



Symptom-network dynamics in irritable bowel syndrome with comorbid panic disorder using electronic momentary assessment: A randomized controlled trial of escitalopram vs. placebo

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ARTICLE INFO

Keywords:

Irritable bowel syndrome
Panic disorder
Experience sampling method
Selective serotonin reuptake inhibitor
Psychological networks

ABSTRACT

Introduction: Momentary ecological assessment indicated alleviated abdominal pain in escitalopram treatment of irritable bowel syndrome (IBS) with comorbid panic disorder. Hitherto, little is known about symptom formation, i.e., how psychological impact physical symptoms, and vice versa, and about the effect of SSRI-treatment on symptom formation.

Objective: To investigate how psychological and somatic symptoms co-vary over time in IBS patients with comorbid panic disorder and how they are affected by escitalopram treatment.

Methods: Experience sampling data from 14 IBS patients with panic disorder were obtained from a single-centre, double-blind, parallel-group, randomized controlled trial on escitalopram versus placebo. At baseline, after three and six months, multilevel time-lagged linear regression analysis was used to construct symptom networks. Network connections represented coefficients between various affect and gastrointestinal items.

Results: Connectivity increased up to 3 months in both groups. Between 3 and 6 months, connectivity decreased for placebo and further increased in the escitalopram group. Additionally, a steep increase in node strength for negative affect nodes was observed in the escitalopram network and the opposite for positive affect nodes. Over time, group symptom networks became increasingly different from each other. Anxious-anxious and enthusiastic-relaxed became significantly different between groups at 6 months. The connection that changed significantly in all analyses was anxious-anxious.

Conclusions: Escitalopram treatment was associated with changes in the symptom networks in IBS patients with panic disorder. While mood and physical symptoms improve over time, mainly connectivity between mood nodes changed, possibly pointing towards a healthier emotion regulation resulting in alleviation of physical symptoms.

1. Introduction

In the population of patients with irritable bowel syndrome (IBS), a considerable part has a comorbid psychiatric disorder [1]. As IBS also has a psychological component, a previous paper studied interplay between abdominal complaints and mood in this population [2]. In addition, when treating IBS and/or the psychiatric comorbidity, this

hypothetically impacts the interplay between abdominal complaints and mood.

IBS is a common disorder of the gut-brain axis [3] characterized by abdominal pain and altered bowel habits, with either predominantly experienced diarrhoea, constipation or both. It is a disorder accompanied with a significant burden on patients and healthcare systems and comes with high direct and indirect costs [4,5], due to its chronic course,

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complex symptomatology and treatment-resistance. The association between IBS and psychological symptoms has been studied extensively. Symptoms of anxiety and depression are among the most frequently reported psychological symptoms in these patients [6] [7,8]. Consequently, prevalence of psychiatric disorders in IBS patients is higher than in the general population [5,9–11], as is the risk of affective disorders [12,13]. The comorbid association seems bi-directional with IBS also being more prevalent in patients with psychiatric disorders [14]. Both IBS and its psychiatric comorbidities are stress-related disorders, where gut and brain interact [15].

The link between brain and gut is evident in the connection between the enteric and central nervous system as well as in the connection through immunological and endocrine interactions [15,16]. In IBS, a variety of disturbances in the complex gut-brain axis has been identified. Hence, based on the latest scientific consensus, IBS is defined as a disorder of the gut-brain interaction [3]. Abnormal gastrointestinal sensitivity, motility and permeability of the gut have been shown [6]. Furthermore, alterations in gut microbiota and aberrant immune function have been observed [6]. Concerning the central nervous system, patients with IBS tend to have a dysregulated autonomic nervous system, which is related to psychological distress and accompanied disturbances in emotion regulation [17–20]. Moreover, coping with distress is a complex sequence of physical, emotional and behavioural reactions [20]. Therefore, disorders in emotion regulation [21], e.g. in relation to childhood trauma [2,20,22], predispose to functional disorders where physical symptoms work as a regulator for preventing awareness of intolerable emotions [23].

