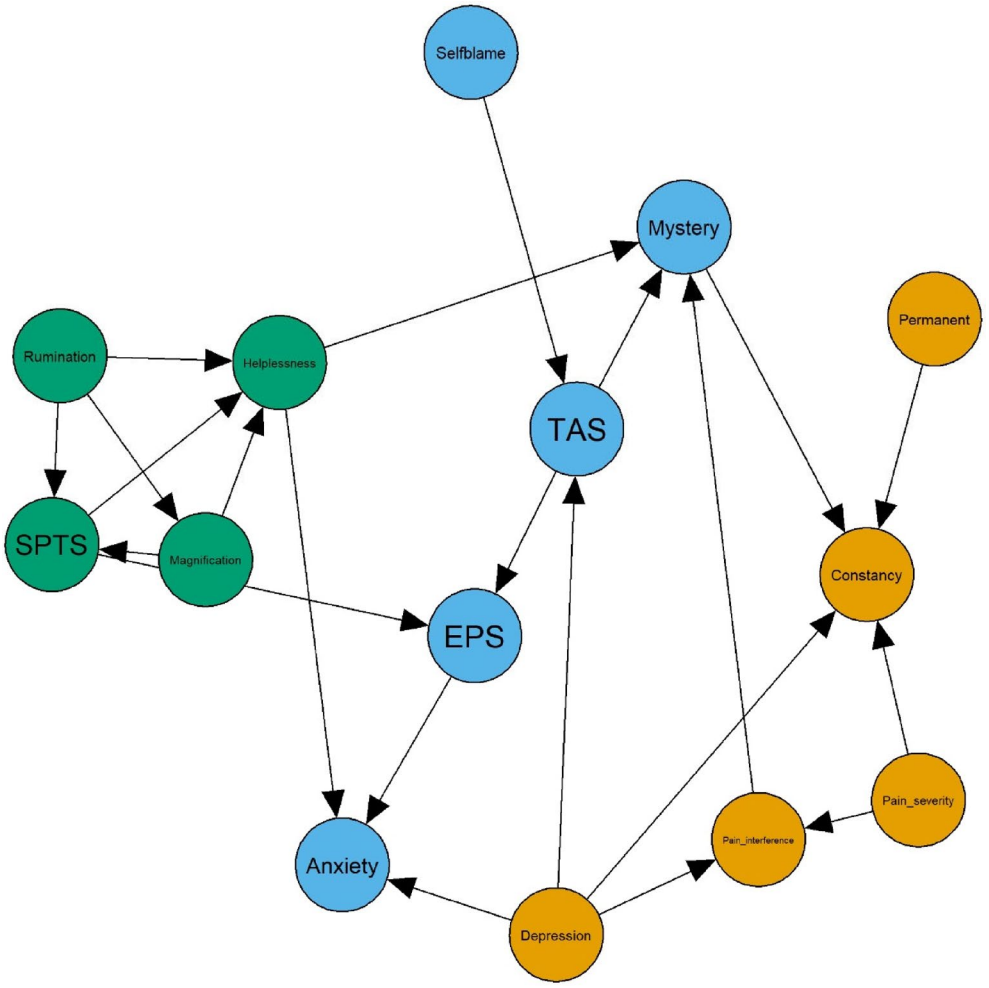

FIGURE 2 | Directed acyclic graph (DAG) of the pain experience in 347 French adults with sickle cell disease. **Communities.** Green (cognitive-evaluative input): Cognitive processes associated with the pain experience (SPTS [Sensitivity to Pain Traumatisation Scale; SPTS-12]—PCS [Pain Catastrophising Scale] Rumination—PCS-Magnification—PCS-Helplessness). Blue (motivational-affective input): Emotional processes triggered by the pain experience (PBPI [Pain Beliefs and Perceptions Inventory] Self-blame—PBPI-Mystery—TAS [Toronto Alexithymia Scale; TAS-20]—EPS [Emotional Processing Scale; EPS-25]—HADS [Hospital Anxiety and Depression Scale] Anxiety). Orange (sensory-discriminative input): Characterisation of the pain experience (PBPI-Permanent—PBPI-Constancy—BPI [Brief Pain Inventory] Pain severity—BPI-Pain interference—HADS-Depression).

Helplessness, SPTS and Magnification emerged as particularly influential within the overall network, demonstrating distinct connectivity patterns. These patterns suggest a potential cumulative mechanism in the development of negative pain-related cognitions. This process may initiate repetitive negative thinking about the pain experience (rumination), which could subsequently progress to an exaggeration of perceived pain stimuli (magnification). This might trigger cognitive, affective and behavioural responses to pain that resemble a traumatic stress reaction (SPTS). Ultimately, a negative appraisal of one's ability to cope with pain (helplessness) may develop. This process could inform the development of targeted interventions aimed at disrupting this cognitive cycle and alleviating the burden of chronic pain in adults with SCD.

