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Bridges Between Bipolar and Borderline Personality Disorders: Clarifying Comorbidity Through the Analysis of Complex Network of Connections Between Symptoms

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Abstract

Background: The reasons for the high rates of comorbidity between Bipolar (BD) and Borderline Personality (BPD) disorders remain elusive, due to the vast array of shared clinical features, which makes the differential diagnosis difficult. This constitutes an obstacle to provide quality of care services, which results in detrimental effects on individual's mental health. The analysis of the complex network of connections between symptoms of both disorders is a promising pathway to uncover the mechanisms underlying the comorbidity structure of both disorders.
Goals: In this study, we explored the comorbidity network that represents the connections between 32 DSM-5 symptoms of BD and BPD in order to (1) compare its modular structure (i.e., the constitution of cohesive subgroups of symptoms within the comorbidity network) with the nosographic proposal of the DSM-5; (2) distinguish between the different roles those symptoms have in the comorbidity network and identify the symptoms that overlap and bridge both disorders, as well as the distinctive symptoms that better discriminate them; (3) identify the most central symptoms and those with the highest impact on the strength or on the structure of the connections on the comorbidity network; and (4) analyze the association between symptoms roles and their centrality and impact.
Methods: An epidemiological sample from the National Comorbidity Survey: Baseline (NCS) was analyzed. Data regarding bipolar and borderline personality symptoms were collected through the Composite Network International Diagnostic Interview (CIDI). The network of complex interactions between symptoms was estimated using the Ising model with the L1-regularization penalty (EBIC) and the nosographic structure was detailed with Moduland algorithms.
Results: Data regarding an overall sample of 7556 individuals was analyzed (48.6% male, M_{age} = 33.400 years, SD_{age} = 10.447). Results revealed differences between the modular structure of the comorbidity network and the DSM-5 nosographic proposal, namely about unstable relationships and substance abuse, that were assigned to the module constituted by symptoms of manic episode (ME). Symptoms such as money spending and sexual indiscretions, that overlap ME and BPD in the DSM-5, were assigned to the ME module. Psychomotor agitation, which overlaps depressive episode (DE) and ME in the DSM-5, was assigned to the DE module. Additionally, emptiness and worthlessness were identified as bridge symptoms between DE and BPD; anger and substance abuse between ME and BPD; and unstable relationships and psychomotor agitation between DE and ME. Fatigue was the most distinctive symptom of the DE module, unstable relationships of the ME module, and anger of the BPD module. Strength centrality (r = .61, *95%CI* [.33, .79], p < .001) and modular bridgeness (r = .64, *95%CI* [.38, .81], p < .001) were positively correlated with the impact on the structure of the comorbidity network; and modular overlap was negatively correlated with the impact on the strength (r = -.43, *95%CI* [-.10, -.68], p = .01) of its connections.
Discussion: Results suggest a similar structure of the comorbidity network to the nosographic proposal of DSM-5. Distinctive and bridge symptoms were identified for each disorder which might help with the differential diagnosis. It can also help us to unveil possible development pathways of comorbidity that might promote an improvement in psychological treatments.

Keywords: Bipolar disorder, Borderline personality disorder, Network analysis, Comorbidity.

Introduction

The differential diagnosis between Bipolar (BD) and Borderline Personality (BPD) disorders remains controversial (Barroilhet, Vohringer, & Ghaemi, 2013; Ghaemi, Dalley, Catania, & Barroilhet, 2014). This controversy is also associated with the high comorbidity rate observed in both community-based (McDermid et al, 2015) and clinical (Henry et al., 2001; Fonseka et al., 2015) samples, and constitutes an obstacle for health care professionals (Bennazi, 2005; Borda, 2016), leads to a high number of misdiagnosed patients (Galione & Zimmerman, 2010) as well as to a large lag between diagnosis and beginning of treatment (Hirschfeld, Lewis, & Vornik, 2003; Zimmerman, Martinez, Young, Chelminski, Morgan & Dalrymple, 2014). The high comorbidity between these disorders was attributed to the vast array of shared clinical features that span from nuclear diagnostic criteria to etiopathogenic mechanisms (Bayes & Parker, 2017; Paris, Gunderson, & Weinberg, 2007) which led to the perspective that BPD is a disorder of the bipolar *spectrum* (e.g., Akiskal, 2004). In this perspective, unstable temperament is considered to play a major role in the etiology of the bipolar *spectrum*, which manifests itself in the emotional instability, unstable interpersonal relationships, anxiety, and impulsivity, observed in individuals diagnosed with BPD (Hatchett, 2010). Contrary to this perspective, some studies observed marked differences between the clinical characteristics associated with BD and the ones associated with BPD, related, for example, with the duration of the episodes, response to pharmacological treatments, mood states, mood prognosis and impulse reactivity (Soler et al., 2013) and led to the conclusion that these disorders constitute distinct conditions (Koenigsberg et al., 2002; Wilson et al., 2007; Zimmerman, Martinez, Young, Chelminski, Morgan, & Dalrymple, 2014). To some extent, this controversy is raised by the focus of previous research on the comparison of individuals diagnosed with both disorders with individuals diagnosed with only one of them, on clinical characteristics related to etiology, treatment response and family history (Paris, Gunderson, & Weinberg, 2007).

In exploring alternative pathways to surpass these problems, it was suggested that detailing their comorbidity structure by focusing on symptoms would constitute a major contribution by allowing the identification and distinction between overlapping symptoms, those symptoms that are shared by both disorders (e.g. emotional dysregulation and impulsivity) and would be associated with comorbidity, and distinctive symptoms (e.g., fear of abandonment and psychomotor agitation) that would enable the distinction between them (Bayes & Parker, 2017; Cassano et al., 2009; Frías, Baltasar, & Birmaher, 2016). On these grounds, a study by Perugi, Angst, Azorin, Bowden, Vieta, and Young (2013) suggested that four out of nine symptoms of BPD also predict BD (unstable and intense interpersonal relations, impulsivity, emotional instability and reactivity and intense and inappropriate anger), and that fear of abandonment, and recurring suicidality or self-mutilation, are specific of BPD. Vohringer and colleges (2016) concluded that the symptoms of manic episode (e.g., elevated mood, increased goal-directed activities) and their duration are exclusive of BD. In addition, although the impulsive behavior is thought to be central to both disorders, most manic and hypomanic episodes don't involve impulsivity (Goodwin & Jamison, 2007). In turn, psychomotor agitation seems to be a more prominent feature of BD than of BPD (Cassano et al., 2009). On the other hand, Benazzi (2008) found no relationship between the symptoms of Bipolar Disorder II (BD-II) and BPD traits. This brief overview makes it noticeable that although this approach is beginning to contribute to surpass the ongoing controversy, some ambiguity around the overlapping and distinctive symptoms of both disorders remains. In fact, studies on the comorbidity between BD and BPD, carried out at the level of symptoms, remain scarce (Barroilhet, Vohringer, & Ghaemi, 2013).

This is unfortunate, as in recent years, a growing body of research, across a wide range of disorders like depression (Fried, Epskamp, Nesse, Tuerlinckx, & Borsboom, 2016), anxiety (Beard et al., 2016), post-traumatic stress (Armour, Fried, Deserno, Tsai, & Pietrzack, 2016), psychosis (Isvonaru, Borsboom, Os, & Guloksuz, 2016), substance abuse (Rhemtulla et al.,

2016) and autism (Anderson, Locke, Kretzmann, & Casari, 2016), has provided consistent evidence that the connections between symptoms constitute an important dimension of the etiopathogeny of mental health disorders; and promoted new insights on phenomena like comorbidity (Cramer, Waldorp, Maas, & Borsboom, 2010) and diversity of clinical presentations (Borsboom & Cramer, 2013) that have a detrimental impact on the validity of the nosography of mental health disorders (Boschloo et al., 2015; Eaton, 2015). Those studies explore the connections between symptoms by using network models that represent those connections. These psychopathological networks (see Borsboom, 2017; Borsboom & Cramer, 2013; Borsboom, Epskamp, Kievit, Cramer, & Schmittmann, 2011; Fried et al., 2017, for reviews) are represented through graphs constituted by vertices, representing symptoms, by edges, representing the connections between symptoms, and by edges-weights, which represent the strength of these connections. Psychopathological networks enable the identification of most central symptoms, the ones that have more diverse or stronger connections with other symptoms, and/or the ones that are involved in the connections between other symptoms (Borsboom, 2017), as well as those symptoms, named bridge symptoms (Cramer, Waldorp, Mass, & Borsboom, 2010), that connect distinct disorders. The identification of central and bridge symptoms fosters an alternative understanding and clarification of the comorbidity structures that usually characterize mental health disorders (Fried et al., 2016), such as the one between BD and BPD. Although no previous study has explored the comorbidity network of BD and BPD (i.e., the network representing the connections between the symptoms of both disorders), Richetin, Preti, Costantini, and De Panfilis (2017) explored the network of connections between symptoms of BPD and found that affective instability, identity disturbance and fear of abandonment are the most central symptoms. As in previous studies on other disorders (e.g., Armour, Fried, Deserno, Tsai, & Pietrzark, 2016; Levinson et al., 2017), the authors suggested that specifically targeting these symptoms during treatment can improve treatment efficacy since the strength and number of connections the central symptoms maintain with the other symptoms is expected to be associated with a high potential to transform the network. Symptoms centrality is therefore hypothesized to be associated with their impact on the network. However, previous studies on psychopathological networks have provided only partial or indirect support for this hypothesis and further evidence is necessary to support it (Fried et al., 2017). This is relevant because if this is the case, then the identification of these symptoms would bring much-needed breakthroughs in the development of precision (Collins & Varmus, 2015; Rugkåsa, Yeeles, Molodynski, & Burns, 2015) and individualized (Fischer, 2015; Fischer & Boswell, 2016) treatments.