Although the presence of psychological symptoms, such as anxiety and/or depression, is frequently reported in IBS [6,24], studies simultaneously addressing somatic and psychological symptoms, as well as their reciprocal temporal relations, including several assessments a day, are sparse [25]. Recently, an exploratory randomized controlled trial (RCT) in patients with IBS and comorbid panic disorder showed that treatment with escitalopram alleviated abdominal pain, when electronically assessed multiple times a day [26], whereas retrospective assessment methods did not show this effect. Since the IBS population is very heterogeneous, the inclusion of a specific subgroup with comorbid panic disorder might enable us to gain a clearer insight into specific symptom dynamics, which may be obfuscated when studying a larger more heterogeneous IBS population. Symptoms can vary considerably during the day within subjects, also because psychological and environmental factors can change from moment to moment, which in turn exerts influence on mental states. Therefore, in order to get appropriate insight into symptom dynamics, data in this RCT were collected by using the experience sampling method (ESM) [27]. At ten random time-points per day, subjects were asked to complete a short electronic questionnaire, including among others gastrointestinal and psychological symptoms. This method is ecologically valid, more sensitive for fluctuations over time and reduces recall bias compared to retrospective assessment methods [26,27]. Furthermore, ESM data are ideally suited to perform network analyses [28,29].

Following the main results of the RCT [26], the next step would be to analyse whether network connections between affect items and gastrointestinal symptoms, assessed by ESM, would change over time in the escitalopram group. It is expected that treatment is associated with changes in connections between psychological distress and abdominal symptoms in daily life. Hence, after treatment, we may expect a change in patients' symptom networks, representing a change in the regulation of emotional symptoms and abdominal complaints, while for the placebo group connections should be affected less. By making network graphs using data from the above-mentioned RCT, we aimed to investigate how these symptoms co-vary over time and how they are affected by treatment.

2. Materials and methods

2.1. Study participants and design

For the present study, data were used from a single-centre, double-blind, parallel-group, RCT. A previous paper provided more details on the design (<https://www.clinicaltrials.gov>, NCT01551225) [26]. The study protocol was approved by the medical-ethics committee of Maastricht University Medical Centre. All subjects gave written informed consent before participation. In this trial, the SSRI escitalopram was compared with placebo in patients with IBS and comorbid panic disorder. Between February 2012 and June 2016, subjects were enrolled via the Maastricht University Medical Centre outpatient clinics of Gastroenterology-Hepatology and the Med-Psych-Centre for patients with somatic and psychiatric comorbidity. Subjects aged between 18 and 70 years, that were clinically diagnosed with IBS and comorbid panic disorder, were eligible. IBS was diagnosed by a gastroenterologist in accordance to the Rome III-criteria [30]. Presence of a comorbid panic disorder was assessed by a psychiatrist using the DSM-IV-TR [31] and the Mini-International-Neuropsychiatric-Interview [32]. Subjects were randomly assigned to either placebo or treatment group. The latter started with an initial dose of 5 mg escitalopram once daily, being increased to 10 mg once daily after the first week. Depending on self-reported symptom improvement, the dose could be gradually increased to a maximum of 20 mg a day.

2.2. Measurements

Assessments were obtained at baseline ($t = 1$), after three months ($t = 2$) and after six months ($t = 3$). At these moments, an ESM period of consecutive 7 days was completed. When patients completed additional days, these observations were also included in the analysis. In the present study, ESM data were analysed to generate symptom networks. By using ESM, affective and gastrointestinal symptoms were assessed multiple times a day. At ten random time-points per day a palmtop computer sent out an auditory signal ("beep") between 7:30 AM and 10:30 PM. After each beep, subjects were asked to complete an electronic questionnaire, with items rated on a 7-point Likert scale (1 = not at all to 7 = extremely). By using this momentary assessment tool, real-time experiences are measured and recall bias is avoided [33]. The ESM included a large variety of items (see appendix for supporting information) and has been described in more detail elsewhere [26,27,34]. For the present networks, an a priori selected set of items was chosen. This set included six items reflecting different affective states: happy, enthusiastic, relaxed, down, irritated and anxious. Furthermore, a social item (lonely) and three scores for somatic symptoms (abdominal pain, nausea, bloating) were included.

2.3. Statistical analysis

Multilevel linear regression analysis was performed using Stata, version 13.1 (Stata Corporation) [35]. The Stata mixed command is ideally suited to analyse multiple assessments clustered in subjects for each of the two treatment groups, at each of the three measurement moments. The yielded coefficients then served to construct a total of six networks. The scores on the ten above-mentioned symptom variables at time point t were included as dependent variables in 10 different regression models. The lag ($t-1$) of the same variables served as independent variables. These time-lagged variables are the scores one time point earlier (which could vary between a minimum of five minutes and a maximum of three hours earlier). Thus, symptom variables at t are being predicted by the same variables at $t-1$. A time variable (i.e., a counting beep number) was included in all models to control for time trends, in line with the methods in earlier similar studies [2,28,36]. The steps above yielded regression models of which this model is an example:

$$\begin{aligned} \text{Down}_{ij} = & (B0 + u_{0j}) + B1 * \text{lag down}_{ij} + B2 * \text{lag irritated}_{ij} + B3 * \text{lag anxious}_{ij} \\ & + B4 * \text{lag happy}_{ij} + B5 * \text{lag enthusiastic}_{ij} + B6 * \text{lag relaxed}_{ij} \\ & + B7 * \text{lag lonely}_{ij} + B8 * \text{lag abdominal pain}_{ij} + B9 * \text{lag nausea}_{ij} \\ & + B10 * \text{lag bloating}_{ij} + (B11 + u_{11ij}) * \text{time}_{ij} + \varepsilon \end{aligned}$$