This hypothesised negative pain-related cognitive process aligned with the Mutual Maintenance Model of chronic pain and PTSD (Sharp and Harvey 2001), which identifies seven factors contributing to the mutual maintenance of chronic pain and PTSD. It includes (i) attentional biases towards painful stimuli (i.e., rumination); (ii) fear of arousal-related sensations (i.e., magnification); (iii) pain as a reminder of trauma, triggering arousal responses to avoid pain and trauma-related memories (i.e., SPTS); (iv) avoidance behaviours to minimise pain and associated thoughts (i.e., SPTS); (v) fatigue and lethargy associated with depression; (vi) general anxiety; and (vii) cognitive demands related to pain and PTSD, which can limit coping skills (i.e., helplessness).

Helplessness emerged as the strongest bridge between communities, directed exclusively to the second community (Mystery and Anxiety): emotions triggered by pain (motivational-affective input). The direction of the connections indicated that emotions might have no direct impact on cognitive processes. Notably, the characterisation of the pain experience (third community: sensory-discriminative input) had no direct or indirect relationship with cognitive processes. This suggests it was not the lived experience of pain itself that matters, but rather its perception and associated memories. This finding was particularly relevant in the context of SCD, where patients frequently experience both

acute and chronic pain (Ballas and Darbari 2020) and may require intensive care unit admission for severe acute VOC (Ballas and Darbari 2020). As suggested by the Triple Vulnerability Model of Pain (Otis et al. 2006), the development of a sense of unpredictability and uncontrollability of pain (helplessness) may precede the development of anxiety-related emotions and chronic pain. This finding underscored the importance of early interventions to manage pain and its psychological consequences following VOC and hospitalisation, especially in cases of intensive care unit admission.

Within the second community (motivational-affective input), encompassing emotions triggered by pain, connectivity patterns were more linear compared to the first community, with anxiety and mystery forming the endpoints of both pathways (PBPI-Self-blame – TAS-20 – EPS-25 – HADS-Anxiety; PBPI-Self-blame – TAS-20 – PBPI-Mystery). Self-blame emerged as the starting point of both pathways with a low strength of association ($r = 0.32$; $s = 0.14$) with alexithymia (TAS-20 total score). While self-blame appeared relatively peripheral, alexithymia played a pivotal role. Alexithymia, consistently associated with pain experiences in various chronic pain conditions (Di Tella and Castelli 2016), may hinder individuals' ability to adequately regulate and process their emotions (Preece et al. 2023). This can lead to misinterpretation of emotional arousal as physical symptoms, potentially resulting in unnecessary medical attention (Lumley et al. 1996). Consequently, alexithymia was directly linked to difficulties in emotion processing (EPS-25), aligning with established theories (Rachman 2001). Notably, the EPS total score was directly connected to sensitivity to pain traumatisation (SPTS-12), consistent with the Shared Vulnerability Model. This model posits that sensitivity to pain traumatisation, combined with difficulties in processing emotions, predisposes individuals to chronic pain, anxiety and PTSD (Asmundson et al. 2002).

The proposed psychological processes (DAG) highlight anxiety, a major bridge between communities, as the endpoint of emotional dysregulation, difficulty in emotion processing and cognitive processes characterised by traumatisation and helplessness. This finding aligned with the literature (Asmundson and Katz 2009; Katz et al. 2014), particularly the Fear-Avoidance Model, which links misinterpretation of physical sensations, often due to alexithymia or dysfunctional emotion processing, with pain-related cognitive biases like catastrophising and avoidance behaviours (Crombez et al. 2012; Vlaeyen et al. 2016). In the context of SCD, these findings were particularly relevant and might explain the high rate of anxiety (27%) found. The evaluation of anxiety could guide the identification of patients at higher risk of developing more complex or chronic psychological distress.

The third community (sensory-discriminative input), characterising pain experience, exhibited limited connectivity with the other two communities. As anticipated, in the proposed psychological processes, pain severity directly influenced pain interference, aligning with previous research (Cleeland and Ryan 1994). Furthermore, temporal perceptions of pain were directly linked, with the perception of pain as potentially chronic (PBPI-Permanent) influencing the perceived cyclicality of pain (constant versus intermittent). Constance emerged as a pivotal node within this community. In a condition where pain is a defining characteristic, understanding its temporal aspects is crucial for effective coping strategies.

Although depression is considered an affective variable, its association with sensory-discriminative input highlights the intricate interplay between the physiopathology of pain and psychopathology (Haapakoski et al. 2015). Estimates of depression prevalence among patients seeking pain treatment range widely, from 1.5% to 100% (Bair et al. 2003), with estimates for SCD patients typically falling between 30% and 50% (Oudin Doglioni et al. 2021). In our NA, depression emerged as a strong bridge between communities, directly and indirectly influencing anxiety through alexithymia, likely through the emotional blunting inherent to depression (Beck and Bredemeier 2016). In line with the recommendations of Oudin Doglioni et al. (2021), we advocate for a more systematic evaluation, during medical consultations, of depression, using the HADS, to prevent the development of more complex psychological distress through an early targeted non-pharmacological intervention.

