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Biopsychosocial theories of borderline personality disorder: a meta-synthesis and psychopathological network model from a systematic review

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Summary. Background. Borderline personality disorder (BPD) is a complex mental health condition with an altered image of self, impulsive acts, suicidal ideation, and self-harm requiring intensive care in outpatient and inpatient settings. The biopsychosocial (BPS) model adopted in the current study extracted the outcomes of a research about the diagnosis, causes and treatment of BPD. A network model helped link these results in a unitary model with applications in clinical practice for assessment and intervention. **Methods.** We conducted a literature review of current studies on the BPS causes of BPD and merged them through meta-synthesis. The results were then elaborated with a psychopathological network analysis for linking the extracted factors with higher degree of centrality in the network and merged in a final comprehensive model. **Results.** The theoretical modelisation suggests that BPS causes merged with the diathesis-stress model persistently activate the cortico-limbic system and prefrontal cortex, induce neuroinflammation, and stimulate suicidal and parasuicidal ideation and behaviours modulated by psychological and pharmacological treatment. **Conclusions.** Using a network model in psychopathology allowed the merging of data about BPD into a unitary and dynamic pattern which can be helpful to direct assessments and interventions in clinical practice.

Key words. Biopsychosocial model, borderline personality disorder, meta-synthesis, network analysis, psychopathology.

Teorie biopsicosociali del disturbo borderline di personalità: un modello di meta-sintesi e di network psicopatologico da una revisione sistematica.

Riassunto. Background. Il disturbo borderline di personalità (BPD) è una condizione di salute mentale complessa con un'immagine alterata di sé, atti impulsivi, ideazione suicidaria e autolesionismo che richiedono cure intensive in ambito ambulatoriale e ospedaliero. Il modello biopsicosociale (BPS) adottato nel presente studio ha estratto i risultati della ricerca sulla diagnosi, le cause e il trattamento del BPD. Un modello di network psicopatologico ha aiutato a collegare tali risultati in uno schema unitario con le applicazioni nella pratica clinica per la valutazione e l'intervento. **Metodi.** Abbiamo condotto una revisione della letteratura degli studi attuali sulle cause BPS del BPD e li abbiamo uniti attraverso la meta-sintesi. I risultati sono stati poi elaborati con analisi dei network per i link concettuali, il grado di centralità dei fattori estratti e riassunti in un modello finale comprensivo e unitario. **Risultati.** La modellizzazione teorica suggerisce che le cause di BPS fuse con il modello diatesi-stress attivano persistentemente il sistema cortico-limbico e la corteccia prefrontale, inducono neuro-infiammazione e stimolano ideazione e comportamenti suicidari e parasuicidari modulati dal trattamento psicologico e farmacologico. **Conclusioni.** L'utilizzo di un modello di rete (network) in psicopatologia ha permesso la fusione delle conoscenze di BPD in uno schema unitario e dinamico che può essere utile per indirizzare valutazioni e interventi nella pratica clinica.

Parole chiave. Analisi dei network, disturbo borderline di personalità, meta-sintesi, modello biopsicosociale, psicopatologia.

Introduction

Epidemiology

Borderline personality disorder (BPD) has a prevalence of 20% in inpatient psychiatric wards, 1.6-5.9% in the community, 10-12% in outpatient psychiatric services, and 50% among psychiatric inpatients with a diagnosis of personality disorder[1-3]. Patients with BPD comprise 9-33% of all suicides and more than 12% of psychiatric emergency visits during a year[2]. BPD is generally complex to diagnose and treat[4,5]. National Institute for Care and Health Excellence (NICE) advocates for multidisciplinary teams to diagnose and treat BPD[6]. Our research shows a prevalence of referrals of persons with BPD in general adult psychiatric wards and admission to emergency departments (ED)[7]. In our longitudinal study of a general adult ward in a teaching hospital in the United Kingdom, about 46% of admissions were from persons with BPD diagnoses[8].

Diagnosis

The World Health Organization (WHO) Classification 1992 for BPD includes at least three of the fol-

lowing: i) perturbations in and ambiguity about self-image, goals and internal preferences; ii) propensity to engage in extreme and unsteady relationships, often resulting in psychological crises; iii) extreme attempts to prevent abandonment; iv) reoccurring risks or practice of self; v) persistent feelings of being empty[9]. In addition, features of a personality disorder must be present in the fields of: i) cognition and in the way of perceiving and interpreting things, people and events; in the way of creating attitudes and images of self and others; ii) affectivity in terms of range, intensity and appropriateness, of emotional arousal and response; iii) control over impulses and gratification of needs; iv) interpersonal behaviour and management of interpersonal circumstances[9]. Furthermore, the skills required by healthcare staff to prevent chronic self-harming and suicidal thoughts in this vulnerable group are complicated; these competencies must be continually updated owing to the propensity of these patients to file complaints against their healthcare providers[10]. Recent research from our group shows that BPD can be comorbid with factitious disorders making the differentiation between the two pathologies complex[11,12].

Network models in BPD studies

Network analysis can provide a topographical and sequential structure of symptoms network by locating some as central and pivotal compared to more peripheral and ancillary symptoms[13]. Network analysis has shown that impulsivity and emotional dysregulations are trigger factors for BPD, antisocial, narcissistic, and histrionic personality traits[13].

A network model has extracted the correlations between BPD and eating disorders[14]. In psychopathology networks, nodes characterise symptoms and their links (edges) represent their relationships[15]. Centrality indices measure several circumstances in which a trait or symptom plays an essential part in the framework provided by other symptoms[15].

Network psychopathology conceptualises mental disorders as networks in which symptoms can trigger the presence of other symptoms, and this can eventually lead to a full-blown mental illness[16]. If this is true, symptom networks may be informative for clinical practice; symptoms that are more central in the network are thus assumed to influence many other symptoms, thus suggesting some logical argument for intervention[16]. The network method is predicated on the premise that symptoms are intimately connected and the relationship between them is actual, not fictitious, as a latent variable model considers it to be[17].

Aim

Despite the extensive research on BPD, the authors of the current study could not find a unitary model that could merge all the findings and theories of BPD into a unique explanation. Furthermore, within the same field of exploration, such as diagnosis, causes, and treatment, there seems to be no network exploration of how multiple factors link together. The authors of the current review are unaware of research that has tried to merge into one unitary model and middle range theory, the biopsychosocial (BPS) model of BPD.

Study question

What is the theoretical model that can summarise and link the current knowledge on diagnosis, causes and treatment of BPD in one BPS paradigm?

Objectives

The primary objective was to extract current literature on the diagnosis, causes, and treatment of BPD. The secondary objective was to use Social Network Analysis (SNA) and meta-synthesis to merge the findings from the literature into a unitary model and measure the degree of prestige (DP) of psychopathological aspects in BPD. Nodes with higher DP are more central in the network as they receive or send more links to other nodes than adjected ones[18].

Methods

Methodology

Qualitative Meta-synthesis (QM), based on the interpretivism approach, combines secondary data from the literature, accounts for similarities and divergencies, and deconstructs and reconstructs the data while the researcher formulates an overarching theory of interpretation[19-24]. The current study's authors adopted an exploratory research approach when they tried to understand psychopathological networks in BPD, generating new ideas about the existing studies and investigating a topic with few or prior studies by using meta-synthesis and an inductive approach[25]. However, the numerical outcomes of SNA, the explanatory analysis, and the measurement of the degree of centralities and prestige (of nodes representing symptoms, causes and treatment) helped understand the causal relationships between the observed facts in a deductive approach[25].

Literature search

Information sources and eligibility criteria

Search engines for the literature review included PubMed, EMBASE, Google Scholar, Web of Science, PsychNet, MEDLINE, grey literature, thematic books, and hand search. PRISMA flowchart summarised the steps[26].

Study selection

The principal researcher (CL) reviewed the search results from the four databases in the preliminary stage of the review to find possibly relevant titles. Two reviewers (CL and MR) read the abstracts of pertinent probable studies. The same two reviewers then scrutinised the complete texts of any abstracts that seemed to satisfy the inclusion requirements, and where necessary, differences were settled through discussion with a third party. After a study was approved for review inclusion, its reference list was also looked through to find any further studies that might be pertinent. The review stage went from January 2020 to August 2022. The authors selected publications in peer-reviewed journals mostly in the last five years and with impact factors. They excluded research studies that did not fulfil robust research criteria and were opinion papers with no outcomes or blogs or studies that were not from accredited sources or authors known in the BPD field. They also used EndNote to eliminate duplicates from the retrieved literature[27,28].