Here *time* indicates the earlier mentioned counting beep number and u_{11ij} is the random slope of time. Furthermore, subscript *i* stands for the assessment level and *j* for individuals.

This results in six 10-by-10 matrices with all regression coefficients between the independent (time-lagged) and the dependent variables for the assessments at baseline and three months as well as six months, stratified by treatment group (escitalopram or placebo). From each of these six matrices, a network could be constructed with the coefficients as edges and symptom variables as nodes [28,29,37]. The networks were visualized using the qgraph package in R [38]. Node sizes represent the node strength of the variable (see Fig. 2).

2.3.1. Centrality indices

Measures of network centrality help us assess the importance of elements in arrays of relationships, in this case consisting of correlations between symptoms. A variety of centrality indices were calculated using R [38]: Outward strength, inward strength, node strength and closeness. Outward strength was calculated by summing the absolute values of all outgoing connections of the node in question, including self-loops [28,29]. The same was calculated for inward strength for the incoming connections. Node strength is the sum of outward and inward strength (also meaning that self-loops are included twice, in accordance with earlier publications) [2,36]. Closeness is defined as the inverse sum of the shortest distances to all other nodes, whereas the shortest distances are the sum of the inverse of the regression coefficients [39,40]. Finally, connectivity was calculated, which is the sum of all regression coefficients in the network.

2.3.2. Permutation testing

In the ideal analysis, not only time but all independent variables should have random slopes [41]. Due to the large number of predictor variables and parameters that would need to be estimated, this is not feasible. An attempt to fit such models would lead to non-convergence. Because standard errors would be incorrect in a simpler model, an alternative method is needed to correctly estimate *p*-values. As a solution, permutation testing was carried out to obtain the distribution of regression coefficients under the null hypothesis. Using this distribution, a valid *p*-value was acquired by placing the coefficient from the real analysis on this normal distribution. Three sets of permutation tests were performed: the first set, to calculate the statistical significance for the regression coefficients (B); the second set to assess whether the coefficients in the escitalopram and the placebo group were statistically different; and the third to analyse whether coefficients changed significantly after 6 months of treatment compared with baseline.

Thus, in the first set, the outcome variable was removed from the data and put back in a random order within the same subject (reshuffle). Reshuffle and analyses were repeated 3000 times to generate the distribution under null hypothesis. For the second set, the same method was applied, but instead of shuffling the outcome variable, the treatment group was removed and then randomly assigned at subject level. For the third set, the time point (baseline, 3 months, 6 months) was shuffled. Similar permutation analyses from earlier work aimed to include 1000 valid permutations because these analyses are time consuming [36]. However, permuted data representing the null hypothesis do not always converge and to keep sufficient valid values, we chose to run 3000 permutations.

3. Results

3.1. Sample characteristics

Of the 29 patients participating in the RCT, 21 agreed to complete the ESM questionnaires, of whom a total of 14 patients completed at least one third of the ESM assessments at each of the three follow up moments (i.e., a minimum of 23 out of 70 assessments per period). Of these 14 patients, 9 received placebo treatment and 5 escitalopram. The placebo group included 5 females (55.5%) and the escitalopram group 3 (66.7%). The mean age of the total sample was 35.6 years (SD 17.0 years); that is 32.7 years (SD 17.1) in the placebo group and 45.2 years (SD 16.3) in the escitalopram group.

In the placebo group, 480, 358 and 397 observations were included in the analyses at the three measurement periods, respectively. In the escitalopram group, 254, 268 and 247, were included respectively. In Table 1, the mean symptom scores for both groups over time are listed. Most ESM symptom scores were similar between groups at baseline. Over time, the physical symptom scores 'abdominal pain', 'bloating' and 'nausea' showed a steady decrease in the escitalopram group, whereas changes were only small in the placebo group. It has to be noted, that these symptom scores were not subject to statistical testing, since the focus of the current study was to assess how physical and psychological symptoms co-vary over time. For the same trial patients, Vork et al. showed previously that mean abdominal pain ESM symptom scores decreased significantly more in the escitalopram group than in the placebo group over the 6-month study period ($-1.4, p = 0.021$; on a 1-to-7 scale; [26]). Looking at the psychological symptom scores, there was a decrease in the negative affect items, 'down' and 'anxious' in the escitalopram group, whereas the placebo group revealed a smaller decrease. The positive affect scores 'happy', 'enthusiastic' and 'relaxed' remained virtually unchanged in both the escitalopram and the placebo group. As for the abdominal symptoms, psychological symptoms were not tested, but only presented as background information.