This work presents novel strategic opportunities for pain management in both acute and chronic situations. Patients who repeatedly experience refractory VOC may develop a detachment from their bodily sensations, leading to a diminished sense of bodily awareness. Alexithymia, a temporary defence mechanism, can become a significant and debilitating trait if left operational. The maladaptive coping strategies employed in SCD often involve a focus on external environments and avoidance of bodily sensations, which may be perceived as potential trauma triggers. Mind–body approaches, such as mindfulness and yoga, have demonstrated efficacy in treating both alexithymia and PTSD. Some studies propose integrated programmes combining various approaches with psychoeducation and psycho-corporeal practices (Cooper et al. 2018; Edwards et al. 2018).

The present study employed a NA approach to investigate the interrelationships between pain, cognitions and emotions in a sample of adult SCD patients. Although this methodology offers a novel perspective on the complexity of pain experiences, we must acknowledge certain limitations. The relatively modest sample size, although comparable to other studies in SCD, may limit the generalisability of our findings. Additionally, while we conducted an extensive evaluation of pain, associated cognitions and emotions, it is possible that other relevant factors not included may influence these relationships, for example, perceived discrimination in healthcare impacting the burden of pain (Haywood et al. 2014), or experience of sexual violence predicting chronic pain (Chopra et al. 2022). Noteworthy, NA is an exploratory method: the identified psychological processes should be interpreted as hypothetical. Further research is needed to validate these findings and to investigate the underlying causal mechanisms. Longitudinal studies or ecological momentary assessment (Shiffman et al. 2008) could provide valuable insights into the temporal dynamics of these relationships and the potential impact of interventions on network structure. Despite these limitations, our model mirrors other findings, especially the explanatory model of Kenney and Smith (2022).

5 | Conclusion

This study aimed to explore the relationship between variables referring to pain, pain-related emotions and cognitions in adults with SCD. Our findings demonstrate that a high intensity of pain might be a risk factor for dysfunctional cognitions and more negative emotions. NA and DAG suggested possible psychological processes to better understand pain in SCD and could serve to develop interventions. This study extends previous research by providing a comprehensive NA of pain-related variables, offering novel insights into the complex interplay between pain, cognitions and emotions. These findings have clinical implications: targeting dysfunctional pain cognitions and negative emotions may be beneficial to pain management; thus, quality of life in SCD. However, these findings are exploratory and need to be replicated. Overall, our study provides valuable insights into pain in SCD.

Author Contributions

D.O.D. designed and performed the research, analysed the data and wrote the first draught. M.C. reviewed the draught. S.F. reviewed the draught. F.G. reviewed the draught. M.-C.G. designed the research, supervised the analyses and reviewed the draught.

Conflicts of Interest

Dr. Oudin Doglioni reported receiving grants from the Fondation des Maladies Rares (French foundation for rare diseases). Dr. Forté reported receiving grants from the Canadian Haematology Society and Pfizer during the conduct of the study and served as a consultant for Novartis. Other authors declare no conflicts of interest.

Data Availability Statement

The datasets generated during and/or analysed during the current study are available from the corresponding author upon a reasonable request and with appropriate ethical considerations.

References

Anie, K. A., and J. Green. 2015. "Psychological Therapies for Sickle Cell Disease and Pain." *Cochrane Database of Systematic Reviews* 5: CD001916. https://doi.org/10.1002/14651858.CD001916.pub3.

Asmundson, G. J. G., M. J. Coons, S. Taylor, and J. Katz. 2002. "PTSD and the Experience of Pain: Research and Clinical Implications of Shared Vulnerability and Mutual Maintenance Models." *Canadian Journal of Psychiatry* 47, no. 10: 930–937. https://doi.org/10.1177/070674370204701004.

Asmundson, G. J. G., and J. Katz. 2009. "Understanding the Co-Occurrence of Anxiety Disorders and Chronic Pain: State-Of-The-Art." *Depression and Anxiety* 26, no. 10: 888–901. https://doi.org/10.1002/da.20600.

Bagby, M., J. Parker, and G. Taylor. 1994. "The Twenty-Item Toronto Alexithymia Scale—I. Item Selection and Cross-Validation of the Factor Structure." *Journal of Psychosomatic Research* 38, no. 1: 23–32.

Bair, M. J., R. Robinson, W. Katon, and K. Kroenke. 2003. "Depression and Pain Comorbidity." *Archives of Internal Medicine* 163: 2433–2445.

Baker, R., S. Thomas, P. W. Thomas, and M. Owens. 2007. "Development of an Emotional Processing Scale." *Journal of Psychosomatic Research* 62, no. 2: 167–178. https://doi.org/10.1016/j.jpsychores.2006.09.005.