Eligibility criteria

SPIDER and PICOS chart guided the choice of the literature, including qualitative research and conclusions from quantitative and mixed-method studies research[29]. The inclusion criteria for the sample in articles were persons diagnosed with BPD in the community or psychiatric wards. The phenomenon of interest was the diagnosis, causes and treatment of BPD. The studies design for inclusion were randomised controlled trials, double-blind and placebo-controlled, systematic reviews, and qualitative, quantitative and mixed-method research. Exclusion criteria were for grey literature, publications not in English, and publications that did not complete the inclusion criteria. A second analysis with the two authors/reviewers extracted only relevant articles. A total of 5,690 articles were extracted during the first search phase, while only 80 were selected for the analysis (table 1).

Quality appraisal

The two researchers separately evaluated the quality of the studies that were part of the review using the Critical Appraisal Skills Programme (CASP) instrument for qualitative research, which was also applied to the qualitative outcomes of quantitative and mixed-method studies[30]. Discussions among the researchers were used to settle any disputes.

Search strategy

Primary keywords used in the Boolean search to extract relevant literature were:

Table 1. The Boolean search of terms.

Keywords and Boolean Connectives	Number of hits, including duplicates
#1 borderline personality disorder	2,625
#2 diagnosis	
#1 and #2	1,320
#3 cause*	
#1 AND #3	91
#4 brain	
#1 AND #4	342
#5 neuroinflammation	
#1 AND #5	4
#6 obesity	
#1 AND # 6	17
#7 child abuse	
#1 AND #7	130
#8 social isolation	
#1 AND #8	28
#9 stress	
#1 AND #9	386
#10 gut microbiome	
#1 AND #10	4
#11 prefrontal cortex	
#1 AND #11	75
#12 psychotherapy	
#1 AND #12	822
#13 mindfulness	
#1 AND #13	61
#14 dialectic behavioural therapy	
#1 AND #14	191
#15 pharmacotherapy	
#1 AND #15	147
#16 antidepressant*	
#1 AND #16	48
#17 mood stabiliser*	
#1 AND #17	24
#18 antipsychotic*	
#1 AND #17	68

- *diagnosis*: "Borderline-Personality-Disorder AND diagnosis AND/OR ICD-11 AND/OR DSM-5";
- *causes:* "Borderline Personality Disorder AND Cause* AND/OR brain AND/OR neuroinflammation AND/OR obesity AND/OR child-abuse AND/OR social-isolation AND/OR stress AND/OR gut-microbiome AND/OR prefrontal-cortex";

- *therapy or psychotherapy:* "borderline-personality-disorder AND psychotherapy AND/OR mindfulness AND/OR dialectic-behavioural-therapy"; "borderline-personality-disorder AND pharmacotherapy AND/OR antidepressant* AND/OR mood-stabiliser* AND/OR antipsychotic*" (figure 1; Appendix, online).

Data extraction

The panel of experts and networking a model

A panel of mental health professionals (MHPs) was set to provide the relationships between the factors emerging from the BPS model of BPD as captured by the selected articles and confirmed by their

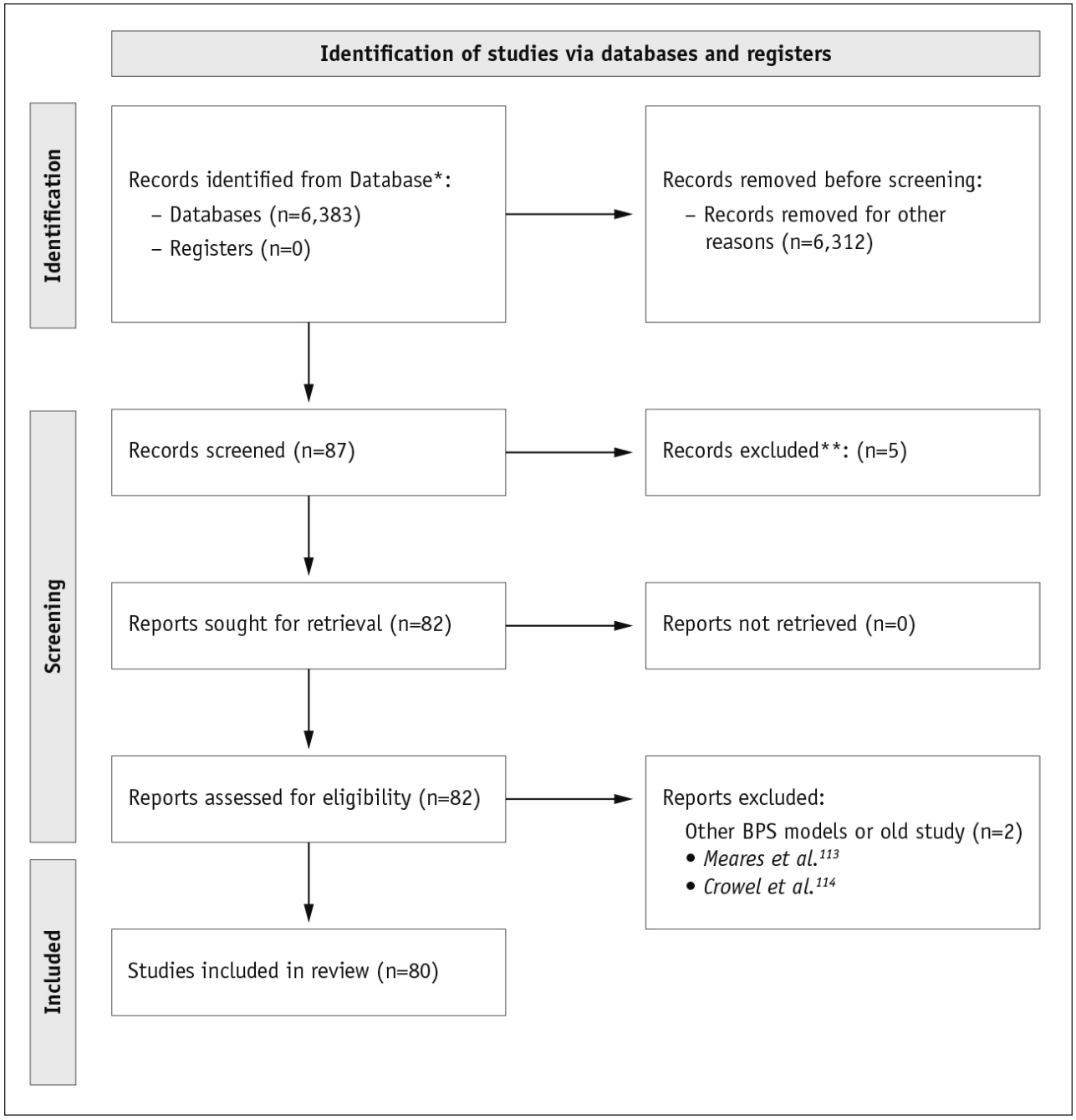

Figure 1. PRISMA flowchart.
*PubMed, EMBASE, Google Scholar, Web of Science, Psych Info, MEDLINE; ** Lazzari et al.8; Slade82; Erwin et al.21; Constantine106; Ateriya et al.108. *Legend:* PRISMA= Preferred Reporting Items for Systematic reviews and Meta-Analyses; BPS= biopsychosocial.

expertise in the field. All the participants were active mental health practitioners in general adult psychiatry with comprehensive knowledge of BPD. The panel included MHPs from general adult wards, psychiatric intensive care units, community psychiatric teams and liaison psychiatry from the local public hospital. The panel comprised four consultant psychiatrists, three senior ward managers, six senior mental health nurses, one clinical psychologist, one clinical pharmacist, one occupational therapist, and three former service users with a diagnosis of BPD fully recovered. During each meeting, for a length of about 30-45 minutes and a total of nine joint sessions live or *via* Microsoft Teams, they were meant to reach an agreement on how the causes (three sessions), symptoms (three sessions), and therapy (three sessions) were linked according to a network model. After the leading authors extracted the central concepts in the BPS model of BPD, the authors proposed targeted discussion according to two leading questions, 'What comes first?' or 'What is causing what?'. The aim was to extract antecedent and consequent factors in a network chain of interrelated concepts. Therefore, they suggested which aspect was linked to which, which was the trigger, and which was the effect. For example, one consultant provided insight into the link between neuroanatomy and mood. A senior member of staff working in liaison linked the presentation to emergency departments and life events. The clinical psychologists provided the links between psychotherapy and pharmacotherapy. A moderator, selected from one of the authors, conducted the discussions and collected the agreed-upon networks from the discussions. The setting was a public mental health setting in the United Kingdom. By processes of subsequent links, networks were constructed. Other times, the findings in the research and the meta-synthesis indicated the correlation between the concepts.

