Journal of Psychosomatic Research 139 (2020) 110261

Contents lists available at ScienceDirect

Journal of Psychosomatic Research

journal homepage: www.elsevier.com/locate/jpsychores

Network approach of mood and functional gastrointestinal symptom dynamics in relation to childhood trauma in patients with irritable bowel syndrome and comorbid panic disorder

Marjan Drukker[a,*,1], Jill C.H. Peters[a,1], Lisa Vork[b], Zlatan Mujagic[b], Bart P.F. Rutten[a], Jim van Os[a,c,d], Ad A.M. Masclee[b], Joanna W. Kruimel[b], Carsten Leue[a]

[a] Department of Psychiatry and Neuropsychology, School of Mental Health and NeuroScience (MHeNS), Maastricht University Medical Centre, Maastricht, the Netherlands
[b] Division of Gastroenterology-Hepatology, Department of Internal Medicine, Maastricht University Medical Centre, Maastricht, the Netherlands
[c] Department of Psychiatry, Brain Centre Rudolf Magnus, University Medical Centre Utrecht, Utrecht, the Netherlands
[d] Department of Psychosis Studies, Institute of Psychiatry, King's Health Partners, King's College London, London, UK

ARTICLE INFO

Keywords:
Childhood trauma
Ecological momentary assessment
Irritable bowel syndrome
Negative affect
Networks of psychological symptoms
Positive affect

ABSTRACT

Objective: Irritable bowel syndrome (IBS) has a high comorbidity with mental disorders. The present paper aims to visualise the interplay between IBS and affect (anxiety and mood) in daily life. Furthermore, this interplay may be different depending on risk factors such as childhood trauma.

Methods: Using momentary assessment (Experience Sampling Method), data of 24 individuals diagnosed with both IBS and panic disorder were analysed (15 non-trauma and 9 low-trauma-score patients). Networks were constructed, based on multilevel time-lagged linear regression analysis. Regression coefficients present network connections including three negative affect items (down, irritated, rushed), three positive affect items (happy, enthusiastic, cheerful), three abdominal complaints (abdominal pain, bloating, nausea) and one social item (feeling lonely). Those networks were stratified by levels of childhood trauma based on the Childhood Trauma Questionnaire.

Results: Connections within the group of mood items and within the group of abdominal complaints were more frequent than between abdominal complaints and mood items. When data were stratified by childhood trauma, networks were different. In addition, node strengths were stronger in low-trauma than in non-trauma, although only one was significantly different (enthusiastic). Overall, there were mainly non-significant connections and a clear pattern was not visible.

Conclusions: A time-lagged network provides additional insight in connections between abdominal complaints and affective complaints, in patients with IBS and panic disorder, with different levels of childhood trauma. More research is needed to gain a better understanding of symptom formation and the impact of variation in context on individual symptom experiences in IBS with affective comorbidity.

Baseline data of a clinical trial: NCT01551225 (http://www.clinicaltrials.gov).

1. Introduction

Within the group of patients diagnosed with irritable bowel syndrome (IBS) a large subgroup has comorbid panic disorder [1]. Both in IBS patients and in the specific patient group diagnosed with both IBS and panic disorder, abdominal complaints often are accompanied by anxiety and depression [1,2]. A graphical presentation of the connections between abdominal complaints and mood assessed several times a day may improve the understanding of this multifactorial interplay. Moreover, those connections may differ depending on childhood trauma.

IBS is a disorder of the gut-brain axis characterized by abdominal

* Corresponding author at: Department of Psychiatry and Psychology, School of Mental Health and NeuroScience (MHeNS), P.O. Box 616, 6200 MD Maastricht, the Netherlands.
E-mail addresses: Marjan.Drukker@MaastrichtUniversity.nl (M. Drukker), jillian.peters@mumc.nl (J.C.H. Peters), l.vork@maastrichtuniversity.nl (L. Vork), z.mujagic@maastrichtuniversity.nl (Z. Mujagic), b.rutten@maastrichtuniversity.nl (B.P.F. Rutten), a.masclee@mumc.nl (A.A.M. Masclee), j.kruimel@mumc.nl (J.W. Kruimel), c.leue@mumc.nl (C. Leue).
[1] Contributed equally.

https://doi.org/10.1016/j.jpsychores.2020.110261
Received 25 February 2020; Received in revised form 28 September 2020; Accepted 28 September 2020
Available online 02 October 2020

pain, and altered bowel habits [3]. It is associated with higher stress-sensitivity and frequent psychological comorbidity [4,5]. Changes in mood and exposure to stress may influence gut motility and visceral pain perception [6,7]. Moreover, abdominal complaints may become more severe when stress levels are higher, while this is associated with higher levels of depression and anxiety in a dose-response fashion [8].

Affective disorders and disorders of the gut-brain interaction are both stress-related conditions, which are moderated by contextual influences impacting each other [9]. In clinical practice, there is a large underdiagnosed group of patients, suffering from IBS and comorbid panic disorder [1]. Previous research showed that these diagnoses frequently co-occur and patients with IBS often have symptoms of anxiety and depression [1,2,10]. Their common presentation often remains undetected leading to refractory treatment [11,12]. Data were collected in this patient group, in order to get more insight in the interplay between abdominal complaints, mood symptoms and social perceptions, as well as possibly shared pathophysiology.

Given that IBS and mental disorders overlap and are described as bi-directionally associated co-morbidities [6], psychiatric symptoms, such as affective complaints, and psychosocial stressors may influence the pathophysiology and symptomatology of IBS [6]. In that manner, negative affect (NA), which plays a key role in anger, anxiety and depression, might lead to deregulation along the brain-gut-axis and may contribute to symptomatology in IBS patients. Consequently, NA is associated with unhealthy physiological functioning, while positive affect (PA) is associated with increased health [13]. In addition, anxiety, depression, stress experience and recurrent negative social interactions are associated with health perception and help-seeking behaviour in IBS [14–16].

Although comorbidity of mental disorders and IBS is acknowledged, both strength and nature of the interaction of the various symptoms are not well understood [6]. Before the introduction of ecological momentary assessment technology in IBS symptom measurement, there was a lack of valid instruments to assess IBS symptoms in real life [17,18]. Daily or weekly retrospective self-reported questionnaires were available, but these bear the risk of recall and contextual biases.