Bakshi, N., I. Lukombo, I. Belfer, and L. Krishnamurti. 2018. "Pain Catastrophizing Is Associated With Poorer Health-Related Quality of Life in Pediatric Patients With Sickle Cell Disease." *Journal of Pain Research* 11: 947–953. https://doi.org/10.2147/JPR.S151198.

Ballas, S. K., and D. S. Darbari. 2020. "Review/Overview of Pain in Sickle Cell Disease." *Complementary Therapies in Medicine* 49: 102327. https://doi.org/10.1016/j.ctim.2020.102327.

Ballas, S. K., K. Gupta, and P. Adams-Graves. 2012. "Sickle Cell Pain: A Critical Reappraisal." *Blood* 120, no. 18: 3647–3656.

Beck, A. T., and K. Bredemeier. 2016. "A Unified Model of Depression: Integrating Clinical, Cognitive, Biological, and Evolutionary Perspectives." *Clinical Psychological Science* 4, no. 4: 596–619. https://doi.org/10.1177/2167702616628523.

Bernstein, E. E., A. Heeren, and R. J. McNally. 2019. "Reexamining Trait Rumination as a System of Repetitive Negative Thoughts: A Network Analysis." *Journal of Behavior Therapy and Experimental Psychiatry* 63: 21–27. https://doi.org/10.1016/j.jbtep.2018.12.005.

Booker, M. J., K. L. Blethyn, C. J. Wright, and S. M. Greenfield. 2006. "Pain Management in Sickle Cell Disease." *Chronic Illness* 2, no. 1: 39–50. https://doi.org/10.1177/17423953060020011101.

Borsboom, D., and A. O. J. Cramer. 2013. "Network Analysis: An Integrative Approach to the Structure of Psychopathology." *Annual Review of Clinical Psychology* 9, no. 1: 91–121. https://doi.org/10.1146/annurev-clinpsy-050212-185608.

Briganti, G., M. Scutari, and R. J. McNally. 2023. "A Tutorial on Bayesian Networks for Psychopathology Researchers." *Psychological Methods* 28, no. 4: 947–961. https://doi.org/10.1037/met0000479.

Bringmann, L. F., T. Elmer, S. Epskamp, et al. 2019. "What Do Centrality Measures Measure in Psychological Networks?" *Journal of Abnormal Psychology* 128, no. 8: 892–903. https://doi.org/10.1037/abn0000446.

Burger, J., M. S. Stroebe, P. Perrig-Chiello, et al. 2020. "Bereavement or Breakup: Differences in Networks of Depression." *Journal of Affective Disorders* 267: 1–8. https://doi.org/10.1016/j.jad.2020.01.157.

Chen, E., S. W. Cole, and P. M. Kato. 2004. "A Review of Empirically Supported Psychosocial Interventions for Pain and Adherence Outcomes in Sickle Cell Disease." *Journal of Pediatric Psychology* 29, no. 3: 197–209. https://doi.org/10.1093/jpepsy/jsh021.

Chen, J., and Z. Chen. 2008. "Extended Bayesian Information Criteria for Model Selection With Large Model Spaces." *Biometrika* 95, no. 3: 759–771. https://doi.org/10.1093/biomet/asn034.

Childerhose, J. E., R. M. Cronin, M. D. Klatt, and A. Schamess. 2023. "Treating Chronic Pain in Sickle Cell Disease—The Need for a Biopsychosocial Model." *New England Journal of Medicine* 388, no. 15: 1349–1351. https://doi.org/10.1056/NEJMp2301143.

Chopra, M., J. Byrd, K. Wuichet, and M. R. DeBaun. 2022. "Sexual Violence as a Precipitator of Chronic Pain in Young Adults With Sickle Cell Disease." *Blood Advances* 6, no. 16: 4831–4833. https://doi.org/10.1182/bloodadvances.2022007600.

Citero, V. d. A., J. L. Levenson, D. K. McClish, et al. 2007. "The Role of Catastrophizing in Sickle Cell Disease – The PiSCES Project." *Pain* 133, no. 1: 39–46. https://doi.org/10.1016/j.pain.2007.02.008.

Cleeland, C., and K. M. Ryan. 1994. "The Brief Pain Inventory." http://www.rygforskning.dk/sites/default/files/files/skemaer/BPI_UserGuide.pdf.

Cooper, D., K. Yap, and L. Batalha. 2018. "Mindfulness-Based Interventions and Their Effects on Emotional Clarity: A Systematic Review and Meta-Analysis." *Journal of Affective Disorders* 235: 265–276. https://doi.org/10.1016/j.jad.2018.04.018.

Costantini, G., S. Epskamp, D. Borsboom, et al. 2015. "State of the Art Personality Research: A Tutorial on Network Analysis of Personality

Data in R." *Journal of Research in Personality* 54: 13–29. https://doi.org/10.1016/j.jrp.2014.07.003.