Data synthesis

Meta-synthesis

Meta-synthesis is a research methodology in which the qualitative results of prior studies are classified or categorised according to particular criteria, and the findings are reinterpreted by comparison[31]. As applied in the current study, the authors used the qualitative or narrative results of quantitative, qualitative and mixed-method research to generate a unitary interpretation model. The qualitative synthesis, applied to systematic reviews, results from the researchers' arrangement of segments of data merged into a new whole; therefore, meta-synthesis prepare the basis for the conversation where hypotheses and proposals are presented, generating a new model or theory about a phenomenon or more powerful explanations[32,33].

Meta-synthesis capitalises on various contexts, techniques, and theoretical orientations to provide a richer, more complex, and more multidimensional approach to a phenomenon[34]. As we account for more layers of the subject matter we are studying, we evaluate it from a greater variety of perspectives[34]. As we question it with more and more theoretical interpretations, we increase the likelihood of grasping its fundamental character or inherent truth[34].

Social Network Analysis

Social Network Analysis (SNA), using the Open Source Social Network Visualizer SocNetv V2.5 (https://socnetv.org) software, combined the themes emerging from meta-synthesis. SNA figuratively captures the relation between concepts and information represented by network nodes; then, it extracts the degree of prestige (DP) where the value of 100% represents more central positions in the network of acquired nodes/concepts[35,36].

In the Network Model of psychopathology, social, biological, and genetic causes are mutually linked and interacting[37-39]. As explored in the current study, SNA has been used to connect related concepts into a network model, providing a pictorial configuration of ideas linked together, while the distance between concepts measured; notions that had more links with others had a higher degree of centrality and prestige compared to more separated themes. SNA is a method where the connections between the individual nodes or edges of the network (people, concepts, organisations, facts, information, and others) are qualitatively and quantitatively described by using pictorial representations of them (qualitative analysis) or by capturing and measuring the intensity of the interunit bonds between them, or by extracting their number or the strength of their links (quantitative analysis)[40]. The individual nodes or edges are linked according to the underlying theoretical modelisation – in this study, their conceptual relatedness – while the central positions in the graphs are occupied by those concepts that are 'central' and play a pivotal role in being more linked to any other concepts or ideas. The lines in a graph can have a 'direction' to denote the flow of influence in a social network, and they can be assigned a 'value' to signify the strength of the relation[18]. Edge weight and differences in the degree of prestige from SNA were assessed for statistical differences with Chi-square statistics. We used a closing hierarchical clustering of the equivalence matrix showing the co-correlation of the nodes with high centrality from all models.

The authors, supported by the panel of expert meetings, assigned their weights independently to the individual themes in the current study. The final averaged weight positioned the pieces into the net-

work as more central or peripheral. Each network was generated by answering the question, 'What comes first?'. For instance, does suicidal ideation come before or after a crisis? If, for example, a problem was regarded as a trigger, then the arrow of network influence went from 'life crisis' to 'suicidal ideation'.

Similarly, for example, if 'relationship splitting' comes before 'life crisis,' then the influence arrow goes from 'splitting' to 'crisis.' By progressive accretion of reciprocal influences, we constructed our SNA networks. More central concepts had multiple causes; for instance, 'suicidal ideation' could be triggered by a 'life crisis,' 'change of medication,' or 'chronic feeling of emptiness.' The Chi-square goodness of fit test for the significance of the aggregated theoretical model elaborated the final numerical results. The authors, specialists in the topic treated, helped locate the themes and edges by linking them sequentially with single-headed arrows for unilateral influence and double-headed arrows for reciprocal influence. The expert panel was also guided by the current theories about the weighed concepts (figure 2).

Results

Diagnosis

Mental disorders are mental health states that affect feelings, behaviours and thoughts[41]. According to The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)[1] and The International Classification of Diseases 11th Revision (ICD-11)[9], persons with BPD present symptoms in five or more of the following area: i) hectic efforts to escape actual or imaginary rejection; ii) turbulent and intense social interactions, characterised by contrasting values, from idealisation to degradation; iii) continuous drastic and unpredictable self-esteem or consciousness of oneself; iv) unpredictability in at least two intrinsically self-damaging aspects, (e.g., money, sexuality, drugs, driving, binge eating); v) chronic suicide conduct, speech and/or threats, or deliberate self-harm (DSH); vi) short-lived psychological unrest due to extreme unplanned mood; vii) durable perceptions of emptiness; viii) severe and irrational anger that may be hard to control; and ix) fleeting paranoid ideas under stress, psychotic symptoms, or extreme dissociative symptoms.

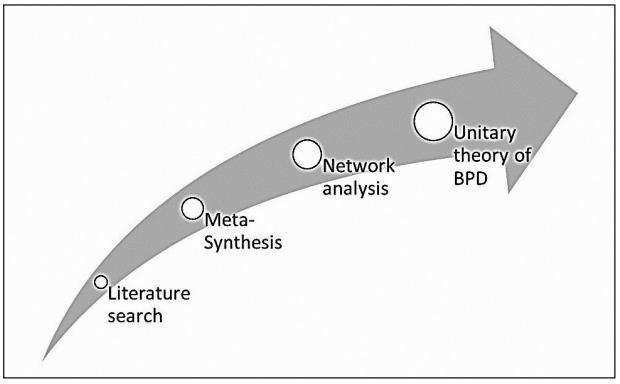

Figure 2. Theoretical modelisation in the current review.
Legend: BPD= borderline personality disorder.

A categorical model is often complemented by a dimensional version of classifying BPD based on the seriousness and frequency of symptoms[1,9,42-44]. The diagnosis of BPD is not always straightforward as it can be comorbid with the factitious disorder[11,12]. The leading author (CL) hypothesises the existence of a syndrome characterised by comorbidity between BPD, depression and factitious disorder as follows: i) fictitious behaviours: asserting more severe physical and mental health issues that do not receive diagnostic and instrumental confirmation; ii) self-inflicted wounds and diseases, in addition to intentional self-harm; iii) seeking invasive diagnostic and treatment procedures; iv) medication craving for major pain killers or sedative medication (*e.g.*, pregabalin, paracetamol); v) construction or intensification of physical symptoms resulting in emergency hospitalisation and admission to medical or surgical wards; vi) claiming various allergies to medications to guide physician's choices of treatment albeit with consequent polypharmacy; vii) clinical presentation mimicking physical conditions; viii) unconsciously seeking invasive therapy or examinations by exaggerating physical and psychological complaints that do not find objective clinical and surgical confirmation; ix) various and migrating forms of pain leading to accretion of painkillers and sedative medication; x) neuropathic pains that are problematic to confirm *via* standard diagnostic and clinical procedures inclusive of diffuse abdominal pains, musculoskeletal pains, headaches[11,45].

The Antecedents, Behaviour, Consequences (ABC) model of Cognitive Behavioural Therapy (CBT) complemented by naturalistic observations helps diagnose symptoms as '**A**ntecedents' or triggers in the environment, impacting the '**B**elief' system and interpretation, hence '**C**ausing' feelings, behaviours, and physical reactions[46,47]. Naturalistic observations of BPD in psychiatric wards and communities suggest that: i) 'A' or triggers of clinical relapses are real or imaginary rejection, loss of face-to-face interaction with carers, social isolation, and turbulent social interactions; ii) they lead to 'B', such as feelings of emptiness, anger towards self and others, paranoia and short psychotic episodes; and iii) these last cause 'C', such as unpredictability, impulsivity, suicidal and parasuicidal acts[48-53].