The present study uses data collected by an electronic momentary assessment tool (i.e. Experience Sampling Method (ESM)) [19,20]. Data on real-time experiences are obtained by sending an auditory signal ('beep') at random moments, inviting persons to fill in questions on a digital device. Thus, patients are actively involved in their own data collection [19]. The associations between a priori selected abdominal complaints, mood symptoms and social perceptions along a time axis can be presented in a network graph were complaints and symptoms are the nodes and regression coefficients are the edges between the nodes. The obtained network could help to understand the symptom formation in patients suffering from IBS and panic disorder because a network approach shows the dynamic and possible causal interaction among symptoms. Symptoms are not only reflective of underlying disorders, a mental disorder constitutes of a causal system of interacting, self-reinforcing symptoms [21]. This way insight in mechanisms of IBS-symptom formation and its connection with PA and NA can be obtained.

Data to generate networks can also be stratified by a variable such as childhood trauma. In individuals with IBS there is a higher prevalence of early adverse life events such as childhood abuse, domestic violence or household mental illness in comparison with healthy controls [22]. Childhood trauma has been associated with a diagnosis of IBS as well as with abdominal complaints and mood [8,22,23]. When childhood maltreatment influences the development of affective tendencies, this could contribute to bodily distress [24]. Hence, it is hypothesized that connections in a network, including abdominal complaints and mood symptoms could be different depending on the level of the subjects' childhood trauma [22,24].

The first aim is to investigate how abdominal complaints, mood symptoms and social perceptions are associated with each other over time in patients with IBS and comorbid panic disorder. The second aim is to investigate whether connections between abdominal complaints and mood differ between patients with different levels of childhood trauma, in order to improve the understanding of this multifactorial interplay.

2. Methods

2.1. Study participants and study design

The data set included baseline data of a "single-centre, double-blind, parallel-group randomized controlled trial of escitalopram versus placebo for patients diagnosed with IBS and comorbid panic disorder" [9,25,26]. Between February 2012 and June 2016, study participants were recruited at two locations in the Maastricht University Medical Centre, that is the outpatient clinic of the Med-Psych-Centre (MPC) and the department of gastroenterology-hepatology. The MPC outpatient clinic delivered integrated care, a combined consultation of a hospital-psychiatrist and a gastroenterologist, as described elsewhere [1]. Inclusion and exclusion criteria are presented in appendix A [9,27,28]. The study protocol was approved in 2011 by the medical-ethics committee of Maastricht University Medical Center (MUMC), Maastricht, the Netherlands, and was registered in the US National Library of Medicine (http://www.clinicaltrials.gov, NCT01551225). The study was executed according to the principles of the revised Declaration of Helsinki (59th WMA General Assembly, Seoul, Republic of Korea, October 2008), also including informed consent. Twenty-nine patients provided ESM data.

2.2. Measurements

2.2.1. Childhood trauma

History of childhood trauma was assessed using the Dutch shortened version of the Childhood Trauma Questionnaire (CTQ) [29]. This questionnaire investigates trauma in youth, in particular the history of abuse (sexual, emotional or physical) and emotional or physical neglect [30]. The answers are scored on a 5 item Likert scale (never true to very often true) and a sum score was generated [30]. A score below 36 points indicated no trauma experiences; a score below 51 points indicated a low level of trauma experiences [31]. Subjects with moderate childhood trauma and severe childhood trauma were not available in the present sample.

2.2.2. Experience Sampling Method (ESM)

ESM is a momentary assessment tool using a digital device or a telephone app to collect data randomly and repeatedly during the day for multiple days [19]. The focus is on the person's momentary mental and physical state and behaviour, and ESM data are collected in the subject's daily life [19]. In this study, ESM data were collected on seven consecutive days, at 10 random moments during the day between 7.30 a.m. and 10.30 p.m., using a palmtop computer. For the scoring, a 7-point Likert scale was used (1 = not at all to 7 = extremely) [19,26]. Among others, ESM items included abdominal complaints, mood (affective states, see below) and social perceptions (e.g. feeling lonely, appendix B [32]). Because part of the missed beeps are missed for valid reasons, a general rule is to include subjects in the analysis when at least 33% of the beeps is answered [19,33].

A relatively small number of subjects was included and the number of subjects was lower in the low-trauma group. The multiple ESM assessments per person increased the power [34].

2.3. Affective states

Two core dimensions of affective states are documented in the emotional experience of psychological distress and wellbeing: PA and NA [13]. Cognitive and emotional components such as happiness,

interest, enthusiasm and motivation can be defined as PA. NA reflects aversive mood states, such as guilt, anger, sadness and depression [13]. For ESM, a standard set of PA and NA items was developed [33,35].

2.4. The construction of networks

Networks were constructed stratified by low childhood trauma and no childhood trauma (hereafter low-trauma and non-trauma). Abdominal complaints, mood items and social items were considered for inclusion. All abdominal pain items without floor effects were selected. Only one social item was included (i.e., "feeling lonely") because others were preceded by a trigger question and thus not answered each beep. Experts decided which mood items were of most interest for the patient group with IBS and comorbid panic disorder. The original selection included "down", "irritated", "enthusiastic", "happy", "abdominal pain", "bloating" and "lonely". Three other selected items, "anxious", "relaxed" and "flatulence", were replaced because regression analyses (see below) did not achieve convergence. When replacing these items by similar items "rushed", "cheerful" and "nausea", respectively, convergence was achieved.

2.5. Statistical analysis

The statistical analysis was performed using Stata version 13 applying multilevel linear regression models [36]. In ESM data, multiple observations per individual are clustered and the mixed command in Stata is ideally suited to deal with this clustering. Down, irritated, rushed, enthusiastic, happy, cheerful, abdominal pain, bloating, nausea and lonely were included as the dependent variables. The lags (t-1) of these dependent variables were the independent variables in the regression models. A lagged variable is the same variable assessed at the previous time point (5 min to three hours before the current). Furthermore, a time variable was added to all the regression models (beepcode = dayno * 10 + beepnumber) to control for time trends [19,37]. This resulted in the following equation:

y_{ij} = (B0 + u_{0j}) + B1 * lag mood down$_{ij}$ + B2 * lag mood irritated$_{ij}$ + B3 * lag mood rushed$_{ij}$ + B4 * lag mood enthusiastic$_{ij}$ + B5 * lag mood happy$_{ij}$ + B6 * lag mood cheerful$_{ij}$ + B7 * lag abdominal pain$_{ij}$ + B8 * lag bloating$_{ij}$ + B9 * lag nausea$_{ij}$ + B10 * lag mood lonely$_{ij}$ + (B11 + u_{11j}) * beepcode$_{ij}$ + e.

Where i is the assessment level and j is the subject level, Y is the dependent variable, and each dependent variable is analysed in a separate regression model. A random intercept (B0 + u_{0j}) and a random slope for beepcode (B11 + u_{11j}) were included in the model, and covariance was unstructured [37,38]. Due to the complexity of the model, inclusion of random slopes for the lagged variables resulted in convergence problems. To obtain correct *p*-values permutations were performed (see below).