Crombez, G., C. Eccleston, S. Van Damme, J. W. S. Vlaeyen, and P. Karoly. 2012. "Fear-Avoidance Model of Chronic Pain: The Next Generation." *Clinical Journal of Pain* 28, no. 6: 475–483. https://doi.org/10.1097/AJP.0b013e3182385392.

Dany, L., P. Roussel, S. Carayon, S. Blois, and T. Apostolidis. 2009. "Adaptation et Validation Française de l'Inventaire de Croyances et Perceptions Associées à la Douleur." *Pratiques Psychologiques* 15, no. 3: 387–404. https://doi.org/10.1016/j.prps.2007.12.009.

Di Tella, M., and L. Castelli. 2016. "Alexithymia in Chronic Pain Disorders." *Current Rheumatology Reports* 18, no. 7: 41. https://doi.org/10.1007/s11926-016-0592-x.

Driscoll, J., M. Bamne, and C. Jonassaint. 2017. "Assessing the Validity of the Brief Pain Inventory for Use Among Adults With Sickle Cell Disease." *Blood* 130, no. Supplement 1: 5579. https://doi.org/10.1182/blood.V130.Suppl_1.5579.5579.

Edwards, C. L., A. Killough, M. Wood, et al. 2014. "Emotional Reactions to Pain Predict Psychological Distress in Adult Patients With Sickle Cell Disease (SCD)." *International Journal of Psychiatry in Medicine* 47, no. 1: 1–16.

Edwards, E., S. Shivaji, and P. Wupperman. 2018. "The Emotion Mapping Activity: Preliminary Evaluation of a Mindfulness-Informed Exercise to Improve Emotion Labeling in Alexithymic Persons." *Scandinavian Journal of Psychology* 59, no. 3: 319–327. https://doi.org/10.1111/sjop.12438.

Edwards, L. Y., and C. L. Edwards. 2010. "Psychosocial Treatments in Pain Management of Sickle Cell Disease." *Journal of the National Medical Association* 102, no. 11: 1084–1094. https://doi.org/10.1016/s0027-9684(15)30737-9.

Epskamp, S., D. Borsboom, and E. I. Fried. 2018. "Estimating Psychological Networks and Their Accuracy: A Tutorial Paper." *Behavior Research Methods* 50, no. 1: 195–212. https://doi.org/10.3758/s13428-017-0862-1.

Epskamp, S., and E. I. Fried. 2018. "A Tutorial on Regularized Partial Correlation Networks." *Psychological Methods* 23, no. 4: 617–634. https://doi.org/10.1037/met0000167.

Epskamp, S., and E. I. Fried. 2023. "bootnet: Bootstrap Methods for Various Network Estimation Routines (Version 1.5.6) [Logiciel]." https://cran.r-project.org/web/packages/bootnet/index.html.

Epskamp, S., L. J. Waldorp, R. Mõttus, and D. Borsboom. 2018. "The Gaussian Graphical Model in Cross-Sectional and Time-Series Data." *Multivariate Behavioral Research* 53, no. 4: 453–480. https://doi.org/10.1080/00273171.2018.1454823.

Fletcher, C. 2000. "Appraisal and Coping With Vaso-Occlusive Crisis in Adolescents With Sickle Cell Disease." *Pediatric Nursing* 26, no. 3: 319–324.

Franco, D., U. Farooq, J. Franco, and M. R. Espinoza-Gutarra. 2022. "Racial and Gender Disparities in the Burden of Depression and Anxiety in Patients With Sickle Cell Disease." *Blood* 140, no. Supplement 1: 11133–11134. https://doi.org/10.1182/blood-2022-164488.

French, D. J., M. Noël, F. Vigneau, J. A. French, C. P. Cyr, and R. Thomas. 2005. "L'Échelle de Dramatisation Face à la Douleur PCS-CF: Adaptation Canadienne en Langue Française de L'Échelle Pain Catastrophizing Scale [PCS-CF: A French-Language, French-Canadian Adaptation of the Pain Catastrophizing Scale]." *Canadian Journal of Behavioural Science = Revue Canadienne des Sciences Du Comportement* 37, no. 3: 181–192. https://doi.org/10.1037/h0087255.

Friedman, J., T. Hastie, and R. Tibshirani. 2008. "Sparse Inverse Covariance Estimation With the Graphical Lasso." *Biostatistics* 9, no. 3: 432–441. https://doi.org/10.1093/biostatistics/kxm045.

Fruchterman, T. M. J., and E. M. Reingold. 1991. "Graph Drawing by Force-Directed Placement." *Software: Practice and Experience* 21, no. 11: 1129–1164. https://doi.org/10.1002/spe.4380211102.

Gay, M.-C., R. Baker, P. Vrignaud, et al. 2019. "Cross-Cultural Validation of a French Version of the Emotional Processing Scale (EPS-25)." *European Review of Applied Psychology* 69, no. 3: 91–99. https://doi.org/10.1016/j.erap.2019.05.002.