3.2. Centrality indices

The generated symptom networks for both groups at the different time points are shown in Fig. 2. There was a difference in the connectivity of the networks at baseline and an increase of connectivity in both

Table 1

Mean symptom scores (SD) on ESM questionnaires. Likert scale ranging from 1 to 7 (1 = not at all, 7 = extremely).

ESM symptom scores	Placebo (n = 9)			Escitalopram (n = 5)		
	mean (SD)			mean (SD)		
Variable	Baseline	3 months	6 months	Baseline	3 months	6 months
Abdominal pain	2.8 (1.4)	2.8 (1.6)	2.6 (1.5)	2.6 (1.2)	1.7 (0.8)	1.5 (0.6)
Bloating	3.5 (2.1)	3.6 (2.1)	3.6 (2.0)	3.2 (1.6)	2.6 (1.8)	2.5 (1.8)
Nausea	1.4 (1.2)	1.5 (1.1)	1.3 (0.8)	1.4 (1.2)	1.2 (0.6)	1.1 (0.6)
Anxious	2.1 (1.4)	1.7 (1.2)	1.4 (0.9)	1.5 (1.0)	1.3 (0.9)	1.1 (0.4)
Down	1.9 (1.4)	1.9 (1.6)	1.8 (1.4)	1.7 (1.3)	1.4 (1.0)	1.2 (0.7)
Irritated	1.9 (1.3)	2.0 (1.5)	2.0 (1.6)	1.6 (1.3)	1.4 (0.9)	1.2 (0.7)
Happy	4.9 (1.4)	4.9 (1.5)	4.8 (1.4)	5.1 (1.1)	5.2 (1.1)	4.9 (1.2)
Enthusiastic	4.5 (1.5)	4.6 (1.9)	4.6 (1.7)	4.8 (1.3)	4.9 (1.2)	5.0 (1.3)
Relaxed	4.3 (1.5)	4.2 (1.6)	4.2 (1.6)	4.8 (1.4)	4.8 (1.4)	4.8 (1.6)
Lonely	1.3 (0.8)	1.8 (1.4)	1.7 (1.5)	1.4 (1.1)	1.4 (1.2)	1.2 (0.8)