Ten independent variables and ten dependent variables resulted in 100 regression coefficients and a 10-by-10 matrix including all regression coefficients (B). Because all analyses were stratified by childhood trauma (non-trauma/low-trauma) two sets of 100 regression coefficients were obtained. These 2 × 100 regression coefficients were visualized in two network graphs using the qgraph package in R to show the bidirectional associations between the ten variables [39,40]. In this way, the connection between the variables (e.g., down) at time point t-1 predicts another variable (e.g., irritated; $B_{down\text{-}irritated}$) at time point t [37]. A self-loop indicates the connection between a specific node at time point t-1 and time point t (e.g., $B_{down\text{-}down}$) [37,41,42].

2.6. Centrality indices

Excel and the qgraph package in R [40], were used to calculate centrality of the network nodes. There are various types of centrality [43]. All centrality measures indicate how central a node is in the network. This is operationalised in several ways. First, the sum of the outgoing nodes (outward strength). Second, the sum of the incoming nodes (inward strength). Third, the sum of the outward strength and the inward strength (node strength). A previous study included the self-loop, both in the inward strength and in the outward strength, thus in the node strength the self-loop is included twice [37]. Finally, closeness is operationalised as the sum of the inverse length of the shortest paths between a node and all the other nodes in the graph [37,44,45]. Here, the shortest path is literally the shortest route between one node and another. Betweenness is another type of centrality, but this is not applicable when studying networks of psychological symptoms [44,46].

2.7. Permutation testing

Given that after including random slopes of all independent variables convergence was not achieved, models including a random slope for beepcode only were run. Because of that, *p*-values obtained from the multilevel linear regression models are too optimistic [34]. Thus, permutation tests were performed [1] to examine the statistical significance of the regression coefficients and [2] to analyse differences in regression coefficients between both trauma strata [37,38]. To test statistical significance of the regression coefficients, the distribution of the regression coefficients under the null hypothesis was obtained by running 3000 permutation tests. For this, the dependent variable was removed from the data and within subjects randomly reordered and merged to the original data. Subsequently, the regression coefficient obtained from the real multilevel regression analysis was placed on that normal distribution. This way, valid *p*-values were obtained.

The second set of permutation tests aimed to test whether slopes in the low-trauma group were different from the non-trauma group. For this, the trauma variable was removed from the data and randomly merged to the original data at subject level. Subsequently, slopes from both networks were subtracted and again the real difference between the slopes was placed on the normal distribution of the differences under the null hypothesis to obtain a p-value [37,38].

3. Results

3.1. Sample characteristics

Of the twenty-nine patients, twenty-four persons completed a minimum of 33% beeps and were included in the analyses. Sixteen patients (66.7%) were female. The mean age in the total sample was 36.8 years (SD 15.5 years; Table 1).

Nine patients (37.5%) experienced low levels of childhood trauma and fifteen (62.5%) had no childhood trauma (Table 1). None of the patients had moderate or severe childhood trauma. In the low-trauma

Table 1
Baseline characteristics.

	All subjects	Range	Low-trauma (n = 9)	Non-trauma (n = 15)	Test[a]
Female gender, n (%)	16 (66.7)		6 (66.7)	10 (66.7)	X^2 = 0, df = 1, p = 0.99
Age in years, mean (sd)	36.8 (15.5)	20–66	36.3 (18.1)	37.0 (14.3)	t = 0.1, df = 22, p = 0.92
CTQ score, mean (sd)	34.2 (1.6)	25–48	42.9 (1.1)	28.9 (1.1)	t = −8.6, df = 22, p < 0.001

[a] *t*-Test for continuous variables by trauma and chi-square test for dichotomous variables by trauma.

Table 2
Descriptives of functional gastrointestinal and mood symptoms by trauma group (all items range 1–7).

	All subjects (n = 24)	Low-trauma; n = 9, 482 beeps	Non-trauma; n = 15, 772 beeps
	Mean (sd[a])	Mean (sd[a])	Mean (sd[a])
Down	2.0 (1.4)	2.6 (1.5)	1.6 (1.1)
Irritated	1.9 (1.3)	2.3 (1.6)	1.6 (1.1)
Rushed	2.2 (1.5)	2.9 (1.6)	1.8 (1.2)
Enthusiastic	4.4 (1.6)	3.9 (1.7)	4.7 (1.4)
Happy	4.9 (1.5)	4.3 (1.6)	5.2 (1.3)
Cheerful	4.1 (1.7)	3.3 (1.7)	4.6 (1.4)
Abdominal pain	2.8 (1.5)	3.4 (1.7)	2.5 (1.3)
Bloating	3.1 (2.0)	3.3 (2.1)	3.0 (1.9)
Nausea	1.4 (1.1)	1.5 (1.2)	1.3 (1.0)
Lonely	1.4 (1.0)	1.9 (1.4)	1.2 (0.6)

[a] Overall sd.

group and the non-trauma group, the mean CTQ sum score was 42.9 and 28.9, respectively. Age and gender did not differ between the low-trauma and the non-trauma group (Table 1). Table 2 shows means of abdominal complaints and mood symptoms by trauma group.

3.2. Network graphs

Fig. 1 shows the network in all subjects. Fig. 2 shows the network in the low-trauma group (A) and in the non-trauma group (B), respectively. In both the low-trauma group and the non-trauma group, self-loops were strongest. Within the set of mood items and within abdominal complaints there were more significant connections, but neither mood nor abdominal complaints items clustered in the network. There were connections between abdominal complaints and mood or vice versa, but only a few were significantly different between the low-trauma and non-trauma group. For example, lonely (at t-1) was associated with nausea (B lonely-nausea) in the non-trauma group but not in the low-trauma group and this was significantly different (non-trauma B = -0.09, low-trauma B = 0.19, p = 0.04).

Overall, the non-trauma and low-trauma networks were rather different. Except for the self-loops, only two regression coefficients were significant in both the low-trauma and the non-trauma group: happy-cheerful and bloating-abdominal pain. Various connections were significantly different in the low-trauma compared with the non-trauma group. However, despite the significant difference these connections were not statistically significant in either the low-trauma or the non-trauma group and a pattern was not visible.

3.3. Centrality indices

Table 3 presents centrality indices stratified by childhood trauma. For example, in the low-trauma group, closeness was highest in nausea, enthusiastic and abdominal pain. This means that these symptoms were closest to the other mood items and abdominal complaints. Only the node strength for enthusiastic differed statistically significant between low-trauma and non-trauma.

For each separate variable node strengths in the low-trauma groups were higher than in the non-trauma group, but only the difference in node strength of the mood state “enthusiastic” reached significance.