Another open question concerning the role of central symptoms refers to the question of knowing if these symptoms correspond to the most characteristic, distinctive symptoms of the disorders being studied. Some studies observed that some of the most central symptoms in psychopathological networks of depression (van Borkulo et al., 2015) or post-traumatic stress disorder (Armour, Fried, Deserno, Tsai, & Pietrzark, 2016) coincide with the core symptoms of these disorders according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders (DSM), but this is not a consistent observation as other studies identified central symptoms that do not coincide with the core symptoms assumed by the DSM (see Boschloo et al., 2015 for an example). Moreover, doubts have been raised on the discriminative power of the DSM core symptoms (Goekoop & Goekoop, 2014). In the case of BD, for example, impulsivity related symptoms (i.e., spending, sexual indiscretions), which are criteria for manic episode in the DSM, do not appear in most manic episodes (Goodwin & Jamison, 2007).

The same kind of questions also apply to the case of overlapping or bridge symptoms since it makes intuitive sense to hypothesize that symptoms that connect two disorders would have a significant impact on the psychopathological network by dissolving it in the case of being removed during treatment. For example, an overlapping symptom between BD and BPD is the engagement in activities that have potentially unpleasant consequences (e.g., sexual indiscretions and spending). Thus, in a patient with BPD that displays sexual indiscretions or spending, also associated

with BD, targeting those symptoms could dissolve the comorbidity network and prevent the patient from also developing BD. However, no direct evidence exists to support this hypothesis. In fact, Afzali and colleagues (2016) compared the complete network of connections between the symptoms of posttraumatic stress disorder and major depressive disorder with the network of connections between these disorders' symptoms after removing the bridge symptoms and observed that a significant number of connections between the symptoms of both disorders emerge even in the absence of bridge symptoms. Furthermore, to date, the identification of the bridge symptoms has been performed by identifying the symptoms of one disorder that have the highest number of connections with symptoms of a different disorder (e.g., Afzali et al., 2016; Beard et al., 2016). This procedure assumes that the empirical structure of the comorbidity network reproduces the nosographic proposal of the DSM (i.e., the symptoms of both disorders correspond to identifiable and especially cohesive subgroups of symptoms in the comorbidity network), but this needs not be the case. Previous studies on the psychopathological networks of other disorders have found only general correspondence between the DSM nosographic proposal and empirical structure of the networks (Jones, Mair, Riemann, Mugno, & McNally, 2017). Factor analytic studies on the empirical structure of BD (Eisner, Johnson, Youngstrom, & Pearlstein, 2017; Ferentinos et al., 2017) and BPD (Lewis, Caputi, & Grenyer, 2012) observed that some symptoms saturate more strongly on a factor corresponding to a different disorder; and previous research on the empirical structure of BD (Angst, 2013) and BPD (Calvo et al., 2016) raised some concerns over the validity of the nosographic proposal of the DSM for these disorders. These observations suggest that it is unlikely that the empirical structure of the comorbidity network replicates the nosographic proposal of the DSM. This, in turn, suggests that, at least from a methodological point of view, the identification of bridge symptoms should be contingent on the identification of distinguishable subgroups of symptoms in the empirical structure of the comorbidity network.

In summary, the reasons for the high rates of comorbidity between BD and BPD remain elusive (Zimmerman & Morgan, 2013). Research focused on characterizing the comorbidity of BD and BPD by focusing on their symptoms has begun to identify the symptoms that better discriminate both disorders, but previous studies are scarce, and some results remain ambiguous. The analysis of psychopathology networks has been revealing itself as one of the most promising pathways to understanding the role of connections between symptoms in the emergence of comorbidity between mental health disorders but some of its central hypotheses are in need of further developments. In this context, the present study explored the comorbidity between BD and BPD by focusing on the network of connections between the symptoms of both disorders. It aimed to: (1) compare the comorbidity network of BD and BPD with the nosographic proposal of the DSM-5 (American Psychiatric Association, 2013), (2) identify overlapping, bridge and discriminative symptoms, (3) identify the most central and impactful symptoms, and (4) explore the association between symptoms' centrality and impact with their roles in the comorbidity network.

Methods

This is a secondary analysis of data gathered in a cross-sectional observational design.

Participants

A community-based sample, representative of the United States of America, from a previous epidemiological study, the National Comorbidity Survey: Baseline (NCS-Baseline; Kessler, Borges, & Walters, 1999), was analyzed. The NCS-Baseline dataset comprises 8098 participants with ages between 15 and 61 years. For this study, participants without at least one symptom of BD and BPD were excluded. Prior to the beginning of every interview, the study was explained, and a verbal informed consent was obtained. These procedures were approved by the Human Subjects Committees of Harvard Medical School and of the University of Michigan.

Symptoms Measures

In the NCS-Baseline study, participants were interviewed through a modified version of the Composite International Diagnostic Interview (CIDI; Kessler & Ustun, 2004). This is a structured interview that assesses symptoms of depression, mania, dysthymia, panic disorder, agoraphobia, social phobia, simple phobia, generalized anxiety disorder, alcohol abuse and dependence, drug abuse and dependence, antisocial personality disorder and non-affective psychosis. CIDI is a tool created under the scope of a WHO initiative, and assesses disorders on basis of the corresponding definitions and criteria from both DSM-III-R and ICD (Robins et al., 1998).

For the present study, CIDI questions that refer to the symptoms of depressive episode (DE) and manic episode (ME) were used as measures of the symptoms of BD. These questions ask participants to rate the occurrence of these symptoms on a "*yes*" or "*no*" format. Although the CIDI does not have a specific measure for the symptoms of BPD, it has a section dedicated to the assessment of personality traits through items that reflect those traits. Each item is rated on a Likert-type scale that ranges from 1 ("*Very true*") to 4 ("*Not true at all*"). Three of these items, addressing BPD symptoms of fear of abandonment, identity disturbance, and emptiness, were selected for the present study. To accurately capture all the criteria proposed by the DSM-5 for the diagnosis of BPD they were complemented with other CIDI questions that assess unstable relationships, substance abuse, unstable affect and anger. Only the DSM-5 symptom of compulsive eating is missing from the assessment of the NCS-Baseline study. In total, 32 DSM-5 symptoms of BD and BPD were selected (25 of BD and 7 of BPD). When necessary, participants' answers were dichotomized prior to data analysis. The CIDI questions selected for this study and the corresponding DSM-5 criteria are presented in Table S1 of the supplementary materials.

Network Estimation and Analysis

The Ising model coupled with the L1-regularization penalty (EBIC) (van Borkulo et al., 2014) was used to estimate the network of connections between the symptoms of BD and BPD. The matrix containing the connections weights is included in Table 2 of the Supplementary materials. Its graphical representation was computed using the Fruchterman-Reingold (Fruchterman-Reingold, 1991) algorithm. R (R Development Core Team, 2008) packages bootnet (Epskamp & Fried, 2017) and qgraph (Epskamp et al., 2012) were used to estimate and represent the comorbidity network. Three measures of symptoms' centrality were computed: strength, betweenness, and closeness (Barrat, Barthelemy, Pastor-Satorras & Vespignani, 2004; Opsahl, Agneessens & Skvoretz, 2010). Symptoms strength is the sum of the weights of all the connections of a specific symptom to all other symptoms in the network. Betweenness is a measure that relies on the number of times a symptom is present on the shortest path between two other symptoms. Closeness is the average distance from a specific symptom to all the other symptoms in the comorbidity network. R package qgraph (Epskamp, Cramer, Waldorp, Schmittmann & Borsboom, 2012) was used to compute centrality measures.