Golino, H., A. Christensen, R. Moulder, L. E. Garrido, L. Jamison, and D. Shi. 2023. "EGAnet: Exploratory Graph Analysis – A Framework for Estimating the Number of Dimensions in Multivariate Data Using Network Psychometrics (Version 2.0.3) [Logiciel]." https://cran.r-project.org/web/packages/EGAnet/index.html.

Golino, H., and S. Epskamp. 2017. "Exploratory Graph Analysis: A New Approach for Estimating the Number of Dimensions in Psychological Research." *PLoS One* 12, no. 6: e0174035. https://doi.org/10.1371/journal.pone.0174035.

Haapakoski, R., J. Mathieu, K. P. Ebmeier, H. Alenius, and M. Kivimäki. 2015. "Cumulative Meta-Analysis of Interleukins 6 and 1β, Tumour Necrosis Factor α and C-Reactive Protein in Patients With Major Depressive Disorder." *Brain, Behavior, and Immunity* 49: 206–215. https://doi.org/10.1016/j.bbi.2015.06.001.

Haute Autorité de Santé. 2020. "Liste des Échelles Acceptées Pour Mesurer la Douleur."

Haywood, C., M. Diener-West, J. Strouse, et al. 2014. "Perceived Discrimination in Health Care Is Associated With a Greater Burden of Pain in Sickle Cell Disease." *Journal of Pain and Symptom Management* 48, no. 5: 934–943. https://doi.org/10.1016/j.jpainsymman.2014.02.002.

Hevey, D. 2018. "Network Analysis: A Brief Overview and Tutorial." *Health Psychology and Behavioral Medicine* 6, no. 1: 301–328. https://doi.org/10.1080/21642850.2018.1521283.

Hildenbrand, A. K., E. G. Nicholls, B. P. Daly, M. L. Marsac, R. Tarazi, and D. Raybagkar. 2014. "Psychosocial and Pharmacological Management of Pain in Pediatric Sickle Cell Disease." *Postgraduate Medicine* 126, no. 2: 123–133. https://doi.org/10.3810/pgm.2014.03.2748.

Hofmann, M., M. de Montalembert, B. Beauquier-Maccotta, P. de Villartay, and B. Golse. 2007. "Posttraumatic Stress Disorder in Children Affected by Sickle-Cell Disease and Their Parents." *American Journal of Hematology* 82, no. 2: 171–172. https://doi.org/10.1002/ajh.20722.

Houwing, M. E., P. J. de Pagter, E. J. van Beers, et al. 2019. "Sickle Cell Disease: Clinical Presentation and Management of a Global Health Challenge." *Blood Reviews* 37: 100580. https://doi.org/10.1016/j.blre.2019.05.004.

Isvoranu, A.-M., E. Abdin, S. A. Chong, J. Vaingankar, D. Borsboom, and M. Subramaniam. 2021. "Extended Network Analysis: From Psychopathology to Chronic Illness." *BMC Psychiatry* 21, no. 1: 119. https://doi.org/10.1186/s12888-021-03128-y.

Jiang, H., X. Fei, H. Liu, et al. 2022. "huge: High-Dimensional Undirected Graph Estimation." *CRAN*. https://cran.r-project.org/web/packages/huge/huge.pdf.

Jonassaint, C. R., C. M. Lalama, C. P. Carroll, et al. 2024. "Digital Cognitive Behavioral Therapy vs Education for Pain in Adults With Sickle Cell Disease." *Blood Advances* 8, no. 24: 6257–6266. https://doi.org/10.1182/bloodadvances.2024013861.

Katz, J., S. Fashler, C. Wicks, et al. 2017. "Sensitivity to Pain Traumatization Scale: Development, Validation, and Preliminary Findings." *Journal of Pain Research* 10: 1297–1316. https://doi.org/10.2147/JPR.S134133.

Katz, J., M. G. Pagé, S. Fashler, B. N. Rosenbloom, and G. J. G. Asmundson. 2014. "Chronic Pain and the Anxiety Disorders: Epidemiology, Mechanisms and Models of Comorbidity, and Treatment." In *Mental Health and Pain: Somatic and Psychiatric Components of Pain in Mental*

Health, edited by S. Marchand, D. Saravane, and I. Gaumond, 119–155. Springer Paris. https://doi.org/10.1007/978-2-8178-0414-9_8.

Kenney, M. O., and W. R. Smith. 2022. "Moving Toward a Multimodal Analgesic Regimen for Acute Sickle Cell Pain With Non-Opioid Analgesic Adjuncts: A Narrative Review." *Journal of Pain Research* 15: 879–894. https://doi.org/10.2147/JPR.S343069.

Kenney, M. O., S. Wilson, N. Shah, et al. 2024. "Biopsychosocial Factors Associated With Pain and Pain-Related Outcomes in Adults and Children With Sickle Cell Disease: A Multivariable Analysis of the GRNDaD Multicenter Registry." *Journal of Pain* 25, no. 1: 153–164. https://doi.org/10.1016/j.jpain.2023.07.029.