4. Discussion

This network study, using repetitive momentary assessment data, is the first demonstrating how abdominal complaints and mood symptoms in IBS patients with comorbid panic disorder are connected with each other over time, from a daily life perspective. To our knowledge, the current study is the first assessing differences in ESM symptom networks between various levels of childhood trauma in IBS patients and results need to be replicated.

Although connections within mood items and within abdominal complaints were stronger than between these constructs, there were also connections between mood and abdominal complaints. The networks in the low-trauma and non-trauma groups were rather different. When a connection was statistically significant in one of the networks, it was weaker in the other network and no longer significant, but none of these connections differed significantly between the networks. Most connections that did differ between the low-trauma and the non-trauma network were not statistically significant in any of the two networks. Node strength was stronger in the low-trauma group, but this was only statistically significant in “enthusiastic”.

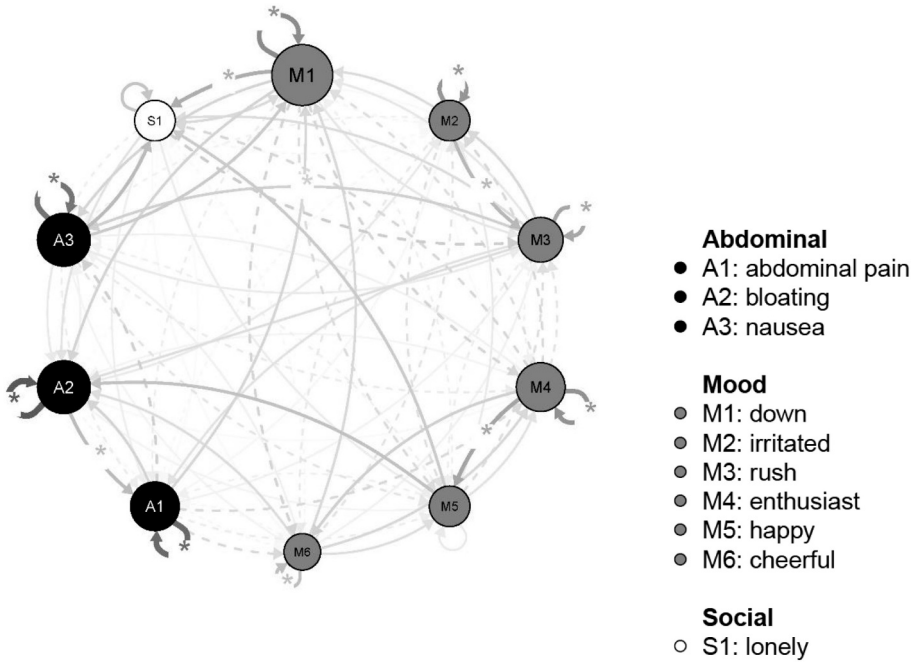

Fig. 1. Psychological symptoms network structure including abdominal complaints, mood and lonely in all subjects.

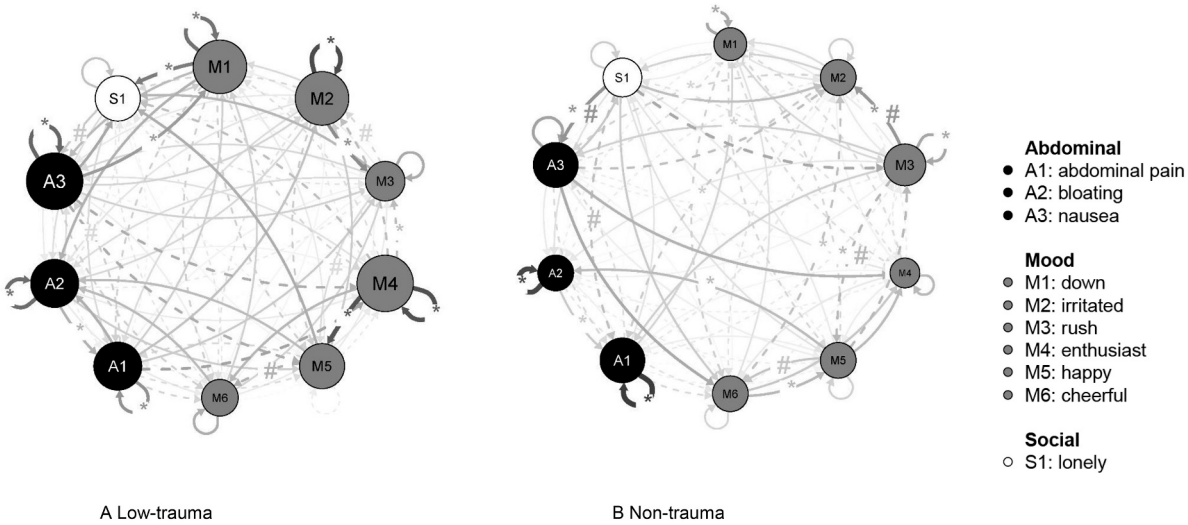

Fig. 2. Network structure for the low-trauma group (A) and the non-trauma group (B).

Table 3
Centrality indices of the networks in the low-trauma and the non-trauma groups.

	All subjects				Low-trauma group				Non-trauma group				p-Value[a]
	Closeness	Inward strength	Outward strength	Node strength	Closeness	Inward strength	Outward strength	Node strength	Closeness	Inward strength	Outward strength	Node strength	
Down	0.007	0.67	0.78	1.45	0.009	0.86	1.08	1.94	0.005	0.57	0.52	1.10	0.09
Irritated	0.005	0.47	0.51	0.97	0.007	0.90	0.96	1.86	0.006	0.70	0.52	1.22	0.43
Rushed	0.005	0.58	0.55	1.13	0.006	0.83	0.61	1.44	0.008	0.64	0.71	1.35	0.77
Enthusiastic	0.005	0.51	0.70	1.21	0.009	0.84	1.19	2.03	0.004	0.65	0.36	1.01	0.01*
Happy	0.006	0.51	0.44	0.96	0.008	0.86	0.70	1.56	0.007	0.55	0.68	1.24	0.83
Cheerful	0.005	0.41	0.47	0.87	0.006	0.77	0.57	1.34	0.007	0.68	0.54	1.21	0.79
Abdominal pain	0.006	0.56	0.68	1.24	0.010	0.68	1.00	1.68	0.005	0.82	0.71	1.53	0.92
Bloating	0.004	0.76	0.51	1.27	0.007	0.97	0.76	1.72	0.004	0.68	0.56	1.24	0.48
Nausea	0.005	0.61	0.64	1.25	0.010	0.81	1.16	1.97	0.008	0.62	0.84	1.46	0.59
Lonely	0.005	0.61	0.41	1.02	0.006	1.02	0.54	1.56	0.009	0.41	0.89	1.29	0.95

[a] Did node strength in low-trauma group differ from node strength in non-trauma group? *p*-Value obtained using permutation testing.
* $p < 0.05$.