The accuracy and stability of the comorbidity network were analyzed by estimating the 95% bootstrapped confidence intervals (CIs) for each of the connections and the correlation stability coefficient (CS-Coefficient; Epskamp, Borsboom, & Fried, 2016). CS-Coefficient estimates the maximum number of cases that can be dropped from the data to retain a correlation of at least .7 (95%) between the statistics of the original network and the statistics obtained with fewer cases (Epskamp & Fried, 2017). CS-Coefficient must not be lower than .25 and should preferably be higher than .5 (Epskamp, Borsboom, & Fried, 2016). R package bootnet (Epskamp & Fried, 2017) was used to estimate the 95% bootstrapped CIs for the connections weights and to compute the CS-coefficients for strength, closeness, and betweenness centrality. These are depicted in Figures S1 and S2 in the supplementary materials. Additionally, Figures S4, S5, and S6 in the supplementary materials depict the bootstrapped difference tests for the centrality measures of every symptom in the network.

The structure and strength impact of each symptom in the comorbidity network was computed using R package networktools (Jones, 2017). Structure impact

measures the influence of each symptom on the connections that constitute the comorbidity network, and strength impact measures the influence of each symptom on the weights of the connections in the comorbidity network. Positive values of strength impact suggest that symptoms increase the connections weights and negative values suggest that symptoms decrease the connections weights. To explore the overall strength impact of each symptom the absolute values were computed.

After estimation of the comorbidity network, its network structure was explored in order to compare it with the nosographic proposal of the DSM-5. To accomplish this, network modules were identified. Modules are constituted by a set of symptoms that have a large mutual influence on each other and therefore form a highly-connected cluster of symptoms. The symptoms in each module are expected to correspond to the symptoms of each disorder if the empirical structure of the comorbidity network corresponds to the nosographic proposal of the DSM-5. Because the nosographic proposal of the DSM-5 includes symptoms that overlap BD and BPD, an algorithm that allows network modules to overlap was used. Moduland algorithm (Szalay-Beko et al., 2012), implemented in Cytoscape 3.5.1. (Shannon et al., 2003), was used to identify modules in the comorbidity network. Each symptom gets module assignment values that represent how much it belongs to each module. Table S3 in the supplementary materials presents module assignment values for the 32 symptoms in the comorbidity network. Modular cores are the symptoms that have the maximal module assignment value in each module. We used this as a measure of the distinctive symptoms (the symptoms that better characterize a module and distinguish it from other modules). Within each module, we considered bridge symptoms to be those symptoms with higher assignment value to each one of the other modules. Moduland also measures modular overlap and bridgeness. Modular overlap is a trans-modularity measure of the effective number of modules that a symptom is assigned to, and modular bridgeness is an inter-modularity measure of the overlap of a given symptom between two or more modules relative to all the other symptoms. Table S4 in the supplementary materials presents the values for symptoms centrality, impact and modular roles (bridgeness and overlap). Data analysis on R was performed in RStudio 1.1.379 (RStudio Team, 2017).

Finally, Pearson correlation coefficients between centrality, impact and modular roles were estimated in JASP (JASP Team, 2016).

Results

Data from 7556 participants, which fulfilled the inclusion criteria, were analyzed and are presented below. These participants are characterized in Table 1. Overall, 2473 (33%) participants met the criteria for DE, 394 (5%) for ME and 2471 (33%) for BPD.

Comorbidity Network of BD and BPD

The comorbidity network of BD and BPD is represented in Figure 1. It is constituted by 224 connections between the 32 symptoms (density = .45), 220 (98.22%) positive, and 4 (1.79%) negative connections. Positive connections weights range from .02 to 3.0 (M = 0.45, SD = 0.451). Negative connections weights range from 0.10 to 1.07 (M = 0.47, SD = 0.42). The accuracy and stability of the comorbidity network were adequate, and the CS-coefficients were also adequate for strength (.75), closeness (.52), and betweenness (.36)

Comorbidity Network Modules

Figure 2 identifies the modules in the comorbidity network and the symptoms that constitute them. Three modules were observed that broadly correspond to the symptoms of DE (green dots in Figure 2), ME (orange dots in Figure 2) and BPD (gray dots in Figure 2) in the DSM-5. Differences with the nosographic proposal of the DSM-5 are visible mainly in ME symptoms with unstable relationships and substance abuse commonly associated with BPD being assigned to this module. The role of DSM-5 overlapping symptoms was also clarified. The impulsivity criteria that overlaps ME and BPD (i.e., money spending and sexual indiscretions) were assigned to ME module in the

.

Table 1. *Participants' sociodemographic characteristics*

		n	*%*	Mean	SD	Minimum	Maximum
Sex	**Male**	3670	48.60				
	Female	3886	51.40				
Age		7556		33.40	10.45	15	61
Marital status	**Married**	3622	47.90				
	Separated	296	3.90				
	Divorced	982	13.00				
	Widowed	71	0.90				
	Single	2585	34.20				
Nationality	**African**	599	7.90				
	American Indian	884	11.70				
	Asian	109	1.40				
	Czechoslovakian	139	1.80				
	English	950	12.60				
	French	953	12.60				
	German	953	12.60				
	Irish	386	5.10				
	Italian	182	2.40				
	Mexican	20	0.30				
	Near Eastern	20	0.30				
	Polish	110	1.50				
	Russian	39	0.50				
	Scandinavian	94	1.20				
	Scottish	31	0.40				
	Dutch	330	4.40				
	Spanish	20	0.30				
	Portuguese	5	0.10				
	Hungarian	8	0.10				
	Lithuanian	3	0.00				
	Greek	5	0.10				
	Swiss	1	0.00				
	Yugoslavian	2	0.00				
	Other Eastern European	3	0.00				
	Other Western European	5	0.10				
	Caribbean Islands	5	0.10				
	Missing values	1700	22.50				
Grade (years)		7556		12.92	2.36	2	17

modular structure of the comorbidity network. Psychomotor agitation, that overlaps ME and DE in the DSM-5, was assigned to the DE module. Figure 2 also depicts the distinctive symptoms of each condition namely, fatigue for DE module, unstable relationships for ME module and anger for BPD module. The bridge symptoms that connect BPD and DE were emptiness and worthlessness, those that link BPD and ME were anger and substance abuse and, finally, those that connect ME and DE were unstable relationships and psychomotor agitation.