Network model of symptoms

In the SNA, suicidal ideation holds the highest DP at 21.50%, triggered mainly by feelings of anger toward self and others (DP=17%), turbu-

lent social interactions (DP=13%), escaping rejection (DP=8.6%), and chronic feelings of emptiness (DP=12%). All these factors are conducive to unpredictability and impulsivity (DP=4.5%), paranoia, and short psychotic episodes (DP=9%) (figure 3).

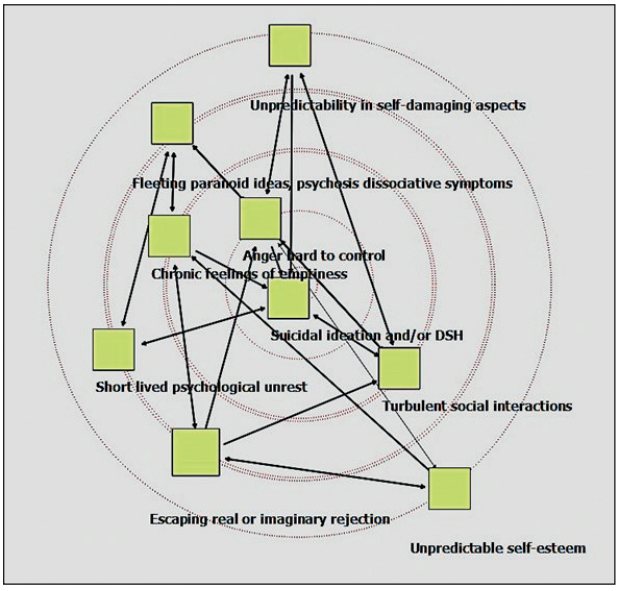

Figure 3. SNA modelisation of BPD symptoms and behaviours.
Legend: SNA= Social Network Analysis; BPD= borderline personality disorder; DSH= deliberate self-harm.

Causes

A *necessary* cause of a mental illness is a required attribute that generates a disorder (*e.g.*, gene Huntingtin in Huntington's disease), a *sufficient* cause ensures its presence, and a *contributory* cause increases its likelihood of developing[51]. The BPS model of causes of BPD emphasises the diathesis-stress paradigm produced by multiplicative effects of individual vulnerability and stressful life events, inclusive of: i) adverse childhood, including abuses, neglect, father-daughter incest, trauma; ii) deprived social conditions; iii) genetic predisposition; iv) problematic parental bonding with lack of affection and autonomy, physical and emotional abuse; and v) family breakdown[51,54-57].

Brain magnetic resonance imaging (MRI) in BPD shows stress-induced hyperactivity of the Hypothalamic-Pituitary-Adrenal (HPA) axis, emotional over-reactivity linked to hyperstimulation of the amygdala, impulsivity liked to a smaller hippocampus, low prefrontal-to-amygdala coupling, and reduced grey matter and white matter diffusion in frontal, parietal and temporal lobes leading to the low inhibiting activity of the prefrontal cortex (figure 4)[51,58-63].

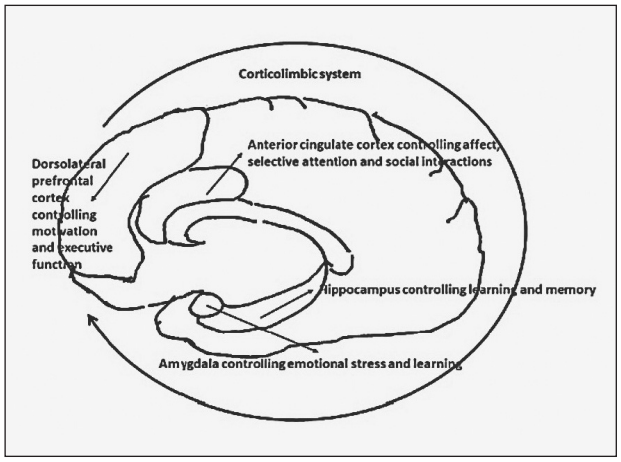

Figure 4. Sagittal section of the brain with the prefrontal cortex and corticolimbic system.

Social isolation enhances stress-related hyperactivity of the HPA axis and anxiety disorders in BPD[64-67]. Chronic psychosocial stresses and abuses during childhood and adolescence increase the inflammatory markers (C-Reactive Protein) in adults and neuroinflammation of the hippocampus and microglia with an augmented incidence of mental illnesses[68-70]. An altered gut-brain-microbiome system also causes neuroinflammation; for instance, altered gastrointestinal metabolism and absorption, inflammatory bowel syndrome, irritable bowel syndrome, chronic diarrhoea or constipation, infections of the intestine, gastrointestinal operations or eating disorders, pathological body mass index (BMI); they can cause physiological stress impacting the HPA axis and brain neurotransmitters with a pathological BMI also being reported for an influence to cognitive function mediated by the hippocampus, amygdala, and reward-processing centres; re-establishing a regular metabolism and adding omega-3-fatty-acids can normalise the gut microbiome and reduce impulsivity[71-76]. SNA of functional MRI studies captures the more stimulated and activated brain in BPD[36]. In a longitudinal study of 10 years in the author's ward for measuring weight gain in psychiatric inpatients, female patients were prevalent with the diagnosis of BPD and a mean pathological BMI of 31.21[77]. In 26.9% of the obese population, a USA report found a prevalence of BPD that ties personality disorder to compulsive eating[78]. Research shows that childhood abuse in women is linked to obesity later in life[79]. A researcher suggested that high pathological BMI might be related to axonal/myelin irregularities in the white matter, with a decrease in the grey matter and consequent damage to neurons[80].

Network model of causes

The SNA disclosed a higher DP for BPS and diathesis-stress model (DP=12%) together with pathological BMI (DP=9%), leading to neuroinflammation

(DP=9%), altered frontal, parietal and temporal lobes functions (DP=6%), followed by increased inflammatory markers (DP=6%) and reduced volume of the hippocampus (DP=6%) (figure 5).

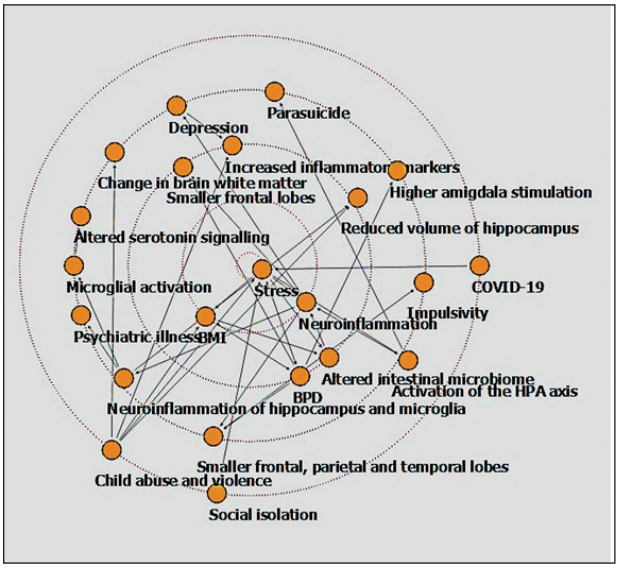

Figure 5. SNA modelisation of causes of BPD.
Legend: SNA= Social Network Analysis; BPD= borderline personality disorder; HPA= Hypothalamic-Pituitary-Adrenal; BMI= body mass index.

Treatment

Psychotherapy is when therapists and clients set a time to discuss the client's current and past life events, feelings, thoughts, and behaviours causing the client's concerns[81]. A therapeutic outcome in psychiatry is what happens to a patient's mental health due to an action by healthcare professionals or services[82].

Psychoanalytic psychotherapy helps elaborate and change the interaction between the patient and the therapist[83]. Dialectic Behavioural Therapy (DBT) helps patients' treatment and prevention while assisting them in accepting themselves, acknowledging their conflicts, and finding a dialectic answer to reconcile and synthesise opposite polarities such as insecurity, social invalidation, defeatism, and evident abilities[84].