Lerman, S. F., Z. Rudich, S. Brill, H. Shalev, and G. Shahar. 2015. "Longitudinal Associations Between Depression, Anxiety, Pain, and Pain-Related Disability in Chronic Pain Patients." *Psychosomatic Medicine* 77, no. 3: 333–341. https://doi.org/10.1097/PSY.0000000000000158.

Levenson, J. L. 2008. "Psychiatric Issues in Adults With Sickle Cell." *Primary Psychiatry* 15, no. 5: 45–49.

Levenson, J. L., D. K. McClish, B. A. Dahman, et al. 2008. "Depression and Anxiety in Adults With Sickle Cell Disease: The PiSCES Project." *Psychosomatic Medicine* 70, no. 2: 192–196. https://doi.org/10.1097/PSY.0b013e31815ff5c5.

Lugthart, S., C. Ginete, P. Kuona, M. Brito, and B. P. D. Inusa. 2024. "An Update Review of New Therapies in Sickle Cell Disease: The Prospects for Drug Combinations." *Expert Opinion on Pharmacotherapy* 25, no. 2: 157–170. https://doi.org/10.1080/14656566.2024.2317336.

Lumley, M., L. Stettner, and F. Wehmer. 1996. "How Are Alexithymia and Physical Illness Linked ? A Review and Critique of Pathways." *Journal of Psychosomatic Research* 41, no. 6: 505–518.

Master, S., C. Arnold, T. Davis, R. Shi, and R. P. Mansour. 2016. "Anxiety, Depression, Pain Intensity and Interference in Adult Patients With Sickle Cell Disease." *Blood* 128, no. 22: 1312.

Melzack, R. 2001. "Pain and the Neuromatrix in the Brain." *Journal of Dental Education* 65, no. 12: 1378–1382. https://doi.org/10.1002/j.0022-0337.2001.65.12.tb03497.x.

Moseley, L. G., and A. Arntz. 2007. "The Context of a Noxious Stimulus Affects the Pain It Evokes." *Pain* 133, no. 1: 64–71. https://doi.org/10.1016/j.pain.2007.03.002.

Newman, M. 2010. *Networks: An Introduction*. 1st éd. ed. Oxford University Press. https://doi.org/10.1093/acprof:oso/9780199206650.001.0001.

O'Brien, J. A., J. A. Drake, D. J. Bearden, et al. 2025. "Cognitive Considerations for Adults With Sickle Cell Disease Completing the Brief Pain Inventory." *Pain Reports* 10, no. 1: e1189. https://doi.org/10.1097/PR9.0000000000001189.

Otis, J. D., D. B. Pincus, and T. M. Keane. 2006. "Comorbid Chronic Pain and PTSD Across the Lifespan: A Review of Theoretical Models." In *Psychological Knowledge in Court: PTSD, Pain, and TBI*, edited by G. Young, A. W. Kane, and K. Nicholson, 242–268. Springer.

Oudin Doglioni, D. 2021. "Facteurs Psychosociaux Influençant L'Observance Thérapeutique des Adultes atteints de Drépanocytose." Paris Nanterre.

Oudin Doglioni, D., V. Chabasseur, F. Barbot, F. Galacteros, and M.-C. Gay. 2021. "Depression in Adults With Sickle Cell Disease: Review on the Methodological Issues in Assessing Prevalence of Depression." *BMC Psychology* 9: 54. https://doi.org/10.1186/s40359-021-00543-4.

Piel, F. B., M. H. Steinberg, and D. C. Rees. 2017. "Sickle Cell Disease." *New England Journal of Medicine* 376, no. 16: 1561–1573. https://doi.org/10.1056/NEJMra1510865.

Poundja, J., D. Fikretoglu, S. Guay, and A. Brunet. 2007. "Validation of the French Version of the Brief Pain Inventory in Canadian Veterans Suffering From Traumatic Stress." *Journal of Pain and Symptom Management* 33, no. 6: 720–726. https://doi.org/10.1016/j.jpainsymman.2006.09.031.

Preece, D. A., A. Mehta, K. Petrova, et al. 2023. "Alexithymia and Emotion Regulation." *Journal of Affective Disorders* 324: 232–238. https://doi.org/10.1016/j.jad.2022.12.065.

Price, D. D. 2000. "Psychological and Neural Mechanisms of the Affective Dimension of Pain." *Science* 288, no. 5472: 1769–1772. https://doi.org/10.1126/science.288.5472.1769.

R Core Team. 2023. "R: A Language and Environment for Statistical Computing (Version 4.3.2) [Logiciel]."

Rachman, S. 1980. "Emotional Processing." *Behaviour Research and Therapy* 35: 43–52.