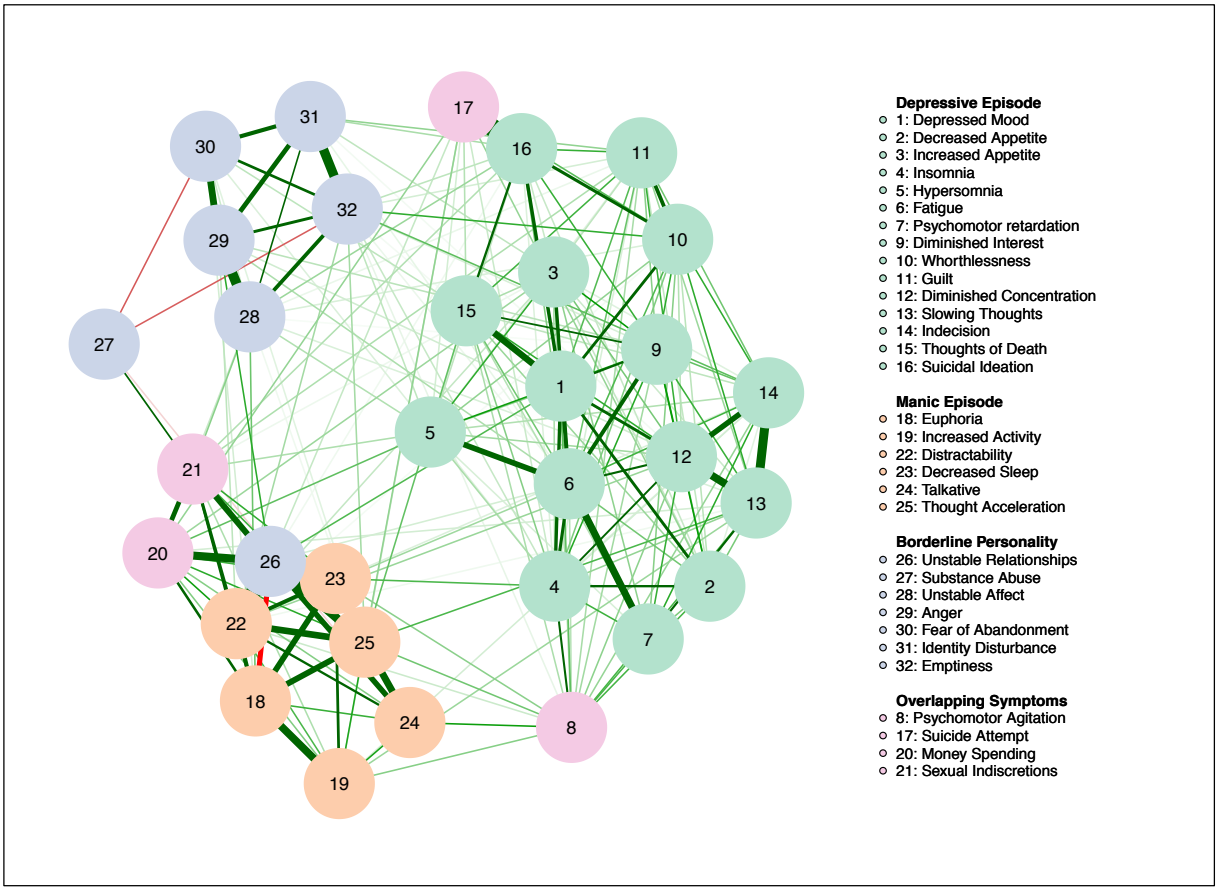

Figure 1. *Comorbidity network of bipolar and borderline personality disorders. Green nodes represent the symptoms of depressive episode in the DSM-5; orange nodes represent the symptoms of manic episode in the DSM-5; grey nodes represent the symptoms of borderline personality disorder in the DSM-5; and purple nodes represent the overlapping symptoms according to the nosographic proposal of the DSM-5: node 8 (psychomotor agitation) overlaps depressive and manic episodes; node 17 (suicidal attempt) overlaps depressive episode and borderline personality disorder; nodes 20 (money spending) and 21 (sexual indiscretions) overlap manic episode and borderline personality disorder. Connections between the symptoms (edges) are represented by the blue lines (positive connections), and the red lines (negative connections). The lines' thickness represents the strength of the connections between the symptoms (edges weights). The thicker the lines are, the stronger the connections between symptoms are.*

Symptoms Modular Roles: Bridgeness and Overlapping

Symptoms' modular bridgeness and overlapping are presented in Figure 3.A. Symptoms of ME and BPD modules revealed the highest modular bridgeness and overlapping. Unstable relationships, distractibility and thought acceleration (ME module), and anger and emptiness (BPD module) revealed the highest modular bridgeness. Substance abuse (ME module), and unstable affect, anger, fear of abandonment, emptiness and identity disturbance (BPD module) revealed the highest modular overlapping.

Symptoms Centrality: Strength, Betweenness, and Closeness

Figure 3.B. presents symptoms centrality. BD symptoms were the most central symptoms in the comorbidity network. Unstable relationships (ME module) and fatigue (DE module) revealed the highest strength centrality. The symptoms with the highest betweenness and closeness centrality were unstable relationships (ME module) and depressed mood (DE module).

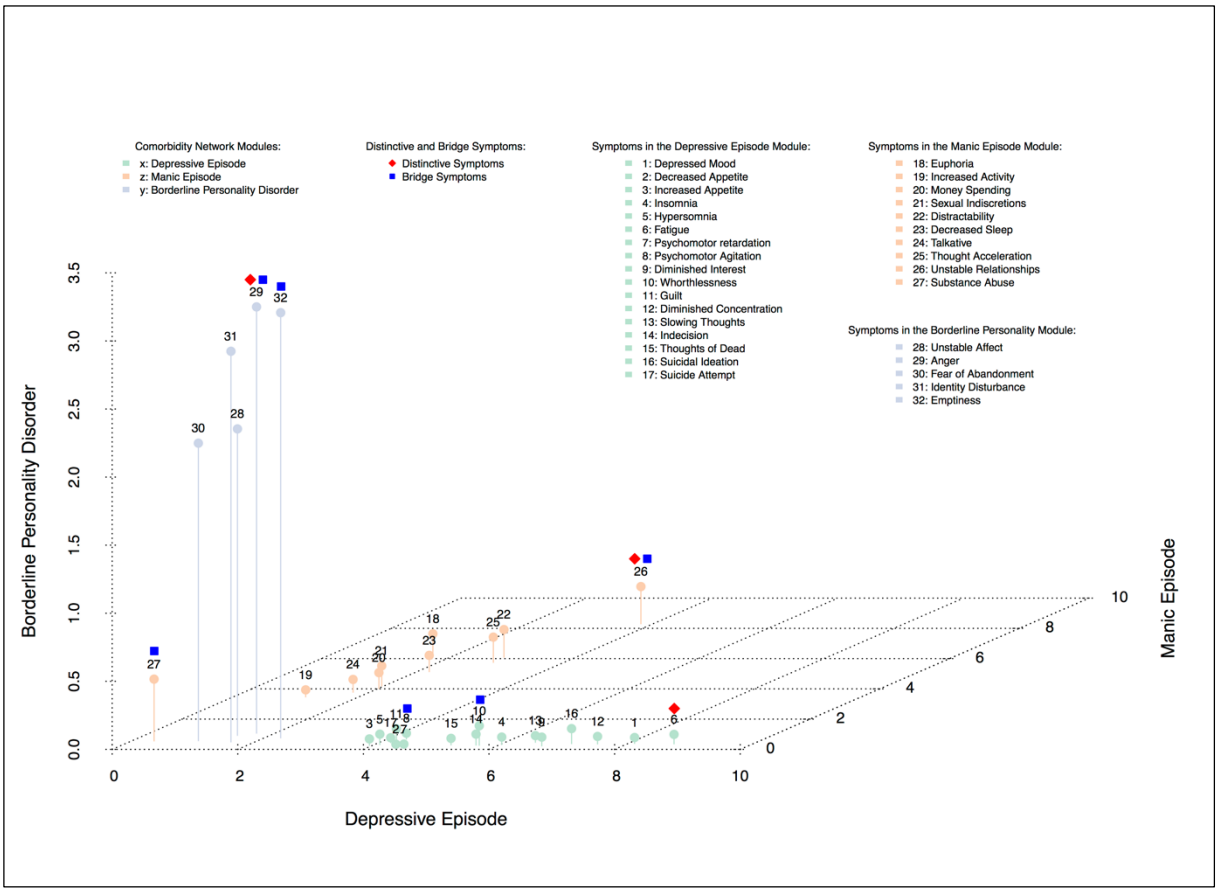

Figure 2. *Comorbidity network modules by Moduland algorithm. Three axes are represented in this figure and each one corresponds to the three conditions analyzed: in green is represented the depressive episode module; in gray, the borderline personality disorder module; and in orange the manic episode module. Each of the three axes show the modular core measure value. In this way, the most distinctive symptoms which are represented in red, are: for depressive episode, fatigue; for manic episode, unstable interpersonal relationships; and for borderline personality disorder, anger. The bridge symptoms which are represented in blue are: for manic and depressive episode, unstable interpersonal relationships and psychomotor agitation; for manic episode and borderline personality disorder, substance abuse and anger; and for borderline and depressive episode, emptiness and worthlessness.*

Symptoms Strength and Structure Impact

Symptoms strength and structural impact are presented in Figure 3.C. Suicidal attempt (DE module), euphoria (ME module) and psychomotor agitation (DE module) are those which exhibited the highest strength impact in the network. On the other hand, the highest structural impact was displayed by unstable relationships and euphoria (ME module).