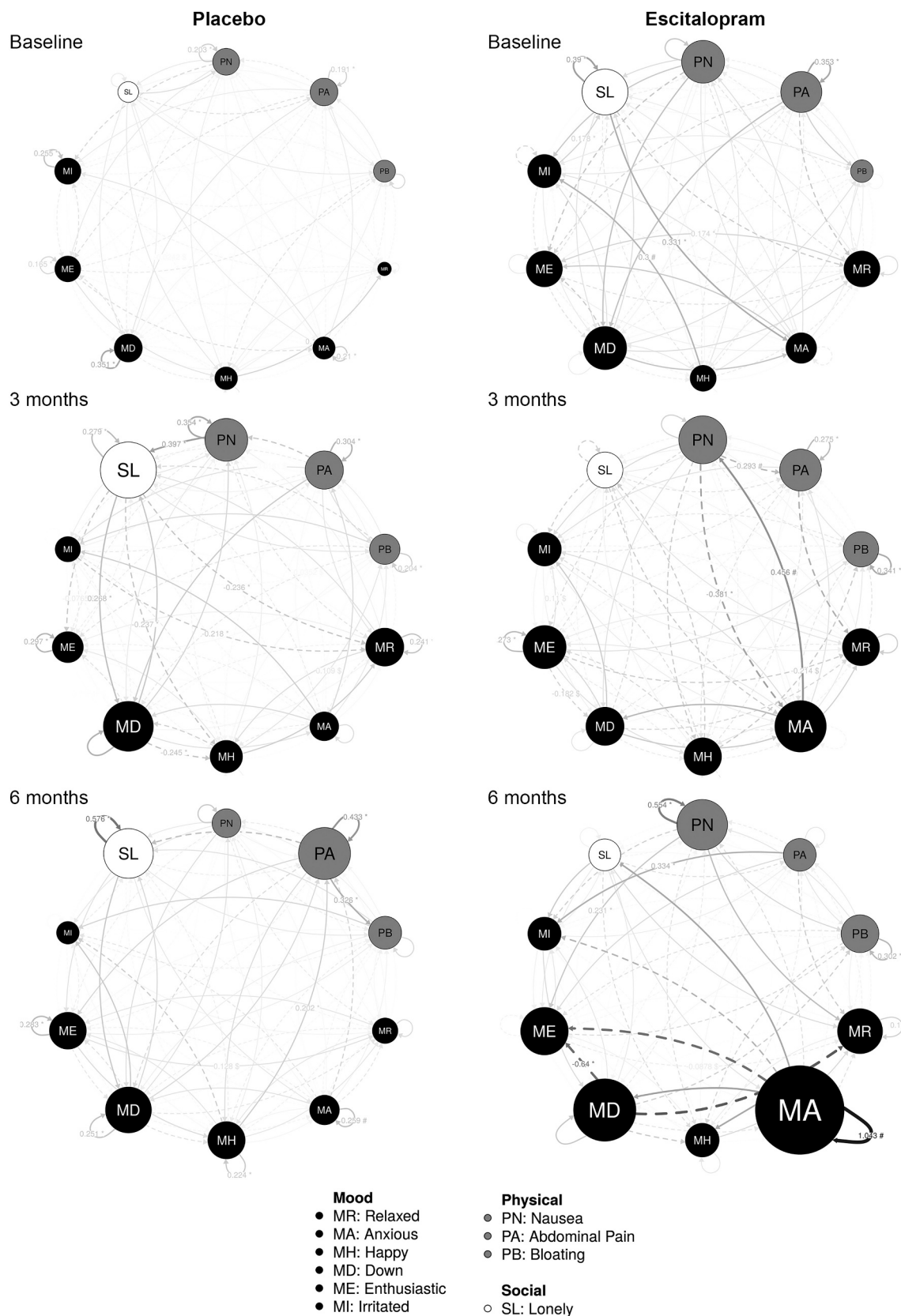


Fig. 2. Network graphs at every follow-up moment for placebo (left) and escitalopram (right). Continuous lines represent positive and dashed lines negative connections. * = statistically significant coefficients, \$ = significantly different compared with the other group, # = statistically significant coefficients that are also significantly different compared with the other group ($\alpha = 0.05$). Node size represents node strength.

Table 2

Centrality indices. Connectivity (sum of all connections in network), node strength (sum of incoming and outgoing connections of a node), outdegree (sum of all outgoing connections), indegree (sum of all incoming connections) for the different symptom nodes. $t = 1$ (baseline), $t = 2$ (3 months) and $t = 3$ (6 months). * $p < 0.05$, ** $p < 0.01$ for the difference between groups.

Connectivity	Placebo			Escitalopram		
	$t = 1$	$t = 2$	$t = 3$	$t = 1$	$t = 2$	$t = 3$
Node strength	6.5	10.2	9.9	9.8	11.0	12.8
Physical	Placebo			Escitalopram		
Abdominal Pain	1.5	2.1	2.8	2.2	2.3	1.8
Bloating	1.2	1.7	1.8	1.2	1.9	2.1
Nausea	1.5	2.3	1.6	2.3	2.6	2.8
Affect						
Anxious	1.2	1.6	1.6*	1.7	2.8	4.9*
Down	1.5	2.7	2.5	2.4	2.1	3.4
Irritated	1.4	1.4	1.2	1.8	1.8	1.8
Happy	1.2	1.8	2.0	1.4	2.1	1.9
Enthusiastic	1.4	1.7	2.0	2.0	2.4	2.6
Relaxed	0.7*	2.1	1.4	2.0*	2.0	2.5
Social						
Lonely	1.1	3.1*	2.7	2.5	2.0*	1.8
Outdegree	Placebo			Escitalopram		
Physical						
Abdominal Pain	0.6	1.0	1.2	1.1	0.9	1.0
Bloating	0.4	0.7	0.7	0.5	0.4	0.7
Nausea	0.6	0.9	0.7	1.3	1.5	1.1
Affect						
Anxious	0.4	0.9	0.7	0.7	1.5	2.5
Down	0.4	1.0	1.1	1.1	1.0	2.2
Irritated	0.4	0.5	0.3	0.5	0.5	0.5
Happy	0.4	0.8	0.9	0.8	1.0	0.5
Enthusiastic	0.6	0.3*	0.7	0.7	1.0*	0.5
Relaxed	0.2	0.6	0.4	0.6	0.5	0.3
Social						
Lonely	0.6	1.3	0.7	0.9	0.9	1.0
Indegree	Placebo			Escitalopram		
Physical						
Abdominal Pain	0.5	0.5	0.8	0.4	0.9	0.6
Bloating	0.5	0.6	0.8	0.7	0.8	0.8
Nausea	0.4	0.8	0.5	0.6	0.8	0.6
Affect						
Anxious	0.4	0.4	0.4	0.8	1.2	0.3
Down	0.5	1.1	0.9	1.1	0.8	0.8
Irritated	0.6	0.9	0.9	1.0	1.2	1.4
Happy	0.6	0.9	0.7	0.5	0.9	1.2
Enthusiastic	0.4	0.9	0.8	1.1	0.8	2.0
Relaxed	0.4	1.0	0.7	1.1	1.2	1.8
Social						
Lonely	0.3	1.2	0.8	0.8	0.7	0.7