When stratifying by childhood trauma, 2 × 100 regression coefficients were presented; differences of the same connection in the two networks and centrality measures were also tested. This is multiple testing. Figs. 1 and 2 present networks and significances, but these should be interpreted with caution. When alpha is 0.05, one in 20 results is false positive. For this reason, we searched for patterns and more general conclusions rather than to scrutinize each significant connection. We could have corrected for multiple testing (e.g., using Bonferroni), but in general those corrections are too strict leading to too many false negatives [47]. When Bonferroni correction was performed (research question 1: 100 connections; research question 2: 2 × 100 connections, 100 differences and 10 node strengths), alpha would have been reduced to 0.05/410 = 0.00021. Only four self-loops remained statistically significant (low-trauma group: down, irritated; non-trauma group: abdominal pain, bloating). The *p*-value of the difference in enthusiastic-irritated between the networks was also lower than 0.00021. However, *p*-values based on approximately 3000 permutations are not precise in small p-values.

4.1. Comparison of current with previous findings

4.1.1. Mood and abdominal complaints

Lagged variables as used in the present analysis are assessed between 10 min and 3 h before the current assessment. It is possible that when shorter time periods were chosen, connections between the constructs (here the constructs mood and abdominal complaints, respectively) would have been stronger. As could have been expected, items that load on the same construct have stronger connections [3,48–50]. Both in the network including all subjects and in the networks stratified by childhood trauma, connections between mood items and abdominal complaints were less strong. This is not surprising. The connections between mood and abdominal complaints are worth mentioning. In research enquiring psychopathology and abdominal complaints cross-sectionally or once every four months, psychopathology was also associated with abdominal complaints [51,52]. The brain-gut axis is hypothesized to be involved in underlying mechanisms. The brain-gut axis is a useful framework under which the interaction between functional gastrointestinal disorders and emotional complaints can be studied, postulating that functional gastrointestinal disorders represent a sensitized response to earlier threats (i.e., childhood adversity, earlier traumatic events), which results in perceived emotional and bodily distress [8,51–54].

4.1.2. Mood, abdominal complaints and childhood trauma

In the presented networks, node strengths in the low-trauma group were higher than in the non-trauma group, but only one was statistically significant: “enthusiastic”. When assessing centrality, the present findings also revealed stronger connections in the low-trauma group

(both total centrality and mood centrality, data not shown), but when checking the individual regression coefficients this difference was not visible (also see methodological issues).

So, there is some evidence for stronger connections between mood items in the low-trauma group than in the non-trauma group, but this is not fully consistent. A previous study in healthy population twins showed some evidence for stronger connections between mood items ("cheerful", "relaxed", "irritated", "anxious", "insecure", "down") in subjects with childhood trauma than in subjects without childhood trauma, but this could not be replicated in another population twin sample [37,41]. In both twin samples, levels of childhood trauma in the trauma group were relatively low, as in the present study.

As opposed to childhood trauma, a previous study included daily stress as a node in the network of individuals with various levels of risk for psychosis [38]. Patients diagnosed with psychotic disorder had stronger network connections than healthy controls and connections in first degree relatives were stronger than in healthy controls, but less strong as in patients [38]. Similarly, in patients diagnosed with psychotic disorder connections were stronger than in healthy controls [42]. Thus, both in subjects with a risk factor for psychopathology such as childhood trauma and in subjects with increasing levels of psychopathology, connections between mood items seemed stronger. However, more evidence is needed.

Although, a clear pattern did not become visible, we may conclude that connections between abdominal symptoms of IBS and mood differ between different levels of childhood trauma. The connections between abdominal complaints on the one hand and increased NA and decreased PA on the other in fact are symptom experiences in IBS patients with panic disorder. Thus, even low levels of trauma might impact symptom experiences. Because causal inferences are difficult [45,55], this conclusion is only tentative. The suggested impact on symptom experiences could be due to differences in emotional awareness between patients of the low-trauma and the non-trauma group [56,57]. There are various reasons why this study did not reveal a clear network pattern, which could better distinguish between non-trauma and low-trauma patients. First, the present data only included a low-trauma and a non-trauma category and not higher levels of trauma (see strengths and limitations). Second, previous $n = 1$ studies with 500–1000 ESM assessments in one patient did show clear differences between networks [44,58]. Although both in the present data and in previous n = 1 analyses, ESM assessments with a lag could be analysed, analyses using extended data sets from a single person might be more sensitive than analyses using standard ESM data collection in multiple persons.

4.2. Strengths and limitations

As described earlier, data collected by ESM has sufficient validity, sensitivity and psychometric properties and it allowed us to compare groups despite of the relatively small number of participants [18–20,26]. In addition, ESM reduces recall bias and gives insight in the symptom formation due to prospectively collected experiences and its behavioural consequences [17–20,26]. The inclusion of lags enabled us to analyse changes in symptom levels over time [19,37]. However, it is important to realize that despite temporal relationships are shown, causality cannot be proven [45,55].

The present paper has some limitations. First, no persons with a moderate or high trauma level were found in this sample. Hence, we emphasize that the results and differences between the groups, as discussed above, were based on the difference between low-trauma and non-trauma. More research including patients with moderate or high trauma experiences is needed to obtain insight in networks in cases of more severe childhood trauma.

Second, power was relatively low, despite the multiple assessments per person. Despite the low power and the few significances, the presented networks give insight in underlying processes in this specific patient group. Some subjects used ESM for a few days more than according to protocol, because of the power we did not remove the days that were additionally filled in. Third, the number of subjects and thus power was lower in the low-trauma group than in the non-trauma group. Possibly due to this, the multilevel regression analysis did not achieve convergence for the a priori selected set of variables. Fortunately, the alternative set was not much different, and we could answer our research questions with this set. Three a priori selected complaints were replaced by similar items. Despite the substantially lower power, the low-trauma group had 23 significant connections as opposed to 28 in the non-trauma group. Finally, for reasons of readability 10 items were included in the networks presented in the current paper.

4.3. Conclusion and clinical implications

The present study showed that the use of ESM data in a time-lagged network model provides insight in the relationship between abdominal complaints and mood in patients with IBS and comorbid panic disorder. The use of ESM in this specific patient group and the generation of networks at the group level is feasible.

Connections within the mood items and within the abdominal complaints were stronger than connections between mood and abdominal complaints and vice versa. In addition, networks of these patients, suffering from IBS and comorbid panic disorder, with low childhood trauma or without childhood trauma were different. Although only one difference was statistically significant, node strength was stronger in patients with low levels of childhood trauma than in patients without childhood trauma.