Associations Between Centrality, Impact and Modular Roles

To evaluate the associations between centrality, impact, and modular roles we analyzed the Pearson correlation coefficients in Table 2. Symptoms modular

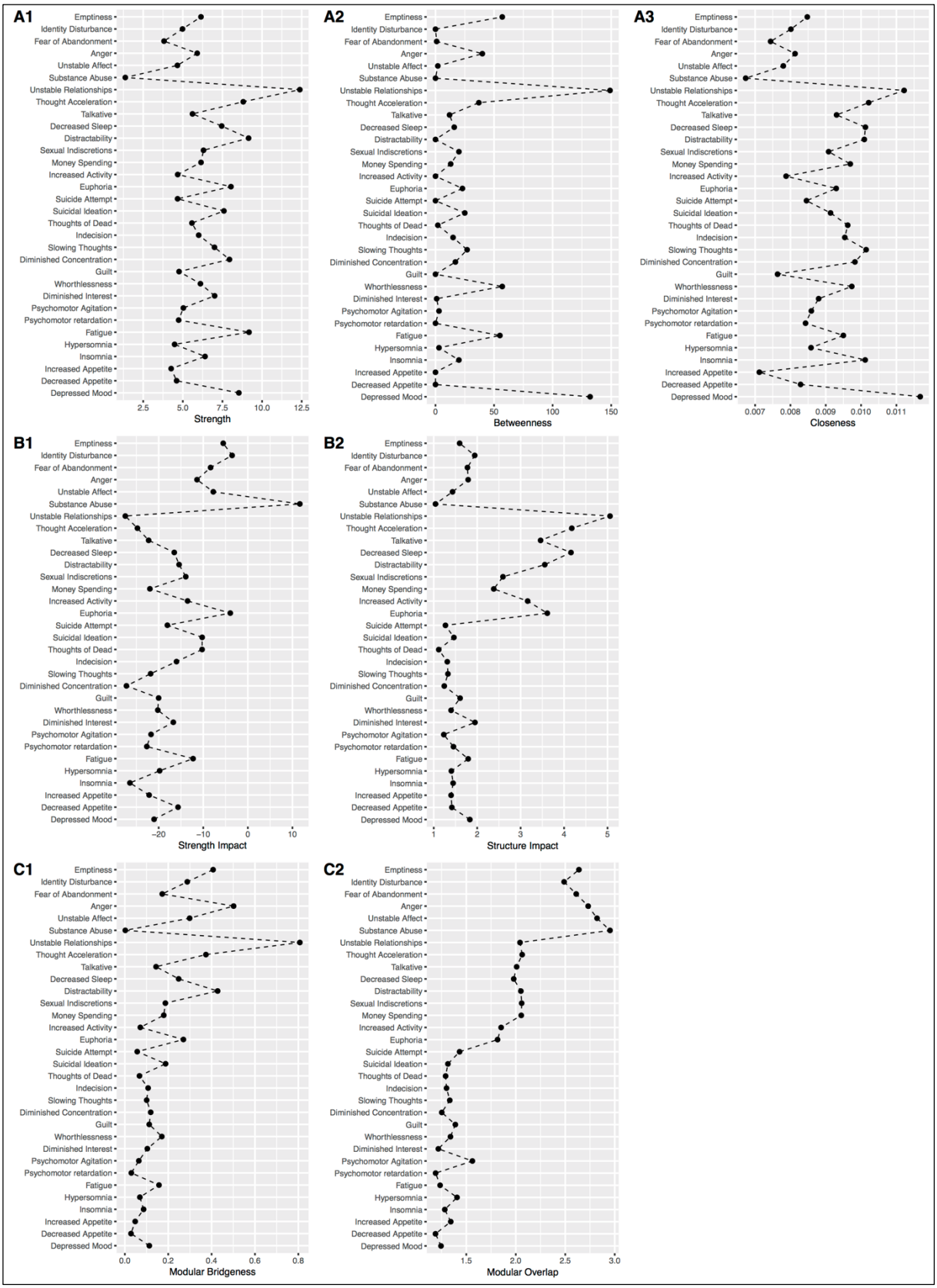

Figure 3. *Symptoms' Centrality, Impact and Modular Role*

bridgness was positively correlated with structure impact (r = .64, *95%CI* [.38, .81], p < .001). Symptoms modular overlap and strength impact correlated negatively (r = -.43, *95%CI* [-.68, -.10], p = .01). In addition, the measures of centrality were associated with impact, especially in the structure of the comorbidity network. Strength centrality (r = .61, *95%CI* [.33, .79], p < 0.001) and betweenness centrality (r = .37, *95%CI* [.02, .64], p = .04) correlated positively with structure impact. Closeness centrality revealed a positive correlation with structure impact (r = .43, *95%CI* [.09, 0.7], p = .02) and a negative correlation with strength impact (r = -.35, *95%CI* [-.63, -.01], p = .05).

Table 2. *Pearson Correlation Coefficients Between Symptoms' Centrality, Impact and Modular Roles*

		Strength Impact	Structure Impact	Strength Centrality	Betweenness Centrality	Closeness Centrality	Modular Bridgeness	Modular Overlap
Strength Impact	Pearson's r	—						
	p-value	—						
	Upper 95% CI	—						
	Lower 95% CI	—						
Structure Impact	Pearson's r	-.33	—					
	p-value	.07	—					
	Upper 95% CI	.02	—					
	Lower 95% CI	-.61	—					
Strength Centrality	Pearson's r	-.27	.61 ***	—				
	p-value	.13	< .001	—				
	Upper 95% CI	.08	.79	—				
	Lower 95% CI	-.57	.33	—				
Betweenness Centrality	Pearson's r	.05	0.37 *	.69 ***	—			
	p-value	.79	0.04	< .001	—			
	Upper 95% CI	.39	0.64	0.84	—			
	Lower 95% CI	-.31	0.02	0.45	—			
Closeness Centrality	Pearson's r	-.35 *	.43 *	.83 ***	.68 ***	—		
	p-value	.05	.02	< .001	< .001	—		
	Upper 95% CI	-.01	.67	.92	.82	—		
	Lower 95% CI	-.63	.09	.68	.40	—		
Modular Bridgeness	Pearson's r	.10	.64 ***	.64 ***	.57 ***	.34	—	
	p-value	.57	< .001	< .001	< .001	.06	—	
	Upper 95% CI	.44	.81	.81	.77	.62	—	
	Lower 95% CI	-.26	.38	.38	.28	-.01	—	
Modular Overlap	Pearson's r	-.43 *	.26	-.21	-.02	-.35 *	.50 **	—
	p-value	.01	.16	.25	.91	.05	.00	—
	Upper 95% CI	-.10	.56	.15	.33	-.01	.72	—
	Lower 95% CI	-.68	-.10	-.52	-.37	-.63	.18	—

*Note. The absolute values of modular overlap were considered. * p < .05, ** p < .01, *** p < .001.*

Discussion

The comorbidity structure of BPD and BD remains unclear due to shared clinical features, which results in enduring uncertainties about BPD belonging to the bipolar spectrum. To contribute to this debate, this paper presents a network analysis having as main goal to explore the underlying mechanisms of comorbidity associated with the connections between the symptoms of both disorders. Our results show three clear modules (DE, ME and BPD) suggesting that the disorders are distinct entities, which is in line with previous studies (e.g., di Giacomo et al., 2017). However, a few inconsistencies were observed between the empirical modular structure of the comorbidity network and the nosographic proposal of the DSM-5. The most noticeable difference is that the symptom "unstable relationships", a symptom of BPD in the DSM-5, was assigned to the ME module. This supports previous

studies that recognized difficulties in interpersonal relationships during manic episodes (Morris et al., 2013; Siegel et al., 2015). Also, impulsivity-related criteria for BPD, namely substance abuse, was assigned to the ME module. This finding might be explained by the high rates of comorbidity between substance abuse and BD (Messer, Lammers, Müller-Siecheneder, Schmidt, & Latifi, 2017) and by the high probability of consumption of substances by individuals diagnosed with BD (Grant et al., 2006). In addition, elevated mood episodes are associated with an increased likelihood of substance abuse (Messer et al., 2017). Lastly, psychomotor agitation, a DSM-5 symptom of both ME and DE, was assigned to the DE module, which is also consistent with previous studies that show a high frequency of psychomotor agitation in depressive episodes (Akiskal, Benazzi, Perugi & Rihmer, 2005). As for the different roles of the symptoms in the modular structure of the comorbidity network, our results suggest that in the case of BPD and ME, bridge and distinctive roles converge in the same symptom (anger), meaning that the symptom that has the most connections within the module is also the one with most connections with the other modules. In fact, anger has a high prevalence in both BPD and BD (Fernandez & Johnson, 2015), and was associated with the misdiagnosis of BD instead of BPD (Rugero, Zimmerman, Chelminski, & Young, 2010). Unstable relationships also seem to perform both roles: as a distinctive symptom of ME and bridge symptom with DE. Moreover, unstable relationships are the most inter-modular symptom of the all network and after substance abuse is the symptom that more strongly connects ME with BPD. Previous studies suggest that "unstable interpersonal relationships" is a non-specific symptom and does not distinguish BPD diagnostically (Perugi et al., 2013). The inter-modularity of this symptom might explain the changes in mood polarity and the development of some symptoms of BPD and, therefore, lead to the difficulties in the differential diagnosis between BPD and BD. Fatigue was identified as a distinctive symptom of DE. This result is in line with other network studies that indicate fatigue as one of the most central symptoms in depression (Bekhuis, Schoevers, Borkulo, Rosmalen, & Boschloo, 2016). Emptiness and worthlessness were identified as bridge symptoms between DE and BPD. This finding is congruent with other studies that found that emptiness is one of the traits of BPD that is most commonly observed in DE (Benazzi, 2005). Also, psychomotor agitation was identified as a bridge symptom between ME and DE, which is line with previous studies that conclude that psychomotor agitation should be considered a core feature of mixed states (Mahli et al., 2016). Substance abuse is also a bridge symptom between BPD and ME and this might be explained due to the impulsivity that characterizes both disorders (Messer et al., 2017; Pennay et al., 2011). Globally, these symptoms demonstrate a high interconnectivity between the symptoms of both disorders and helps explain the mechanisms of comorbidity.