Mindfulness-based therapy entails mindfulness and knowledge of everyday experience to favour a fast change in attention from complete engagement in the emotion or behaviour to self-observation and self-reflection; this loop of self-reflection about an experience allows patients to control the impact of a situation[50].

Mindfulness increases the brain grey matter in the right orbitofrontal area and the lower brain stem while reducing the hyperactivation of the prefrontal cortex (PFC) and frontal-limbic system involved in emotion regulation and modulates the midline prefrontal and posterior cingulate cortex by increasing self-awareness[85-90]. DBT modulates the brain's cortico-limbic and PFC and reduces amygdala hyperactivity[91]. Overall, patients with BPD have an overactive and smaller amygdala (emotional propeller) and underactive prefrontal and cortico-limbic system (emotional brake)[92,93].

Pharmacotherapy suggests that selective serotonin reuptake inhibitors (SSRIs), such as sertraline, fluoxetine, and fluvoxamine, positively affect the PFC and reduce depression and lability of mood, impulsivity, anxiety and aggression[94-96]. Mood stabilisers (*e.g.*, lithium and carbamazepine) decrease emotional instability and behavioural dysregulation by activating Beta-1-adrenergic and Dopamine-D2 receptors in the PFC; atypical antipsychotics (*e.g.*, olanzapine, risperidone, aripiprazole, clozapine) control psychotic symptoms and anger[94,97-99]. However, there are debates about the possible effect of antidepressants on impulsivity. At the same time, our research group has found positive results with antipsychotic depot injections (*e.g.*, Zuclopenthixol) while avoiding, when possible, prescribing SSRI antidepressants alone, which are often accompanied, in our studies, by increased suicidal and parasuicidal behaviours[12].

Network model of treatment

In the SNA, psycho-pharmacotherapy in BPD targets PFC (DP=57%), frontal-limbic network (DP=29%), and HPA axis (DP=21%) by modulating their activities (figure 6).

Meta-aggregation of results

The theoretical modelisation of BPD suggests that BPS causes merged with the diathesis-stress model persistently activate the cortico-limbic system and prefrontal cortex, induce neuroinflammation, and stimulate suicidal and parasuicidal ideation and behaviours modulated by psychological and pharmacological treatment. The aggregated model confirmed a different DP for all edges except for the causes of BPD that aggregate equally. The effect sizes were large for symptoms, diagnosis and treatment. Suicidal ideation and psychological-psychopharmacological treatment targeting the prefrontal cortex are two aspects that attract more meaning, research, and weight in the integrated BPS model (tables 3 and 4; figures 7 and 8).

Conclusions

Our study is a novel approach to condensing and linking theories and findings in BPD research. Using a network model allowed us to capitalise on the relevant information and merge it in a unitary model of explanation, albeit not the only one possible. Using meta-theories impacts clinical settings where mental health practitioners look for cause and effect or psychopathological causality to plan their actions, rem-

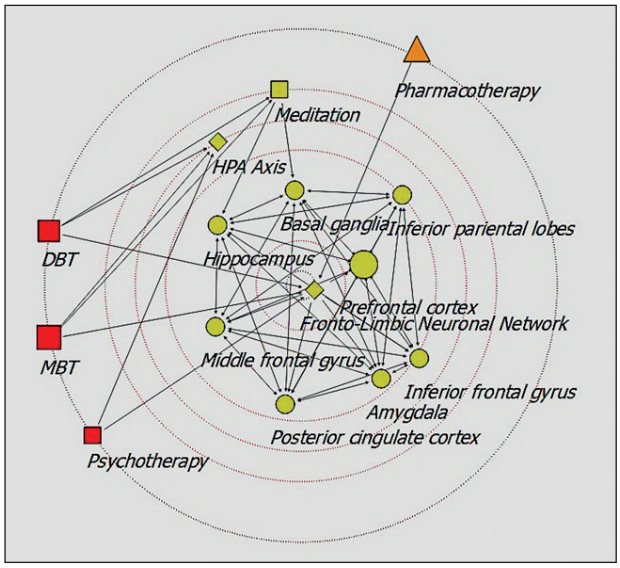

Figure 6. SNA modelisation of BPD therapy.
Legend: SNA= Social Network Analysis; BPD= borderline personality disorder; HPA= Hypothalamic-Pituitary-Adrenal; DBT= Dialectic Behavioural Therapy; MBT= Mindfulness-based therapy.

edies, therapies and clinical interventions. Therefore, the model helps understand priorities of action, for example, correcting pathological BMI and metabolic imbalance and consensually reducing social isolation and initiating psychotherapy to reduce impulsivity. Or pharmacological intervention combined with psychotherapy will impact the corticolimbic system and help mitigate impulsive acts, anger outbursts and suicidal ideation (figure 9).

The network model of the psychopathology of BPD helps link symptoms, causes, and treatments to find central factors in the network, such as suicidal and parasuicidal behaviour and address them in care plans. However, as all elements are correlated, no etiological cause should be considered necessary or sufficient. For instance, childhood sexual abuse is a contributory cause, while family instability is a mediator[100]. Furthermore, all psychotherapies have positive outcomes, mostly on DSH and suicidal ideation, as long as they are provided by judicious therapists forming a robust therapeutic alliance realistically, using outcome measures to target symptoms[101]. In addition, medication should be used with caution as it has been suggested that there might be increased impulsivity, suicidal ideation and aggression risk from treatment with SSRI antidepressants and adverse side effects with polypharmacology[102,103].

Therefore, multidisciplinary teams should be mindful in confirming presentation symptoms, causes and treatments as these are all dynamically networked.

Limitations

The current study has several limitations. The first is linked to meta-analysis as it is a qualitative approach to theorisation; it retains the subjective choices of participants, authors and panel members in indicating the links between concepts. Other researchers and panels could have expressed different or diverging opinions. Another limitation of our transtheoretical model is that it did not receive experimental confirmation. Efforts were made to collate the findings into a unitary and quantitative model. Therefore, it could be argued that the current study has limited external validity, although it can still hold clinical validity.

Suggestions for future research

Since the current psychopathology model of summing up symptoms has information gaps, the authors suggest that future research should use a small-world *social network theory of psychopathology* where diagnosis, causes, and treatment are dynamically interdependent, showing networks structured between regular to random configurations[38,104,105]. SNA will identify those central nodes of the network that are important in creating and maintaining clusters of symptoms; this would determine the focus of therapy since it reveals the casual interaction between nodes/symptoms[38,39,104,106,107].

Telemedicine and teleconsultation[108] are promising areas for future research. Whatever the therapeutic intervention proposed, there should be relevant outcome studies regarding the quality of life and pertinent signs for patients, families, and care providers[6]. A longitudinal study found similar effects in anxiety outcomes between online and face-to-face counselling[109]. A hybrid technology merging online with face-to-face psychotherapy, based on smartphone technology, will allow service users to access the required resources despite geographical barriers and limited resources while implementing continuity of care and reducing barriers to consultation, especially during Covid-19 restrictions[110-112].

Take home messages.

- Using a network model allows one to capitalise on a psychopathology's relevant information and merge it into a unitary model of explanation.
- A network theory of psychopathology allows us to link diagnosis, causes, and treatment of psychiatric pathologies into dynamic systems of reciprocal influences.
- Network analysis may reveal a topographical and sequential structure of symptoms by identifying specific signs as core and essential compared to other peripheral and auxiliary symptoms.
- Psychopathology networks may be helpful in clinical treatment because concepts more central in the network are presumed to impact many other symptoms; therefore, there may be some justification for intervention if those symptoms are more prevalent.

Competing interests: no competing interests were disclosed.

Table 3. Edge weight and differences in the degree of prestige from SNA.

Domain	Node number	Subdomain	Edge weight (%) and degree of prestige	χ^2	Significance P	Effect size
Symptoms/ diagnosis	7	Suicidal ideation	21.50			
	4	Feelings of anger	17.00			
	3	Turbulent social interactions	13.00			
	5	Chronic feelings of emptiness	12.0			
	2	Paranoia and short psychotic episodes	9.0			
	1	Escaping rejection	8.6			
	6	Unpredictability and impulsiveness	4.5	15.75	0.015	0.43
Causes	13	Diathesis stress model	12.0			
	12	Pathological BMI	9.0			
	11	Neuroinflammation	9.0			
	10	Smaller frontal, parietal and temporal lobes	6.0			
	9	Increased inflammatory markers	6.0			
	8	Reduced volume of the hippocampus	6.0	3.75	n.s.	0.28
Psychopharmaco-therapy	17	Targets PFC	57.0			
	15	Targets the fronto-limbic system	29.0			
	16	Targets the HPA axis	21.0	20.03	<0.001	0.43

Legend: SNA= Social Network Analysis; BMI= body mass index; HPA= Hypothalamic-Pituitary-Adrenal; PFC= prefrontal cortex.