This study provides more insight in the relationship between various symptoms in this specific underdiagnosed patient group with complex psychosomatic complaints. Connections as shown in a network may foster doctors to:

- better understand patients with comorbidities and, therefore, may help to personalize diagnostic procedures and to provide tailor-made treatment options for IBS-patients, ultimately leading to less somatic, as well as less affective symptoms and a better quality of life in this patient group.
- develop an integrated and customized care trajectory including cognitive behavioural therapy. When individuals collect ESM for a longer period, single persons' networks can give even more insight with respect to the individual patient's needs. Previously, individual networks were generated in a patient with psychotic disorder, bipolar disorder and Parkinson's disease, respectively [44,45,58].
- apply trauma related interventions, such as Eye Movement Desensitization and Reprocessing (EMDR) specified on trauma processing, when a patient reports childhood trauma.

In addition, the association between childhood trauma and IBS symptom formation may profit from the use of trauma questionnaires in order to provide important information in the diagnostic process of IBS-patients with comorbid psychopathology. When a particular patient had childhood trauma, one should keep in mind that this may impact affective as well as somatic symptoms.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of Competing Interest

None.

Appendix A. Inclusion and exclusion criteria

Inclusion criteria:
- Written informed consent
- Age between 18 and 70 years
- The presence of a panic disorder diagnosed by a psychiatrist (CL) based on the DSM IV criteria [27]
- A diagnosis of IBS with subtyping according to the Rome III criteria by a gastroenterologist (JWK) [28]
- The absence of other causes for the abdominal complaints based on previous examination and medical history

Exclusion criteria:
- Pregnancy and lactation
- Cardiac disease or known prolongation of the QT-interval or long QT-syndrome or the use of medication which could cause this QT-prolongation
- Inability to stop medication with an influence on the gastrointestinal motility or perception
- Administration of escitalopram in 180 days prior to the study
- Other treatment for anxiety or IBS or co-intervention (except transient administration of alprazolam)
- Abdominal surgery (except for uncomplicated appendectomy, cholecystectomy and hysterectomy) and drug abuse or excessive alcohol consumption [25]

Appendix B. ESM 'beep' questions

1. I FEEL ENTHUSIASTIC
2. I FEEL DOWN
3. I FEEL IRRITATED
4. I FEEL SATISFIED
5. I FEEL RUSHED
6. I FEEL RESTLESS
7. I FEEL HAPPY
8. I FEEL LONELY
9. I FEEL STRONG
10. I FEEL ANXIOUS
11. I FEEL RELAXED
12. I FEEL WORRIED
13. I FEEL INSPIRED
14. I FEEL DISAPPOINTED
15. I FEEL UNCERTAINLY
16. I FEEL EXCITED
17. I FEEL GUILTY
18. I AM AFRAID TO LOSE MY SELF-MANAGEMENT
19. I HAVE THE FEELING TO BE SEPARATE FROM MYSELF
20. I CANNOT RELEASE MY THOUGHTS
21. I AM WORRYING
22. GLOBALLY, I AM FEELING OKAY RIGHT NOW
23. WHERE I AM?
24. WITH WHO ARE I?
25. AND ALSO WITH …
26. AND ALSO WITH …
27. I FIND THIS COMPANY PLEASANT
28. I FEEL ACCEPTED
29. IN THIS COMPANY I FEEL COMFORTABLE
30. I PREFER TO BE ALONE
31. WE ARE DOING SOMETHING TOGETHER
32. I FIND IT PLEASANT TO BE ALONE
33. I PREFER TO BE IN COMPANY OF OTHER PEOPLE
34. WHAT AM I DOING (just before the beep)?
35. AND NEXT …
36. AND …
37. I WOULD LIKE TO DO SOMETHING ELSE
38. I THINK I AM ACTIVE
39. I LIKE THIS ACTIVITY
40. THIS TAKES EFFORT FOR ME
41. I CAN DO THIS
42. THIS IS A CHALLENGE
43. I AM HUNGRY
44. I AM TIRED
45. I AM NOT FEELING WELL
46. I HAVE PALPATIONS
47. I TRANSPIRE
48. I HAVE NERVES TINGLES
49. I AM SHORT OF BREATH
50. I HAVE A LUMP IN MY THROAT
51. I HAVE A PRESSURE ON MY CHEST
52. I AM DIZZY
53. I HAVE A HOT FLASH
54. I HAVE CHILLS
55. I HAVE PAIN IN UPPER ABDOMEN
56. I HAVE PAIN IN THE LOWER ABDOMEN
57. I HAVE HEARTBURNS
58. I AM NAUSEOUS
59. I HAVE ABDOMINAL DISTENSION
60. I SUFFER FROM FLATULENCE
61. I HAVE TO BURP
62. SINCE THE PREVIOUS BEEP I DID PHYSICAL EXERCISE
63. SINCE THE PREVIOUS BEEP I …
64. SINCE THE PREVIOUS BEEP I USED…
65. SINCE THE PREVIOUS BEEP I USED ALSO…
66. THINK OF THE MOST IMPORTANT EVENT SINCE THE PREVIOUS BEEP
67. THIS EVENT WAS (unpleasant-enjoyable)
68. THIS EVENT WAS (unimportant-important)
69. SINCE THE PREVIOUS BEEP I HAD DEFECATION
70. MY STOOL SEEMED AS: Figure of Bristol Stool Scale [32]

Appendix C. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychores.2020.110261.