groups after 3 months (difference between groups at 3 months 0.80; $p = 0.99$) (see Table 2 and Fig. 1). After 6 months, the connectivity of symptoms further increased in the escitalopram group while there was a decrease in the placebo group. However, permutation analyses showed that the difference is not statistically significant (difference between groups at 6 months 2.87; $p = 0.92$).

3.3. Node strength

Breaking this down, the increase in connectivity after 3 months in the placebo group was a result of an increase in all node strengths (see Table 2). In the escitalopram group, most node strengths increased too, except for the negative affects 'down' and 'irritated', and the social affect 'lonely'. However, only the node strength of 'lonely' was significantly lower in the escitalopram group than in the placebo group at 3 months (difference between groups of 1.11, $p = 0.009$). After 6 months, most nodes in the placebo network lost strength, except for 'abdominal pain', 'bloating' and 'enthusiastic'. In the escitalopram group, a steep increase in the node strengths of negative affects 'anxious' and 'down'

was present, while the other strengths remained quite similar. However, at 6 months only the node strength for 'anxious' was significantly higher in the escitalopram group compared with placebo (difference between groups of 3.26, $p = 0.049$). The values of the closeness centrality measure showed a similar pattern to the node strength (see supplement 1).

Dissecting this steep increase in node centrality for 'anxious' and 'down' further, the outdegree and indegree indices showed, that these changes were a consequence of the diminishing incoming connections (see Table 2), while, on the contrary, outgoing connections became more prominent in the escitalopram group. Which is also clearly visible in the network graphs (see Figs. 2, for network graphs with only significant edges, see supplement 3).

For the positive affect nodes (i.e., 'enthusiastic', 'happy' and 'relaxed') the exact opposite occurred: The incoming connections increased, and the outgoing ones diminished. Regarding centrality of the physical symptoms, most changes were minor and did not show a clear pattern. It has to be noted that none of the in- or outdegree indices, except for 'enthusiastic' after 3 months, were statistically significant in comparative permutation analysis between the escitalopram and placebo group.

3.4. Coefficients

Fig. 2 shows which of the coefficients itself were statistically significant and, in addition, which were significantly different compared with the other treatment group. At the three measurement moments respectively, 7/7, 12/6, 9/9 (placebo/escitalopram) out of 100 coefficients in the networks were proven to be significant in permutation testing. At baseline, the only connection that was significantly different between groups after permutations, was happy-irritated (difference between groups of 0.32; $p = 0.026$). At 3 months, the following connections were significantly different (difference between groups, p -value): anxious-nausea (0.49, $p = 0.008$), nausea-abdominal pain (0.31; $p = 0.038$), happy-bloating (0.32; $p = 0.005$), enthusiastic-down (0.19; $p = 0.043$), enthusiastic-irritated (0.12, $p = 0.046$). Finally, at 6 months: enthusiastic-relaxed (0.22; $p = 0.027$) and anxious-anxious (0.78; $p = 0.021$) proved to be significantly different (see supplement 2 for the complete overview of all coefficients and their p -values).

Further testing addressed whether coefficients of treatment groups were significantly different at 6 months compared with baseline. This shows 9 out of 100 coefficients were significantly different from baseline in the placebo group (i.e., abdominal pain to bloating, abdominal pain and enthusiastic; enthusiastic-anxious; happy-happy; nausea-down; lonely-lonely; down-irritated; anxious-irritated) compared with 11 out of 100 in the escitalopram group (i.e., anxious-nausea; enthusiastic-nausea; bloating-bloating; anxious-anxious; down-relax; abdominal pain, anxious-irritated; happy-irritated; anxious, irritated and enthusiastic to enthusiastic).

Finally, the only connection, that was significantly different in all three permutation analyses (for itself, between escitalopram and placebo group, and between 6 months and baseline), was anxious-anxious.