Rachman, S. 2001. "Emotional Processing, With Special Reference to Post-Traumatic Stress Disorder." *International Review of Psychiatry* 13, no. 3: 164–171. https://doi.org/10.1080/09540260120074028.

Roussel, P., S. Carayon, T. Apostolidis, L. Dany, and S. Blois. 2010. "Étalonnage de L'Inventaire de Croyances et Perceptions Associées à la Douleur (ICPD)." *Douleur et Analgésie* 23: 239–245.

Ruta, N. S., and S. K. Ballas. 2016. "The Opioid Drug Epidemic and Sickle Cell Disease: Guilt by Association." *Pain Medicine* 17, no. 10: 1793–1798. https://doi.org/10.1093/pm/pnw074.

Schlaeger, J., M. Ezenwa, Y. Yao, et al. 2019. "Association of Pain, Anxiety, Depression, and Fatigue With Sensitization in Outpatient Adults With Sickle Cell Disease." *Journal of Pain* 20, no. 4, Supplement: S24–S25. https://doi.org/10.1016/j.jpain.2019.01.117.

Schneider, M. B., A. Manikowski, L. Cohen, C. Dampier, and S. Sil. 2022. "The Distinct Longitudinal Impact of Pain Catastrophizing on Pain Interference Among Youth Living With Sickle Cell Disease and Chronic Pain." *Journal of Behavioral Medicine* 45, no. 4: 622–631. https://doi.org/10.1007/s10865-021-00280-4.

Scutari, M., T. Silander, and R. Ness. 2023. "bnlearn: Bayesian Network Structure Learning, Parameter Learning and Inference (Version 4.9.1) [Logiciel]." https://cran.r-project.org/web/packages/bnlearn/index.html.

Shah, N., M. Bhor, L. Xie, et al. 2019. "Treatment Patterns and Economic Burden of Sickle-Cell Disease Patients Prescribed Hydroxyurea: A Retrospective Claims-Based Study." *Health and Quality of Life Outcomes* 17, no. 1: 155. https://doi.org/10.1186/s12955-019-1225-7.

Sharp, T. J., and A. G. Harvey. 2001. "Chronic Pain and Posttraumatic Stress Disorder: Mutual Maintenance?" *Clinical Psychology Review* 21, no. 6: 857–877. https://doi.org/10.1016/S0272-7358(00)00071-4.

Shiffman, S., A. A. Stone, and M. R. Hufford. 2008. "Ecological Momentary Assessment." *Annual Review of Clinical Psychology* 4: 1–32. https://doi.org/10.1146/annurev.clinpsy.3.022806.091415.

Sullivan, M. J., S. R. Bishop, and J. Pivik. 1995. "The Pain Catastrophizing Scale: Development and Validation." *Psychological Assessment* 7, no. 4: 524.

Tanhehco, Y. C., and M. Bhatia. 2019. "Hematopoietic Stem Cell Transplantation and Cellular Therapy in Sickle Cell Disease: Where Are We Now?" *Current Opinion in Hematology* 26, no. 6: 448–452. https://doi.org/10.1097/MOH.0000000000000541.

Taylor, L. E. V., N. A. Stotts, J. Humphreys, M. J. Treadwell, and C. Miaskowski. 2010. "A Review of the Literature on the Multiple Dimensions of Chronic Pain in Adults With Sickle Cell Disease." *Journal of Pain and Symptom Management* 40, no. 3: 416–435. https://doi.org/10.1016/j.jpainsymman.2009.12.027.

The Jamovi Project. 2020. "Jamovi (Version 2.3.21) [Logiciel]."

Traag, V. A., and J. Bruggeman. 2009. "Community Detection in Networks With Positive and Negative Links." *Physical Review E* 80, no. 3: 036115. https://doi.org/10.1103/PhysRevE.80.036115.

Van Zyl, C. 2021. "A Network Analysis of the General Health Questionnaire." *Journal of Health Psychology* 26, no. 2: 249–259. https://doi.org/10.1177/1359105318810113.

Vlaeyen, J. W. S., G. Crombez, and S. J. Linton. 2016. "The Fear-Avoidance Model of Pain." *Pain* 157, no. 8: 1588–1589. https://doi.org/10.1097/j.pain.0000000000000574.

Williams, D. A., and B. E. Thorn. 1989. "An Empirical Assessment of Pain Beliefs." *Pain* 36, no. 3: 351–358.

Williams, H., and P. Tanabe. 2016. "Sickle Cell Disease: A Review of Non-Pharmacological Approaches for Pain." *Journal of Pain and Symptom Management* 51, no. 2: 163–177. https://doi.org/10.1016/j.jpainsymman.2015.10.017.

Zigmond, A. S., and R. P. Snaith. 1983. "The Hospital Anxiety and Depression Scale." *Acta Psychiatrica Scandinavica* 67, no. 6: 361–370. https://doi.org/10.1111/j.1600-0447.1983.tb09716.x.

Supporting Information

Additional supporting information can be found online in the Supporting Information section.