References

[1] J. Kruimel, C. Leue, B. Winkens, D. Marcus, S. Schoon, R. Dellink, et al., Integrated medical-psychiatric outpatient care in functional gastrointestinal disorders improves outcome: a pilot study, Eur. J. Gastroenterol. Hepatol. 27 (6) (2015) 721–727.
[2] M. Fadgyas-Stanculete, A.M. Buga, A. Popa-Wagner, D.L. Dumitrascu, The relationship between irritable bowel syndrome and psychiatric disorders: from molecular changes to clinical manifestations, J. Mol. Psychiatry 2 (1) (2014) 4.
[3] D.A. Drossman, W.L. Hasler, Rome IV-functional GI disorders: disorders of gut-brain interaction, Gastroenterology 150 (6) (2016) 1257–1261.
[4] B.G. Meerveld, A.C. Johnson, Mechanisms of stress-induced visceral pain, J. Neurogastroenterol. Motil. 24 (1) (2018) 7–18.
[5] M. Zamani, S. Alizadeh-Tabari, V. Zamani, Systematic review with meta-analysis: the prevalence of anxiety and depression in patients with irritable bowel syndrome, Aliment. Pharmacol. Ther. 50 (2) (2019) 132–143.
[6] M. Fadgyas-Stanculete, A. Buga, A. Popa-Wagner, D. Dumitrascu, The relationship between irritable bowel syndrome and psychiatric disorders: from molecular changes to clinical manifestations, J. Mol. Psychiatry 2 (2014) 1–7.
[7] A.Y. Thijssen, D.M. Jonkers, C. Leue, P.P. van der Veek, M. Vidakovic-Vukic, Y.R. van Rood, et al., Dysfunctional cognitions, anxiety and depression in irritable bowel syndrome, J. Clin. Gastroenterol. 44 (10) (2010) e236–e241.
[8] C. Leue, J. Kruimel, D. Vrijens, A. Masclee, J. van Os, G. van Koeveringe, Functional urological disorders: a sensitized defence response in the bladder-gut-brain axis, Nat. Rev. Urol. 14 (3) (2017) 153–163.
[9] C. Leue, Hyperarousal in the Hospital and What to Do about it. The MED-PSYCHNET – A Transitional Network Approach Fostering Personalized Care in Psychosomatic Medicine, Datawyse University Press Maastricht, Maastricht, 2017.
[10] A. Mykletun, F. Jacka, L. Williams, J. Pasco, M. Henry, G.C. Nicholson, et al., Prevalence of mood and anxiety disorder in self reported irritable bowel syndrome (IBS). An epidemiological population based study of women, BMC Gastroenterol. 10 (2010) 88.
[11] C. Leue, G. Driessen, J.J. Strik, M. Drukker, R.W. Stockbrugger, P.M. Kuijpers, et al., Managing complex patients on a medical psychiatric unit: an observational study of