4. Discussion

Using network analysis with data from an RCT, we investigated how psychological and somatic symptoms co-varied over time, and how these complaints were affected by treatment with the SSRI escitalopram. The presented symptom networks clearly show that networks in the escitalopram group evolved differently from the placebo group over time, suggesting that there is in fact an effect of the SSRI on symptom dynamics. This is in line with our hypothesis that on top of the previously reported alleviation of physical symptoms by Vork et al. [26], that SSRI treatment would also impact connections between psychological distress and abdominal symptoms in daily life. We aimed to identify general patterns, instead of considering each network coefficient individually, in order to avoid overinterpretation of the results. The negative

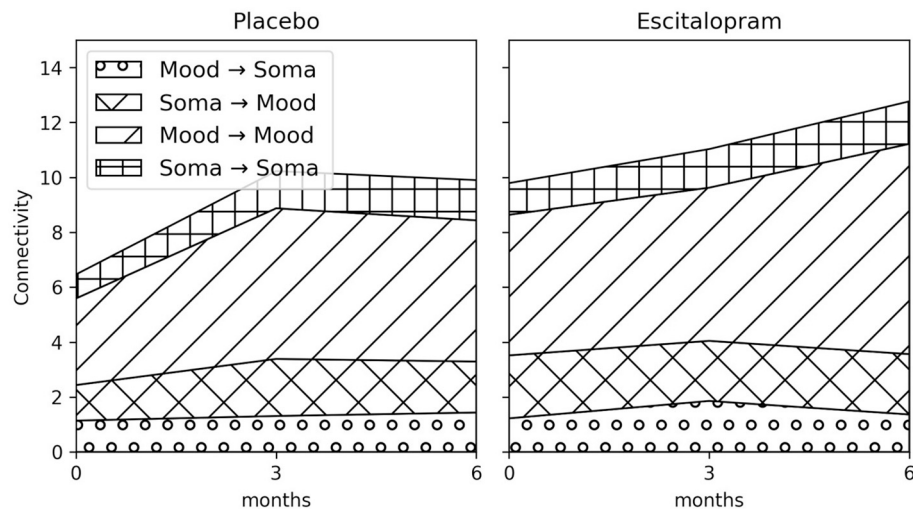


Fig. 1. Connectivity (sum of all coefficients in the network) split up by connection type: Connections from mood to somatic nodes (mood - soma), from somatic to mood nodes (soma - mood), from mood to mood nodes (mood - mood) and from somatic to somatic nodes (soma - soma).

affect scores decreased in the escitalopram group, whereas positive affect scores remained similar. Moreover, network connectivity remained higher in the escitalopram group and increased at every follow up moment, although not statistically significant compared with placebo. This increase in connectivity was largely due to a steep increase in node strength for 'anxious' and 'down'. The node strength for 'anxious' was significantly higher at 6 months compared with the placebo group. For 'down' the difference was not statistically significant. Both nodes had increasing outdegrees and decreasing indegrees over time. With the opposite happening for the positive affect nodes, showing smaller outdegrees and greater indegrees. A possible explanation for these findings might be that SSRI treatment has a beneficial effect on emotion regulation, compared to placebo, leading to a healthier condition with increased network connectivity. Lastly, the node strength of 'lonely' was significantly higher in the placebo group after 3 months, while the 'lonely' symptom score remained similar between the two groups. We did not find a fitting explanation for this increase in 'lonely' node strength. However, this finding could also reflect a false positive effect due multiple testing (see 'Limitations' below).

One would intuitively expect network connectivity to decrease as symptoms ameliorate. The reason being that when correlations between symptoms become weaker, they are less easily triggered by other symptoms [42]. Studies using a between-subject design to investigate depressed patients indeed found more weakly connected networks, e.g., in remitted patients [43] and healthy controls [44] compared with depressed patients. However, for within-subject study designs (like the current study), as opposed to between-subject study designs, increased network connectivity, going hand in hand with improving symptoms, is consistent with what is reported in previous work [42,45]. For example, Bos et al. adapted cross-sectional network analysis to investigate symptom connectivity in depressed patients, comparing before and after SSRI treatment [42]. The authors used data from the SSRI arm of two RCTs. They found that severity of all individual depressive symptoms significantly decreased after 8 weeks of paroxetine treatment and that connectivity of symptoms increased. However, there was no control group hampering conclusions on the potential effects of the SSRI on network connectivity [42]. Hence, increased network connectivity in the escitalopram group may support the assumption that SSRIs might influence functional intestinal complaints by strengthening emotion regulation. In that regard, after 6 months, two coefficients were statistically different between the treatment group and the control group. Firstly, anxious-anxious of which the connection became substantially stronger in the escitalopram group, while only a minimal increase in the placebo group occurred. Secondly, enthusiastic-relaxed became slightly