In addition, our results show the importance of the identification of different roles for the symptoms since different roles seem to be associated with different types of impact in the network. Symptoms modular bridgeness was associated with structural impact; while modular overlap was negatively associated with strength impact. This means that symptoms of one disorder that interact the most with symptoms of another disorder, if removed from the network, cause a change in how it is connected, changing the connections between the remaining symptoms. In the case of symptoms that are present in different disorders, if they are removed from the network, the connections between the remaining symptoms stay mostly unchanged, but a reduction in the strength of the connections takes place. Since a highly and strongly connected psychopathological network is thought to be more resistant to change (Borsboom, 2017), these results suggest that targeting a specific symptom, more than promoting faster dissolution of the network, can have more specific consequences, like halting the progression of the disorder. Therefore, since acting on inter-modular symptoms breaks the connection between disorders and acting on overlapping symptoms reduces the resistance of the network to change, more than recognizing the most central symptoms, it seems important to identify the symptoms roles in order to develop precision treatments (i.e. treatments specifically developed for targeting symptoms with a particular role in a specific network),

that can allow therapists to fasten the resolution of the pathology and to prevent the development of more complex pathologies with interventions directed at those symptoms that connected the disorders or that are strengthening the network not allowing for a proper resolution of the pathology. As proposed by previous studies in network analysis, the centrality measures (i.e. strength, betweenness, and closeness) were associated with the impact on the network (e.g. Fried et al., 2016; Richetin et al., 2017). However, this impact is mainly structural; and without a well-defined role for these symptoms, it is harder to predict the outcome of an intervention in those symptoms. Overall, our results indicate that the identification of different roles for the symptoms might help with the differential diagnosis by distinguishing between distinctive and bridge symptoms. In addition, it can also help us to map possible pathways of development that would allow us to foresee the emergence of comorbidity with other disorders and promote an improvement in psychological treatments.

Our results should be carefully interpreted due to the use of a community-based sample that might not be representative of clinical populations. Moreover, symptoms of BD were assessed by a diagnostic interview which follows a skip logic, meaning that if participants do not answer positively to the screening questions of a specific disorder, the following questions pertaining the remaining symptoms are not done. We followed the same procedure used in previous studies (e.g., Boschloo et al., 2015) and considered skip related missing values correspond to absent symptoms but this may have had an impact on the estimation of the connections between the symptoms. The results of the comparison between the structure of the comorbidity network with the diagnostic structure proposed by the DSM-5 should be interpreted cautiously because data was collected on the basis of the DSM-III-R. Despite this, there are no fundamental differences between the DSM-III-R and the DSM-5 criteria for the disorders studied in this paper (Mason, Brown, & Croarkin, 2016). These issues, added to the need to resort to non-specific questions to encompass all the symptoms of BPD might have influenced the identification of the modules. In this way, future research should aim to replicate these results, especially in clinical samples, and differentiate other roles for symptoms since its plausible that more qualitative differences exist between them. Another important research topic is to empirically test the association of the impact in the network with other measures and roles because it can allow us to develop more efficient and precise treatments.

References

Afzali, M., Sunderland, M., Teesson, M., Carragher, N., Mills, K., & Slade, T. (2016). A network approach to the comorbidity between posttraumatic stress disorder and major depressive disorder: the role of overlapping symptoms. *Journal of Affective Disorders, 208*, 490-496. doi: 10.1016/j.jad.2016.10.037

Akiskal, H. S., (2004). Demystifying borderline personality: critique of the concept and unorthodox reflections on its natural kinship with the bipolar spectrum. *Acta Psychiatrica Scandinavica, 110*(6), 401–407. doi: 10.1111/j.1600-0447.2004.00461.x

Akiskal, H. S., Benazzi, F., Perugi, G., & Rihmer, Z. (2005). Agitated "unipolar" depression re-conceptualized as a depressive mixed state: implications for the antidepressant-suicide controversy. *Journal of Affective Disorders, 85*(3), 245–258. doi: 10.1016/j.jad.2004.12.004

American Psychiatric Association (2013). *Diagnostic and Statistical Manual of Mental Disorders (5th edition)*. Washington: United States of America.

Anderson, A., Locke, J., Kretzmann, M., Kasari, C. (2016). Social network analysis of children with autism spectrum disorder: predictors of fragmentation and connectivity in elementary school classrooms. *Autism, 20*(6), 700–709. doi: 10.1177/1362361315603568.Social

Angst, J. (2013). Bipolar disorders in DSM-5: strengths, problems and perspectives. International *Journal of Bipolar Disorders, 1*(12), 1-3. doi:10.1186/2194-7511-1-12

Armour, C., Fried, E., Deserno, K., Tsai, J., & Pietrzak, H. (2016). A network analysis of DSM-5 posttraumatic stress disorder symptoms and correlates in U.S. military veterans. *Journal of Anxiety Disorders, 45*, 49–59. doi: 10.1016/j.janxdis.2016.11.008

Barrat, A., Barthelemy, M., Pastor-Satorras, R., & Vespignani, A. (2004). The architecture of complex weighted networks. *Proceedings of the National Academy of Sciences of the United States of America, 101*(11), 3747-3752. doi: 10.1073/pnas.0400087101

Barroilhet, S., Vöhringer, P. A., & Ghaemi, S. N. (2013). Borderline versus bipolar: differences matter. *Acta Psychiatrica Scandinavica, 128*(5), 385–386. doi: 10.1111/acps.12107

Bayes, A. J., & Parker, G. B. (2017). Clinical vs. DSM diagnosis of bipolar disorder, borderline personality disorder and their co-occurrence. *Acta Psychiatrica Scandinavica, 135*(3), 259–265. doi: 10.1111/acps.12678

Beard, C., Millner, J., Forgeard, C., Fried, I., Hsu, J., Treadway, T., & Björgvinsson, T. (2016). Network analysis of depression and anxiety symptom relationships in a psychiatric sample. *Psychological Medicine, 46*(16), 3359–3369. doi: 10.1017/S0033291716002300

Bekhuis, E., Schoevers, A., van Borkulo, D., Rosmalen, M., & Boschloo, L. (2016). The network structure of major depressive disorder, generalized anxiety disorder and somatic symptomatology. *Psychological Medicine, 46*(14), 1–10. doi:10.1017/S0033291716001550

Benazzi, F. (2005). Borderline personality-bipolar spectrum relationship. *Progress in Neuro-Psychopharmacology and Biological Psychiatry, 30*(1), 68–74. doi: 10.1016/j.pnpbp.2005.06.010

Benazzi, F. (2008). A relationship between bipolar II disorder and borderline personality disorder? *Progress in Neuro-Psychopharmacology and Biological Psychiatry, 32*(4), 1022–1029. doi: 10.1016/j.pnpbp.2008.01.015

Borda, J. P. (2016). Self over time: another difference between borderline personality disorder and bipolar disorder. *Journal of Evaluation in Clinical Practice, 22*(4), 603–607. doi: 10.1111/jep.12550

Borsboom, D. (2017). A network theory of mental disorders. *World Psychiatry 16*(1), 5–13. doi: 10.1002/wps.20375

Borsboom, D. & Cramer, A. O. J. (2013). Network analysis: an integrative approach to the structure of psychopathology. *Annual Review of Clinical Psychology, 9*(1), 91–121. doi: 10.1146/annurev-clinpsy-050212-185608

Borsboom, D., Epskamp, S., Kievit, R. A., Cramer, A. O. J., & Schmittmann, V. D. (2011). Transdiagnostic networks. *Perspectives on Psychological Science, 6*(6), 610–614. doi: 10.1177/1745691611425012

Boschloo, L., Van Borkulo, C. D., Rhemtulla, M., Keyes, K. M., Borsboom, D., & Schoevers, R. A. (2015). The network structure of symptoms of the diagnostic and statistical manual of mental disorders. *PLOS ONE, 10*(9), 1–12. doi: 10.1371/journal.pone.0137621