Table 4. Hierarchical clustering of equivalence matrix showing co-correlation of nodes.

Segment	Level	Nodes
1	1.414	8 16
2	1.414	9 12
3	1.732	10 14
4	1.984	8 16 9 12
5	2.000	1 2
6	2.000	1 2 3
7	2.000	1 2 3 4
8	2.000	1 2 3 4 5
9	2.152	8 16 9 12 10 14
10	2.414	1 2 3 4 5 8 16 9 12 10 14
11	2.449	15 17
12	2.660	1 2 3 4 5 8 16 9 12 10 14 15 17
13	2.790	1 2 3 4 5 8 16 9 12 10 14 15 17 11
14	2.899	1 2 3 4 5 8 16 9 12 10 14 15 17 11 13
15	3.215	1 2 3 4 5 8 16 9 12 10 14 15 17 11 13 6
16	3.359	1 2 3 4 5 8 16 9 12 10 14 15 17 11 13 6 7

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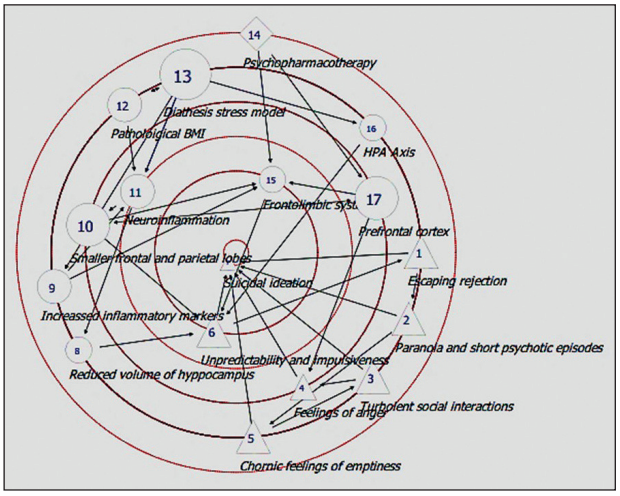

Figure 7. SNA aggregate model from nodes with a higher degree of prestige.
Legend: SNA= Social Network Analysis; BMI= body mass index; HPA= Hypothalamic-Pituitary-Adrenal.

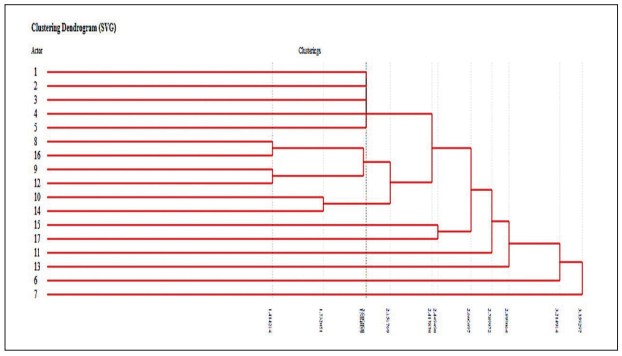

Figure 8. Clustering dendrogram of nodes with a higher degree of prestige.

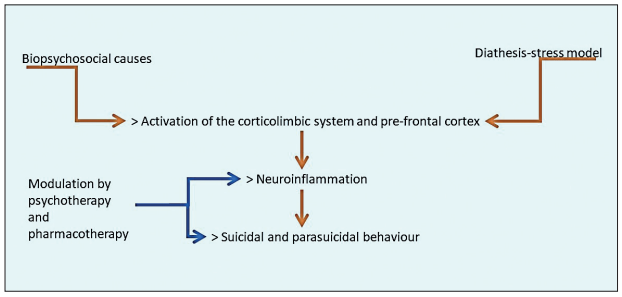

Figure 9. Meta-aggregated model of BPD.
Legend: BPD= borderline personality disorder.

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Appendix. PICOS (Population, Intervention, Comparison, Outcome, Study type) SoF (Summary of Findings) for the selected studies included in the network model.

Author, Reference	Population	Intervention	Comparison	Outcome	Study type
Andrews & Tennant[57]	-	The link between life events and stress	Theoretical paper	Comparing literature	Review
Arnau-Soler et al.[56]	4919	Diathesis-stress model	Observational-Experimental	diathesis-stress theory, which assumes a multiplicative gene-by-environment interaction effect on risk	Quantitative
Bach & First[44]	Five clinical cases	Clinical diagnosis of personality disorder	Case report	How the ICD-11 Personality Disorder classification may be applied in clinical practice using five short cases	Qualitative
Baek[64]	-	How different mental health disorders provoke social isolation	Theoretical paper	Comparison of personality disorder and types of social isolation	Qualitative
Barsaglini et al.[85]	42 papers were selected as relevant	How psychotherapy affects brain function	A systematic and critical review	Psychotherapy is linked to measurable changes in the brain structure	Review
Bateman & Krawitz[50]	-	Borderline personality disorder theory	Theoretical exploration of BPD	Different aspects of BPD	Book
Borsboom[37]	-	Network theory to explain psychopathology	Theoretical paper	Symptoms of psychopathology are causally linked through multitudes of biological, psychological, and societal mechanisms	Qualitative
Bos et al.[16]	104 patients	Network theory to explain psychopathology	Patients rated their momentary mental states on a 7-point Likert scale ten times a day for five days, resulting in a maximum of 50 measurement points per individual	To examine the co-occurrence of symptoms and provide insight into patterns of present symptom comorbidity across individuals, cross-sectional networks may be helpful	Quantitative
Boschloo et al.[38]	34,653	According to the second wave of the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC; N = 34,653) cross-sectional data were used in this study to build an empirically based network structure that included 120 mental symptoms of the twelve primary DSM-IV diseases	Experimental	Some symptoms demonstrated strong links with symptoms of other disorders, which may help explain comorbidity across diagnoses	Quantitative
Bozzatello et al.[73]	43 BPD patients	Studying symptoms changes of BPD after 12-week period with Omega-3 Fatty Acids	Follow-up study with ANOVA between treatment group and untreated	Improvement of BPD symptoms after Omega-3-fatty acid diet on assessment scales	Quantitative
Bozzatello et al.[74]	126 articles	Literature review	102 RCTs, and 24 were reviews and meta-analyses	Efficacy of omega-3 fatty acids has been obtained in treating depressive symptoms in patients with major depression	Review

Continue

Continue **Appendix**

Author, Reference	Population	Intervention	Comparison	Outcome	Study type
Bradley et al.[100]	524 adult patients with personality disorders	Survey	Multiple regression analysis of etiological factors	Family environment, parental psychopathology, and history of abuse independently predicted BPD symptoms in multiple regression analyses	Quantitative
Brambilla et al.[58]	Patients with BPD	Patients with borderline personality disorder underwent anatomical MRI studies.	For current and historical Axis I and II comorbidities as well as histories of childhood abuse, ten unmedicated BPD cases and twenty healthy controls were examined	Compared with healthy controls, BPD participants showed significantly reduced right and left hippocampus volumes and increased right and left putamen sizes	Quantitative
Bullmore[75]	-	-	Theoretical exploration of the concept of an inflamed mind	-	Book
Butler et al.[65]	Long-Evans male rats were group-housed (GH) or socially isolated (SI) for six weeks during adolescence	Evaluation of the impact of social isolation on HPA axis function, anxiety-like behaviours, and ethanol drinking	Corticosterone (CORT) response to stress with and without dexamethasone (DEX) and anxiety-like behaviours	These data suggest that the HPA axis function is affected by SI, and this is related to antecedent anxiety-like behaviour	Experimental
Cacioppo et al.[67]	-	Exploratory research on the effect of loneliness	Lonely vs non-lonely individuals in terms of their emotions	Lonely individuals have lower emotional self-regulation	Review
Cacioppo et al.[66]	-	Exploratory research on the effect of loneliness	Lonely vs non-lonely individuals in terms of their HPA activity	Social isolation increases sympathetic tonus, and HPA activation decreases inflammatory control, immunity, and sleep and reduces glucocorticoid gene response	Review
Calcia et al.[68]	18 studies scrutinised animal models	Seven different psychosocial stressors, in mice and rats and their effect on the brain	Review of the literature about the effect of stress on neuroinflammation	Microglial activation in the hippocampus and other brain regions is increased by psychosocial stressors	Systematic review
Chafos & Economou[86]	-	Effect of mindfulness on patients with BPD		Long-term mindfulness (>8 wks) is associated with more grey matter in the anterior cingulated gyrus, the lower area of the somatosensory cortex, and the right hemisphere	Review
Collerton[87]	-	Effect of psychotherapy on the brain	Before and after psychotherapy	It is suggested that after psychotherapy, there are changes in the frontal, cingulate and limbic cortex	Mini Review