university hospital costs associated with medical service use, length of stay, and psychiatric intervention, J. Psychosom. Res. 68 (3) (2010) 295–302.
[12] H.B. El-Serag, P. Pilgrim, P. Schoenfeld, Systemic review: natural history of irritable bowel syndrome, Aliment. Pharmacol. Ther. 19 (8) (2004) 861–870.
[13] M.R. Muscatello, A. Bruno, G. Scimeca, G. Pandolfo, R.A. Zoccali, Role of negative affects in pathophysiology and clinical expression of irritable bowel syndrome, World J. Gastroenterol. 20 (24) (2014) 7570–7586.
[14] J.M. Lackner, C.X. Ma, L. Keefer, D.M. Brenner, G.D. Gudleski, N. Satchidanand, et al., Type, rather than number, of mental and physical comorbidities increases the severity of symptoms in patients with irritable bowel syndrome, Clin. Gastroenterol. Hepatol. 11 (9) (2013) 1147–1157.
[15] Z. Weerts, L. Vork, Z. Mujagic, D. Keszthelyi, M.A.M. Hesselink, J. Kruimel, et al., Reduction in IBS symptom severity is not paralleled by improvement in quality of life in patients with irritable bowel syndrome, Neurogastroenterol. Motil. 31 (8) (2019) e13629.
[16] N.A. Koloski, P.M. Boyce, M.P. Jones, N.J. Talley, What level of IBS symptoms drives impairment in health-related quality of life in community subjects with irritable bowel syndrome? Are current IBS symptom thresholds clinically meaningful? Qual. Life Res. 21 (5) (2012) 829–836.
[17] Z. Mujagic, C. Leue, L. Vork, R. Lousberg, D.M. Jonkers, D. Keszthelyi, et al., The experience sampling method—a new digital tool for momentary symptom assessment in IBS: an exploratory study, Neurogastroenterol. Motil. 27 (9) (2015) 1295–1302.
[18] L. Vork, D. Keszthelyi, Z. Mujagic, J.W. Kruimel, C. Leue, I. Ponten, et al., Development, content validity, and cross-cultural adaptation of a patient-reported outcome measure for real-time symptom assessment in irritable bowel syndrome, Neurogastroenterol. Motil. 30 (3) (2018).
[19] S.J. Verhagen, L. Hasmi, M. Drukker, J. van Os, P.A. Delespaul, Use of the experience sampling method in the context of clinical trials, Evid. Based Ment. Health. 19 (3) (2016) 86–89.
[20] J. van Os, S. Verhagen, A. Marsman, F. Peeters, M. Bak, M. Marcelis, et al., The experience sampling method as an mHealth tool to support self-monitoring, self-insight, and personalized health care in clinical practice, Depress Anxiety 34 (6) (2017) 481–493.
[21] R.J. McNally, Can network analysis transform psychopathology? Behav. Res. Ther. 86 (2016) 95–104.
[22] S.H. Park, E.J. Videlock, W. Shih, A.P. Presson, E.A. Mayer, L. Chang, Adverse childhood experiences are associated with irritable bowel syndrome and gastrointestinal symptom severity, Neurogastroenterol. Motil. 28 (8) (2016) 1252–1260.
[23] T. Ju, B.D. Naliboff, W. Shih, A.P. Presson, C. Liu, A. Gupta, et al., Risk and protective factors related to early adverse life events in irritable bowel syndrome, J. Clin. Gastroenterol. 54 (2018) 63–69.
[24] D. Kealy, S.M. Rice, J.S. Ogrodniczuk, A. Spidel, Childhood trauma and somatic symptoms among psychiatric outpatients: investigating the role of shame and guilt, Psychiatry Res. 268 (2018) 169–174.
[25] J.W. Kruimel, C. Leue, Protocol: Randomized Controlled Trial of Escitalopram Versus Placebo for Patients With Irritable Bowel Syndrome and Panic Disorder, Maastricht University Medical Centre, 2011 NCT01551225 2011. Available from: https://www.clinicaltrials.gov.
[26] L. Vork, Z. Mujagic, M. Drukker, D. Keszthelyi, J.M. Conchillo, M.A.M. Hesselink, et al., The experience sampling method-evaluation of treatment effect of escitalopram in IBS with comorbid panic disorder, Neurogastroenterol. Motil. 31 (1) (2019) e13515.
[27] American Psychiatric Association, Diagnostic and Statistical Manual of Mental Disorders, 5th ed., American Psychiatric Association, Washington, DC, 2013.
[28] D.A. Drossman, D.L. Dumitrascu, Rome III: New standard for functional gastrointestinal disorders, J. Gastrointestin. Liver Dis. 15 (3) (2006) 237–241.
[29] D.P. Bernstein, L. Fink, L. Handelsman, J. Foote, M. Lovejoy, K. Wenzel, et al., Initial reliability and validity of a new retrospective measure of child abuse and neglect, Am. J. Psychiatry 151 (8) (1994) 1132–1136.
[30] B.D. Thombs, D.P. Bernstein, J. Lobbestael, A. Arntz, A validation study of the Dutch childhood trauma questionnaire-short form: factor structure, reliability, and known-groups validity, Child Abuse Negl. 33 (8) (2009) 518–523.
[31] D.P. Bernstein, L. Fink, Childhood Trauma Questionnaire Manual, Psychological Corporation, Orlando, 1998.
[32] S.J. Lewis, K.W. Heaton, Stool form scale as a useful guide to intestinal transit time, Scand. J. Gastroenterol. 32 (9) (1997) 920–924.
[33] P.A.E.G. Delespaul, M.W.D. Vries (Ed.), Assessing Schizophrenia in Daily Life the Experience Sampling Method, Universitaire Pers Maastricht, Maastricht, 1995.
[34] T. Snijders, R. Bosker, Multilevel Analysis, an Introduction to Basic and Advanced Modeling, SAGE Publications, London, 1999 (266 pp.).
[35] N. Jacobs, C. Menne-Lothmann, C. Derom, E. Thiery, J. van Os, M. Wichers, Deconstructing the familiality of variability in momentary negative and positive affect, Acta Psychiatr. Scand. 127 (4) (2013) 318–327.
[36] StataCorp, C. Station (Ed.), Stata Statistical Software: Release 13, TX: StataCorp, LP, 2013.
[37] L. Hasmi, M. Drukker, S. Guloksuz, W. Viechtbauer, E. Thiery, C. Derom, et al., Genetic and environmental influences on the affective regulation network: a prospective experience sampling analysis, Front. Psychiatry 9 (2018) 602.
[38] A. Klippel, W. Viechtbauer, U. Reininghaus, J. Wigman, C. van Borkulo, Merge, et al. the Cascade of stress: a network approach to explore differential dynamics in populations varying in risk for psychosis, Schizophr. Bull. 44 (2) (2018) 328–337.
[39] TeamR, R: A Language and Environment for Statistical Computing, R-Foundation for Statistical Computing, Vienna, 2013.
[40] Sacha Epskamp, Angelique O.J. Cramer, Lourens J. Waldorp, V.D. Schmittmann, D. Borsboom, qgraph: network visualizations of relationships in psychometric data, J. Stat. Software 48 (4) (2012) 1–18.
[41] L. Hasmi, M. Drukker, S. Guloksuz, C. Menne-Lothmann, J. Decoster, R. van Winkel, et al., Network approach to understanding emotion dynamics in relation to childhood trauma and genetic liability to psychopathology: replication of a prospective experience sampling analysis, Front. Psychol. 8 (2017) 1908.
[42] J.T. Wigman, J. van Os, D. Borsboom, K.J. Wardenaar, S. Epskamp, A. Klippel, et al., Exploring the underlying structure of mental disorders: cross-diagnostic differences and similarities from a network perspective using both a top-down and a bottom-up approach, Psychol. Med. 45 (11) (2015) 2375–2387.
[43] T. Opsahl, F. Agneessens, J. Skvoretz, Node centrality in weighted networks: generalizing degree and shortest paths, Soc. Networks 32 (2010) 245–251.
[44] M. Bak, M. Drukker, L. Hasmi, J. van Os, An n = 1 clinical network analysis of symptoms and treatment in psychosis, PLoS One 11 (9) (2016) e0162811.
[45] R.M.J. van der Velden, A.E.P. Mulders, M. Drukker, M.L. Kuijf, A.F.G. Leentjens, Network analysis of symptoms in a Parkinson patient using experience sampling data: an n = 1 study, Mov. Disord. 33 (12) (2018) 1938–1944.
[46] L.F. Bringmann, T. Elmer, S. Epskamp, R.W. Krause, D. Schoch, M. Wichers, et al., What do centrality measures measure in psychological networks? J. Abnorm. Psychol. 128 (8) (2019) 892–903.
[47] S. Nakagawa, A farewell to Bonferroni: the problems of low statistical power and publication bias, Behav. Ecol. 15 (6) (2004) 1044–1045.
[48] R. Goekoop, J.G. Goekoop, A network view on psychiatric disorders: network clusters of symptoms as elementary syndromes of psychopathology, PLoS One 9 (11) (2014) e112734.
[49] S.J.W. Verhagen, J.A. Berben, C. Leue, A. Marsman, P. Delespaul, J. van Os, et al., Demonstrating the reliability of transdiagnostic mHealth routine outcome monitoring in mental health services using experience sampling technology, PLoS One 12 (10) (2017) e0186294.
[50] I. Myin-Germeys, F. Peeters, R. Havermans, N.A. Nicolson, M.W. DeVries, P. Delespaul, et al., Emotional reactivity to daily life stress in psychosis and affective disorder: an experience sampling study, Acta Psychiatr. Scand. 107 (2) (2003) 124–131.
[51] N.A. Koloski, N.J. Talley, P.M. Boyce, Does psychological distress modulate functional gastrointestinal symptoms and health care seeking? A prospective, community Cohort study, Am. J. Gastroenterol. 98 (4) (2003) 789–797.
[52] J.M. Lackner, J. Jaccard, E.B. Blanchard, Testing the sequential model of pain processing in irritable bowel syndrome: a structural equation modeling analysis, Eur. J. Pain 9 (2) (2005) 207–218.
[53] J.M. Lackner, G.D. Gudleski, E.R. Thakur, T.J. Stewart, G.J. Iacobucci, B.M. Spiegel, The impact of physical complaints, social environment, and psychological functioning on IBS patients' health perceptions: looking beyond GI symptom severity, Am. J. Gastroenterol. 109 (2) (2014) 224–233.
[54] T.C. Olde Hartman, P.L. Lucassen, E.H. van de Lisdonk, H.H. Bor, C. van Weel, Chronic functional somatic symptoms: a single syndrome? Br. J. Gen. Pract. 54 (509) (2004) 922–927.
[55] S. Epskamp, C.D. van Borkulo, D.C. van der Veen, M.N. Servaas, A.M. Isvoranu, H. Riese, et al., Personalized network modeling in psychopathology: the importance of contemporaneous and temporal connections, Clin. Psychol. Sci. 6 (3) (2018) 416–427.
[56] R.D. Lane, F.S. Anderson, R. Smith, Biased competition favoring physical over emotional pain: a possible explanation for the link between early adversity and chronic pain, Psychosom. Med. 80 (9) (2018) 880–890.
[57] R. Smith, G.D. Gudleski, R.D. Lane, J.M. Lackner, Higher emotional awareness is associated with reduced pain in irritable bowel syndrome patients: preliminary results, Psychol. Rep. 123 (2020) 2227–2247 (33294119868778).
[58] A. Voigt, D. Kreiter, C. Jacobs, E. Revenich, N. Serafras, M. Wiersma, et al., Clinical network analysis in a bipolar patient using an experience sampling mobile health tool: an n = 1 study, Bipolar Disord. Open Access. 4 (1) (2018) 121.