Calvo, N., Valero, S., Sáez-Francàs, N., Gutiérrez, F., Casas, M., & Ferrer, M. (2016). Borderline personality disorder and personality inventory for DSM-5 (PID-5): dimensional personality assessment with DSM-5. *Comprehensive Psychiatry, 70*, 105–111. doi: 10.1016/j.comppsych.2016.07.002

Cassano, B., Mula, M., Rucci, P., Miniati, M., Frank, E., Kupfer, J., & Fagiolini, A. (2009). The structure of lifetime manic-hypomanic spectrum. *Journal of Affective Disorders, 112*(1–3), 59–70. doi: 10.1016/j.jad.2008.04.019

Collins, F. S. & Varmus, H. (2015). A new initiative on precision medicine. *The New England Journal of Medicine, 372*(9), 793-795. doi: 10.1056/NEJMp1500523

Cramer, A., Waldorp, L., Maas, H., & Borsboom, D. (2010). Comorbidity: a network perspective. *Behavioral and Brain Sciences, 33*(2), 137–193. doi:10.1017/S0140525X09991567

di Giacomo, E., Aspesi, F., Fotiadou, M., Arntz, A., Aguglia, E., Barone, ... , Clerici, M. (2017). Unblending borderline personality and bipolar disorders. Journal of Psychiatric Research, 91, 90–97. doi: 10.1016/j.jpsychires.2017.03.006

Eaton, R. (2015). Latent variable and network models of comorbidity: toward an empirically derived nosology. *Social Psychiatry and Psychiatric Epidemiology, 50*(6), 845–849. doi:10.1007/s00127-015-1012-7

Eisner, R., Johnson, L., Youngstrom, A., & Pearlstein, G. (2017). Simplifying profiles of comorbidity in bipolar disorder. *Journal of Affective Disorders, 220*, 102–107. doi: 10.1016/j.jad.2017.05.045

Epskamp, S., & Fried, I. (2017). Bootnet: Bootstrap methods for various network estimation routines. R package version 1.0.1. Retrieved from http://cran.r-project.org/package=bootnet.

Epskamp, S., Borsboom, D., & Fried, I. (2016). Estimating psychological networks and their accuracy: a tutorial paper. *Behavior Research Methods, 50*(10), 195-212. doi: 10.3758/s13428-017-0862-1

Epskamp, S., Cramer, A., Waldorp, J., Schmittmann, D., & Borsboom, D. (2012). qgraph: network visualizations of relationships in psychometric data. *Journal of Statistical Software, 48*(4). doi: 10.18637/jss.v048.i04

Ferentinos, P., Fountoulakis, N., Lewis, M., Porichi, E., Dikeos, D., Papageorgiou, C., & Douzenis, A. (2017). Validating a two-dimensional bipolar spectrum model integrating DSM-5's mixed features specifier for major depressive disorder. *Comprehensive Psychiatry, 77*, 89–99. doi: 10.1016/j.comppsych.2017.06.007

Fernandez, E., & Johnson, L. (2015). Anger in psychological disorders: prevalence, presentation, etiology and prognostic implications. *Clinical Psychology Review, 46*, 124–135. doi: 10.1016/j.cpr.2016.04.012

Fisher, A. J. (2015). Toward a dynamic model of psychological assessment: implications for personalized care. *Journal of Consulting and Clinical Psychology, 83*(4), 825–836. doi: 10.1037/ccp0000026

Fisher, A. J., & Boswell, J. F. (2016). Enhancing the personalization of psychotherapy with dynamic assessment and modeling. *Assessment, 23*(4), 496–506. doi: 10.1177/1073191116638735

Fonseka, T. M., Swampillai, B., Timmins, V., Scavone, A., Mitchell, R., Collinger, K. A., & Goldstein, B. I. (2015). Significance of borderline personality-spectrum symptoms among adolescents with bipolar disorder. *Journal of Affective Disorders, 170*, 39–45. doi: 10.1016/j.jad.2014.08.046

Frías, Á., Baltasar, I., & Birmaher, B. (2016). Comorbidity between bipolar disorder and borderline personality disorder: prevalence, explanatory theories, and clinical impact. *Journal of Affective Disorders, 202*, 210–219. doi: 10.1016/j.jad.2016.05.048

Fried, E., Epskamp, S., Nesse, R., Tuerlinckx, F., & Borsboom, D. (2016). What good depression symptoms? comparing the centrality of DSM and non-DSM symptoms of depression in a network analysis. *Journal of Affective Disorders, 189*, 314-320. doi: 10.1016/j.jad.2015.09.005

Fried, E., van Borkulo, D., Cramer, A., Boschloo, L., Schoevers, A., & Borsboom, D. (2017). Mental disorders as networks of problems: a review of recent insights. *Social Psychiatry and Psychiatric Epidemiology, 52*(1), 1–10. doi: 10.1007/s00127-016-1319-z

Fruchterman, T., & Reingold, E. (1991). Graph drawing by force directed placement. *Software-Practice and Experience. 21*(11), 1129-1164. doi: 10.1002/spe.4380211102

Galione, J. & Zimmerman, M. (2010). A comparison of depressed patients with and without borderline personality disorder: implications for interpreting studies of the validity of the bipolar spectrum. *Journal of Personality Disorders, 24*(6), 763–772. doi: 10.1521/pedi.2010.24.6.763

Ghaemi, N., Dalley, S., Catania, C., & Barroilhet, S. (2014). Bipolar or borderline: a clinical overview. *Acta Psychiatrica Scandinavica, 130*(2), 99–108. doi: 10.1111/acps.12257

Goekoop, R. & Goekoop, J. G. (2014). A network view on psychiatric disorders: network clusters of symptoms as elementary syndromes of psychopathology. *PLOS ONE, 9*(11), 1–47. doi: 10.1371/journal.pone.0112734

Goodwin, F. & Jamison, K. (2007). *Manic-Depressive Illness Bipolar Disorders and Recorrent Depression*. New York: Oxford.

Grant, B., Stinson, F., Dawson, D., Chou, P., Dufour, M., Compton, W. Pickering, R., Kaplan, K. (2006). Prevalence and co-occurrence of substance use disorders and independent mood and anxiety disorders: results from the national epidemiologic survey on alcohol and related conditions. *Alcohol Research & Health, 29*(2), 107–120. doi: 10.1001/archpsyc.61.8.807

Hatchett, G. (2010). Differential diagnosis of borderline personality disorder from bipolar disorder. *Journal of Mental Health Counseling, 32*(3), 189–205. doi: 10.17744/mehc.32.3.n682682184554445

Henry, C., Mitropoulou, V., New, S., Koenigsberg, W., Silverman, J., & Siever, J. (2001). Affective instability and impulsivity in borderline personality and bipolar II disorders: similarities and differences. *Journal of Psychiatric Research, 35*(6), 307–312. doi: 10.1016/S0022-3956(01)00038-3

Hirschfeld, M., Lewis, L., & Vornik, L. (2003). Perceptions and impact of bipolar disorder: how far have we really come? results of the national depressive and maniac-depressive association 2000 survey of individuals with bipolar disorder. *Journal of Clinical Psychology, 64*(2), 161-74. doi: 10.4088/JCP.v64n0209

Isvoranu, M., Borsboom, D., van Os, J., & Guloksuz, S. (2016). A network approach to environmental impact in psychotic disorder: brief theoretical framework. *Schizophrenia Bulletin, 42*(4), 870–873. doi: 10.1093/schbul/sbw049

JASP Team. (2016). *JASP (Version 0.8.0.0)*. Retrieved from https:// jasp-stats.org/

Jones, P. (2017). Impact: a new network statistic for network analysis (networktools). R package version 1.2.0. Retrieved from http://cran.r-project.org/package=networktools.