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Continue **Appendix**

Author, Reference	Population	Intervention	Comparison	Outcome	Study type
Comtois et al.[4]	A random sample of persons aged 18 to 60 years who had received at least one outpatient mental health service in the previous 90-day period and were enrolled in one of the participating mental health centres; 29 BPD persons	Degree of use of public mental health services	Low vs high usage of public health services	Fifty-two per cent of BPD were high-frequency users of mental health services, with seventy-six per cent being females	Quantitative
Cottraux & Blackburn[84]	Handbook of Personality Disorder	-	-	-	Book
Cramer et al.[17]	-	Network model of psychopathology	Comparison between latent and network model	The usefulness of a network model in psychopathology	Theoretical
Danese & Tan, 2013[79]	41 studies selected	Review of the literature. In non-human primates, childhood experiences may influence obesity risk	Aggregation of results from different studies	Childhood maltreatment is a potential risk for obesity, with the association being higher for women and the white population	Systematic review and meta-analysis
Danese & Tan[79]	A characteristic birth cohort of 1000 individuals followed up to age 32 was assessed for a history of childhood maltreatment and depression	Assessing inflammatory markers in a follow-up study	Comparison of depression with healthy individuals	Persons with history of childhood, maltreatment has comorbid depression and inflammation, have high levels of high-sensitivity C-reactive protein	Quantitative follow-up study
De Paoli et al.[14]	Seven hundred fifty-three adults (81.5% women), of whom 109 reported a lifetime eating disorder diagnosis	Network analysis to explore associations between specific groupings of BPD and eating disorder	Comparison and aggregation between symptoms	Comorbidity BPD and an eating disorder. Centrality in the network of emotional dysregulation and abandonment	Quantitative
De Zutter et al.[10]	57 cases of allegations of rape in the Netherlands	Assessment of false allegations of rape	False vs true allegations	A significant reason for false allegations was emotional gain and desire to receive attention from friends, family and organisations	Retrospective, Mixed-method and review

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Author, Reference	Population	Intervention	Comparison	Outcome	Study type
Eidson et al.[70]	Animal model; Male (n = 38) and female (n = 57) C C57BL/6 mice C57BL/6 mice	Effect of social isolation on mice	Chronically stressed mice beginning in adolescence; stressed animals were single-housed, controls pair-housed to prevent social isolation stress	Stressed animals had dysregulated neuroinflammation, altered social behaviours, and increased adiposity	Quantitative experimental
Ellison et al.[2]	Eighteen thousand adults from 5 catchment areas	Epidemiology of BPD	BPD in various settings	The prevalence of BPD in the inpatient population is 24% and the outpatient 11.8%, and 1% in the general population	Quantitative, epidemio-logical
Gunderson et al.[5]	-	-	-	BPD is found in ~1.7% of the general population but in 15-28% of patients in psychiatric clinics or hospitals	Quantitative epidemio-logical
Hengartner et al.[102]	27 studies, including 1.45 million subjects	Risk of suicide with the use of SSRI and new antidepressants	Comparing high with low risk of suicide	Adult routine-care patients with depression and other treatment reasons are more likely to commit suicide when exposed to newer antidepressants	Systematic review and meta-analysis
Herpertz et al.[59]	-	Neuroscientific techniques help elucidate the mechanisms behind affective dysregulation, impulsivity/disinhibition, and poor social cognition in BPD, as well as the neurobiological underpinnings of these behaviours	-	fMRI results show that while amygdala activity is increased, associated brain circuits such as the superior-temporal gyrus and the superior temporal sulcus are less active	Mini review
Jovev et al.[60]	Twenty patients meeting DSM-IV criteria for BPD and aged between 15 and 19 years who never received treatment for BPD	MRI	Pituitary gland volume (PGV) and the total number of parasuicidal behaviours in a teenage BPD patient with a first presentation	Increased hypothalamic-pituitary-adrenal (HPA) axis activation may be linked to parasuicidal behaviour in BPD patients	Quantitative experimental
Kaunomäki et al.[42]	Three hundred thirty-one patients with a mean age of 42.9 years mainly suffering from mood, schizophrenia-related and substance use disorders	The staff assessed the patients daily with the Dynamic Appraisal of Situational Aggression (DASA)	Comparison of rapid tranquillisation methods	Violence in inpatient wards is usually treated with Pro Re Nata (PRN) medication	Quantitative

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Author, Reference	Population	Intervention	Comparison	Outcome	Study type
Lam & Gale[46]	Case reports	CBT intervention	-	The ABC theory of emotional disturbance is one of the essential concepts in cognitive behaviour therapy (CBT). 'A' is an activating event or the existence of a situation; 'C' is the individual's emotional and behavioural consequence or reaction; 'B', the person's interpretations of and assumptions about 'A', is mainly responsible for 'C', the emotional and behavioural responses	Qualitative
Lazarus et al.[52]	53 (27 BPD, 26 healthy control)	examining crucial aspects of relationships (such as satisfaction, intimacy, support, conflict, and criticism) over six months	BPD with healthy controls	Those in the BPD group were thought to have more unstable relationships than women in the control group	Quantitative longitudinal
Lazzari & Nusair[11]	Case reports of BPD comorbid with the comorbid factitious disorder (FD)	Clinical characteristics of BPD when comorbid with FD	BPD with FD	Persons with BPD present with a high comorbidity with FD in community and hospitals	Qualitative
Lazzari & Shoka[53]	-	Theoretical exploration of the management of BPD in psychiatric wards	-	Corporate management of BPD requires specific skills in the personnel, which pose challenges to interpersonal relationships with patients	Theoretical exploratory
Lazzari et al.[77]	240 non-forensic psychiatric inpatients	Assessment of weight gain of inpatient population in 10 years	Patients with different psychiatric diagnoses	Female patients with BPD present with pathological BMI (Body Mass Index) compared to patients with other diagnoses	Quantitative, longitudinal and cross-sectional
Lazzari et al.[7]	-	Retrospective study of the impact of BPD on healthcare services	-	The authors suggest that the increase in observed cases of BPD is a challenge for the whole healthcare system with the risk of false allegations against staff	Qualitative exploratory
Lazzari et al.[8]		Analysis of prevalent diagnoses of admission in adult psychiatric wards	Comparison of rate of psychiatric admissions according to psychiatric diagnosis	Patients with borderline personality disorder, especially females, are heavy service users and outnumber the rate of admission compared to other pathologies	Quantitative
Lazzari et al.[45]	Several case reports	Studying the comorbidity of BPD, depression and FD	Persons with or without the comorbidity	The authors hypothesise that there is evidence that BPD is often comorbid with FD and depression	Qualitative
Luders & Kurth[88]	12 studies	Neurofunctional analysis of brain during meditation	An individual may have become interested in meditation because of brain anatomy connected to certain personality types, interests, or mental abilities	Short-term and long-term meditation affect neuroplasticity	Review