Jones, J., Mair, P., Riemann, B. C., Mugno, B. L., & McNally, R. J. (2017). A network perspective on comorbid depression in adolescents with obsessive-compulsive disorder. *Journal of Anxiety Disorders, 53*, 1-8. doi: 10.1016/j.janxdis.2017.09.008

Kessler, B., Borges, E., & Walters, E. (1999). Prevalence of and risk factors for lifetime suicide attempts in the national comorbidity survey. *Archives of General Psychiatry, 56*(7), 617–626. doi: 10.1001/archpsyc.56.7.617

Kessler, R. C. & Üstün, B. B. (2004). The world mental health (WMH) survey initiative version of the world health organization (WHO) composite international diagnostic interview (CIDI). *International Journal of Methods in Psychiatric Research, 13*(2), 93–117. doi: 10.1002/mpr.168

Koenigsberg, H. W., Harvey, P. D., Mitropoulou, V., Schmeidler, J., New, A. S., Goodman, M., & Siever, L. J. (2002). Characterizing affective instability in borderline personality disorder. *American Journal of Psychiatry, 159*(5), 784–788. doi: 10.1176/appi.ajp.159.5.784

Levinson, A., Zerwas, S., Calebs, B., Kordy, H., Hofmeier, S., Collaborative, V., & Bulik, M. (2017). The core symptoms of bulimia nervosa, anxiety, and depression: a network analysis. *Journal of Abnormal Psychology, 126*(3), 340–354. doi: 10.1037/abn0000254

Lewis, K., Caputi, P., & Grenyer, B. (2012). Boderline personality disorder subtypes: a factor analysis of the DSM IV criteria. *Personality and Mental Health, 6*(3), 196-206. doi: 10.1002/pmh.1183

Malhi, S., Fritz, K., Allwang, C., Burston, N., Cocks, C., Devlin, J., & Lyndon, W. (2016). Are manic symptoms that "dip" into depression the essence of mixed features? *Journal of Affective Disorders, 192*, 104–108. doi: 10.1016/j.jad.2015.12.009

Mason, B. L., Brown, E. S., & Croarkin, P. E. (2016). Historical underpinnings of bipolar disorder diagnostic criteria. *Behavioral Sciences, 6*(14), 1-19. doi: 10.3390/bs6030014

McDermid, J., Sareen, J., El-Gabalawy, R., Pagura, J., Spiwak, R., & Enns, M. W. (2015). Co-morbidity of bipolar disorder and borderline personality disorder: findings from the national epidemiologic survey on alcohol and related conditions. *Comprehensive Psychiatry, 58*, 18–28. doi: 10.1016/j.comppsych.2015.01.004

Messer, T., Lammers, G., Müller-Siecheneder, F., Schmidt, R.-F., & Latifi, S. (2017). Substance abuse in patients with bipolar disorder: a systematic review and meta-analysis. *Psychiatry Research, 253*, 338–350. doi: 10.1016/j.psychres.2017.02.067

Morris, R., Yang, M., Chopra, A., Bentall, R., Paykel, E., & Scott, J. (2013). Differential effects of depression and mania symptoms on social adjustment: prospective study in bipolar disorder. *Bipolar Disorders, 15*(1), 80–91. doi: 10.1111/bdi.12036

Opsahl, T., Agneessens, F., & Skvoretz, J. (2010). Node centrality in weighted networks: Generalizing degree and shortest paths. *Social Networks, 32*, 245-25. doi: 10.1016/j.socnet.2010.03.006

Paris, J., Gunderson, J., & Weinberg, I. (2007). The interface between borderline personality disorder and bipolar spectrum disorders. *Comprehensive Psychiatry, 48*(2), 145–154. doi: 10.1016/j.comppsych.2006.10.001

Pennay, A., Cameron, J., Reichert, T., Strickland, H., Lee, N. K., Hall, K., & Lubman, D. I. (2011). A systematic review of interventions for co-occurring substance use disorder and borderline personality disorder. *Journal of Substance Abuse Treatment, 41*(4), 363–373. doi: 10.1016/j.jsat.2011.05.004

Perugi, G., Angst, J., Azorin, J. M., Bowden, C., Vieta, E., & Young, A. H. (2013). The bipolar-borderline personality disorders connection in major depressive patients. *Acta Psychiatrica Scandinavica, 128*(5), 376–383. doi: 10.1111/acps.12083

R Development Core Team. (2008). *R: A language and environment for statistical computing*. Vienna, Austria: R Foundation for Statistical Computing.

Rhemtulla, M., Fried, E., Aggen, H., Tuerlinckx, F., Kendler, S., & Borsboom, D. (2016). Network analysis of substance abuse and dependence symptoms. *Drug and Alcohol Dependence, 161*, 230–237. doi: 10.1016/j.drugalcdep.2016.02.005

Richetin, J., Preti, E., Costantini, G., & De Panfilis, C. (2017). The centrality of affective instability and identity in borderline personality disorder: evidence from network

analysis. *PLOS ONE, 12*(10). doi: 10.1371/journal.pone.018669

Robins, L., Wing, J., Wittchen, U., Helzer, J, Babor, T., Burke, J., Farmer, A., Jablenski, A., Pickens, R., Regier, D., Sartorius, N. & Towle, L. (1998). The composite international diagnostic interview an epidemiologic instrument suitable for use in conjunction with different diagnostic systems and in different cultures. *Archives of General Psychiatry, 45*(12), 1069-1077. doi: 10.1001/archpsyc.1988.01800360017003

RStudio Team (2017). *RStudio: Integrated Development for R*. RStudio, Inc., Boston, MA URL http://www.rstudio.com/.

Ruggero, C. J., Zimmerman, M., Chelminski, I., & Young, D. (2010). Borderline personality disorder and the misdiagnosis of bipolar disorder. *Journal of Psychiatric Research, 44(*6), 405–408. doi: 10.1016/j.jpsychires.2009.09.011

Rugkåsa, J., Yeeles, K., Molodynski, A., & Burns, T. (2015). Reply. *Acta Psychiatrica Scandinavica, 132*(4), 310–310. doi: 10.1111/acps.12465

Shannon, P., Markiel, A., Owen Ozier, 2, Baliga, N. S., Wang, J. T., Ramage, D., Amin, N., Schwikowski, B, & Ideker, T. (2003). Cytoscape: a software environment for integrated models of biomolecular interaction networks. *Genome Research, 13*(11), 2498–2504. doi: 10.1101/gr.1239303.metabolite

Siegel, R., Hoeppner, B., Yen, S., Stout, R., Weinstock, L., Hower, H., Birmaher, B., Goldstein, T., Goldstein, B., Hunt, J., Strober, M., Axelson, D., Gill, M., & Keller, M. (2015). Longitudinal associations between interpersonal relationship functioning and mood episode severity in youth with bipolar disorder. *Journal of Nervous and Mental Disease, 203*(3): 194–204. doi:10.1097/NMD.0000000000000261

Soler, A., Soler, J., Elices, M., Pascual, J. C., Pérez, J., Martín-Blanco, A., & Portella, M. J. (2013). Differences in attention and impulsivity between borderline personality disorder and bipolar disorder. *Psychiatry Research, 210*(3), 1307–1309. doi: 10.1016/j.psychres.2013.09.011

Szalay-Beko, M., Palotai, R., Szappanos, B., Kovács, I. A., Papp, B., & Csermely, P. (2012). ModuLand plug-in for cytoscape: determination of hierarchical layers of overlapping network modules and community centrality. *Bioinformatics, 28*(16), 2202–2204. doi:10.1093/bioinformatics/bts352

van Borkulo, C. D., Borsboom, D., Epskamp, S., Blanken, T. F., Boschloo, L., Schoevers, R. a, & Waldorp, L. J. (2014). A new method for constructing networks from binary data. *Scientific Reports, 4*(5918). doi: 10.1038/srep05918

van Borkulo, C., Boschloo, L., Borsboom, D., Penninx, H., Waldorp, J., & Schoevers, A. (2015). Association of symptom network structure with the course of longitudinal depression. *JAMA Psychiatry, 72*(12), 1219-26. doi:10.1001/jamapsychiatry.2015.2079

Vöhringer, A., Barroilhet, A., Alvear, K., Medina, S., Espinosa, C., Alexandrovich, K., Riumallo, P., Leiva, F., Hurtado, E., Cabrera, J., Sullivan, M., Holtzman, N., & Ghaemi, S. N. (2016). The international mood network nosology project: differentiating borderline personality disorder from bipolar illness. *Acta Psychiatrica Scandinavica, 134*(6), 504-510. doi: 10.1111/acps.12643

Wilson, T., Stanley, B., Oquendo, A., Goldberg, P., Zalsman, G., & Mann, J. (2007). Comparing impulsiveness, hostility, and depression in borderline personality disorder and bipolar II disorder. *Journal of Clinical Psychiatry, 68*(10), 1533–9. doi: 10.1001/archpsyc.1992.01820080032005

Zimmerman, M., & Morgan, T. A. (2013). The relationship between borderline personality disorder and bipolar disorder. *Dialogues in Clinical Neuroscience, 15*(2), 155–169. doi: 10.1176/appi.ajp.163.7.1126

Zimmerman, M., Martinez, J., Young, D., Chelminski, I., Morgan, A., & Dalrymple, K. (2014). Comorbid bipolar disorder and borderline personality disorder and history of suicide attempts. *Journal of Personality Disorders, 28*(3), 358-364. doi: 10.1521/pedi_2013_27_122

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