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Author, Reference	Population	Intervention	Comparison	Outcome	Study type
Lyoo et al.[61]	25 BPD persons	Brain MRI	Brain magnetic resonance imaging was used to compare the volumes of the frontal lobes, temporal lobes, lateral ventricles, and cerebral hemispheres in 25 BPD patients with age- and gender-matched healthy comparison participants (n=25)	Compared to control people, BPD subjects' frontal lobes were noticeably smaller	Quantitative
Marceau et al.[89]	14 studies with data from 467 individuals with BPD	Studies satisfied the criteria for inclusion if they investigated either (a) biomarkers predicting BPD psychotherapy response or (b) neurobiological components affected by psychotherapy	Comparison within selected studies	The anterior cingulate, amygdala, insula, and prefrontal cortex activity was significantly reduced after psychotherapy, particularly in the ventrolateral and right hemisphere regions	Review
Markowitz[94]	-	Theoretical paper on pharmacotherapy of personality disorder			Book
Marques et al.[80]	Winstar rats	In mice lacking obesity, a high-fat (HF) diet alters the gut microbiome, which decreases memory and increases anxiety and stereotyped behaviours. Low-grade chronic inflammation and aberrant cytokine production are features of obesity and associated metabolic comorbidities	Mice with and without HF diet	Many depressive risk factors, including stress and sleep disturbances, are characterised by inflammation, which, along with obesity, also results in altered gut flora	Letter to editor, quantitative
Mercer et al.[98]	-	Literature review of psychopharmacology in BPD	Comparing mood stabilisers, antipsychotics and antidepressants	Except for divalproic acid, mood stabilisers were found to have a significant pooled effect size for rage. Antidepressants had a minimal impact on sadness but a considerable impact on reducing anger. Antipsychotics' influence on anger was mild	Systematic review
Miller & Spencer[71]	-	Literature review	-	Cognitive dysfunction and age-related cognitive illnesses like dementia seem to be strongly influenced by obesity and/or a high-fat diet	Review
Montezinho et al.[99]	Animal model	After five days in culture, cortical neurones were pre-exposed to therapeutic-relevant doses of LiCl (1 mM), valproate (0.05 mM) or carbamazepine (0.5 mM) for two days. Non-exposed cultures served as a control	Lithium, valproate and carbamazepine treated and not treated Wistar rats	Dopamine D2 and b1-adrenergic receptors are co-localised in the rat prefrontal cortex, and their protein levels are changed by mood stabilisers, as determined by immunohistochemistry and immunoblotting, respectively	Quantitative experimental

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Author, Reference	Population	Intervention	Comparison	Outcome	Study type
Mousailidis et al.[12]	One case report	Patients with comorbid FD and BPD	-	FD is frequently comorbid with BPD requiring a detailed assessment of the presentation and a multidisciplinary approach to reduce gaps of information and care for this complex case	Qualitative case report
Nelson et al.[55]	-	Children who experience trauma (such as seeing a family member's murder or being sexually assaulted) are more likely to develop depression, PTSD, behavioural issues, substance misuse, self-harm, and suicidal thoughts and attempts.	Children victims of adversities compared to normal children	Childhood adversity has been related to a higher risk of adult chronic diseases such cardiovascular disease, stroke, cancer (apart from skin cancer), asthma, chronic obstructive pulmonary disease, renal disease, diabetes, overweight or obesity, and depression, as well as higher risk behaviours.	Systematic review
Nelson et al.[13]	197 BPD persons	Network Analysis of Cluster B symptoms and BPD	Cluster B personality disorders	Network analysis findings revealed that borderline qualities were closely related to antisocial, narcissistic, and histrionic tendencies, severe self-injurious conduct, and aggressive behaviour toward others. In addition, borderline characteristics were crucial for connecting antisocial traits with aggressive actions	Quantitative
NICE[6]	-	-	-	Recommendations for BPD treatment	Government recommen-dations
Paris[54]	-	-	-	Social factors linked to BPD	Book
Piper & Joyce[83]	-	-	-	Theory on BPD and psychosocial treatment	Book chapter
Porr[92]	-	-	-	Theory on the treatment of BPD	Book
Rea et al.[76]	-	Review of the literature on the microbiota, which is the term for the diverse community of microorganisms that live in the human gut and include bacteria, archaea, yeasts, single-celled eukaryotes, helminth parasites, viruses, and bacteriophages	Along with the enteric nervous system, sympathetic and parasympathetic divisions of the autonomic nervous system, and neuroendocrine and neuroimmune components of the central nervous system, the gut microbiota is a component of a complex network known as the microbiota-gut-brain axis	The study hypothesises that the richness and diversity of the gastrointestinal microbiota may have a role in the resilience to immune- and stress-related illnesses and the malfunction of these systems	Review

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Author, Reference	Population	Intervention	Comparison	Outcome	Study type
Richetin et al.[15]	1,317 university students with a diagnosis of at least one personality disorder	Network analysis of BPD psychopathology using Fused Graphical Lasso	Comparison within the sample	Identity issues and affective instability are essential components of the psychopathology associated with BPD. Cognitive-behavioural approaches have long hypothesised that BPD disorder's fundamental emotional regulation problems cause affective instability	Quantitative
Rinne et al.[95]	Experimental group, N=20; placebo group at week 6, N=18	Efficacy of fluvoxamine following the study's six-week double-blind, placebo-controlled phase	fluvoxamine vs placebo	Effect of fluvoxamine on the frequency of abrupt mood changes	Quantitative, RCT
Ross et al.[49]	100 inpatients	The DSM-IV manual updated the diagnostic criteria of borderline personality disorder (BPD) to include dissociative and paranoid symptoms. A body of research has shown that dissociative disorders are frequent in BPD	BPD +/- dissociative identità disorder (DID)	The DID+BPD group had the most significant rate (100 per cent childhood physical and/or sexual abuse), according to the participants, who also reported significant levels of adult physical and sexual abuse	Quantitative
Ruocco et al.[93]	Eleven studies involving 205 BPD patients and 222 healthy controls	MRI studies of amygdala and hippocampus size	BPD vs healthy controls	The decrease in volume of the right amygdala might be a biological marker for BPD	Systematic review and meta-analysis
Sagarwala et al.[62]	-	Studies of brain white matter (WM) among different psychopathologies	-	BPD has been associated with diffuse WM pathology	Systematic review
Sansone & Sansone[78]	-	To explore the comorbidity between BPD and eating disorders	-	Physical, emotional, and sexual maltreatment repeatedly experienced as a kid is likely to increase the likelihood of developing general psychopathology in adulthood, including eating disorders.	Review
Schmahl et al.[91]	-	Effect of psychotherapy on BPD brain	Comparison of brain effect of psychotherapy in BPD	after effective Dialectical Behaviour Therapy decreased amygdala activity that was earlier present (DBT)	Review
Sharma et al.[103]	70 trials with 18,526 patients	Effect of antidepressants on suicide	Comparison of studies	The risk of violence and suicidality doubled in kids and teenagers	Systematic review and meta-analysis
Stapleton & Wright[24]	Eight primary studies and three first-hand accounts met the inclusion criteria	Effects of CBT on BPD	Comparing positive and negative experiences	Positive aspects of inpatient care were time away from daily life, the ability to be heard and talked to by staff and other patients, and a sense of safety and control	Meta-synthesis
Tang et al.[90]	12 studies scrutinised	Effect of mindfulness meditation on the brain	Comparing the effect of mindfulness therapy on different functions of the prefrontal cortex	Much of this research is motivated by the idea that mindful emotion regulation reduces activity in areas involved in affect processing, such as the amygdala, via enhancing prefrontal cognitive control mechanisms	Review

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Author, Reference	Population	Intervention	Comparison	Outcome	Study type
Völlm et al.[63]	7 males with BPD	To investigate the morphological and functional alterations in borderline personality disorder patients' brains (BPD)	Persons with BPD compared with controls, not with the diagnosis	Compared to healthy men, males with BPD exhibited equal WM volumes but reduced grey matter (GM) volumes in the frontal, temporal, and parietal cortices. These two variables have a poor correlation with trait impulsivity	Quantitative
Watts & Strogatz[105]	-	To present a theory of collective dynamics of "small-world" networks	-	To investigate the nature of small-world networks	Theoretical experimental; letter to the editor
Zanarini[101]	-	To investigate the effect of psychotherapy on BPD	Comparison between different forms of psychotherapy	Comprehensive, protracted psychotherapy may be a beneficial method of BPD treatment	Systematic review