stronger in the placebo group. However, because the absolute change for enthusiastic-relaxed is minimal, it seems less likely that this is a clinically relevant change. Comparing within the groups between 6 months and baseline, the number of significant different connections was similar (9 for the escitalopram and 8 for the placebo group). There was no apparent pattern in what connections were significantly different over time when we compared the sets of changed connections between the two groups (e.g., if there were more mood-physical connections that significantly changed in one of the groups compared with the other group). One of the few things really standing out is that the 'anxious' self-loop connection strength shows a large difference over time between the two groups. This also was the only connection that had significant change in its coefficient in all three permutation analyses (the regression coefficient itself, the difference between the escitalopram and placebo groups and when comparing 6 months and baseline), while the mean symptom score for 'anxious' for the escitalopram group decreased over time. Our theory is that this is the result of healthier emotion regulation. This is reflected by the overall lower burden of anxiety after SSRI treatment (shown by the lower symptom scores), but when there is anxiety in these patients, the anxiety symptom node specifically interacts with the mood nodes in the network (i.e., higher 'anxious' node strength). Looking specifically at 'anxious' in the network, mainly the connections between anxious and the other mood nodes became stronger (sum of outgoing connections from anxious to other mood nodes at 6 months vs. baseline; escitalopram 3.96 vs. 0.57, placebo 0.97 vs. 0.56) compared with the placebo group. In contrast, the connections from anxious to the physical symptom nodes show little change (sum of outgoing connections from anxious to physical symptom nodes at 6 months vs. baseline; escitalopram 0.22 vs. 0.20, placebo 0.27 vs. 0.19).

Present results indicate that treatment with the SSRI escitalopram indeed has impact on emotion regulation in a tertiary IBS population with comorbid panic disorder. This impacts predominantly connections between mood nodes and foremost anxiety. The increased connectivity and node strengths in combination with lower negative affect symptom scores possibly reflects healthier emotional regulation. A conceivable explanation for why this in turn causes a reduction in physical symptoms might be found in the light of the biased competition theory in psychosomatics: 'being more in touch with one's own emotions reduces the need for physical symptoms as a psychological regulator to prevent awareness of intolerable emotions' [23]. This could explain why we found no evident change in connectivity between mood and physical nodes, like we initially hypothesized, but that in spite of this there still was alleviation of physical symptoms. As mentioned earlier, Vork et al. showed a decrease in abdominal pain during escitalopram treatment in

this study population when assessed multiple times per day [26]. Additionally, they showed that when levels of anxiety are higher, there is a larger treatment effect of SSRIs on abdominal pain. Added to the present results, this possibly underlines a modulating effect of anxiety in the degree of physical symptoms, at least in an IBS population with comorbid panic disorder. Furthermore, our findings reflect also a possible pathway for SSRI effects, given that there is a clear impact of the SSRI on the 'anxious' node in the symptom network. Overall, this study adds value to psychosomatic and in particular to IBS research, to better understand why emotional (e.g., anxiety), sensational (e.g., abdominal pain) and behavioural (i.e., functional intestinal symptoms) complaints are related with regard to daily life's stress experiences [20].

4.1. Strengths & limitations

The present study has several strengths. First, ESM data yields multiple momentary assessments per day and this makes the study less vulnerable to recall bias. Furthermore, it has the potential to detect within-subject changes with high sensitivity [26,27]. Second, the use of RCT data enabled us to look at the treatment effect over time and additionally to compare it with a control group. Third, including mood as well as physical symptoms gives additional insight into the dynamics of the complete spectrum of the symptomatology in IBS. Finally, using a well-characterized tertiary IBS population has the advantage of a more homogenous population and could give a clearer insight into specific symptom dynamics. On the other hand, one has to be careful generalizing the results of this study to a broader IBS population.

The current study also has several limitations. First, only a small number of subjects completed sufficient momentary assessments, resulting in limited power and an imbalance in sample size between the groups. This is partly due to the high test burden of the experience sampling method [46]. A part of the limited power is overcome by taking into account multiple repeated measurements for each patient, which especially increases power to detect changes within subjects over time. However, despite the high number of observations the additional power is limited for some variables because the intraclass correlation was high. Second, there were some baseline differences between the groups which may have influenced the results. The sample from the escitalopram group was on average 12.5 years older. Also, some of the symptom scores were different at baseline, most prominently for 'anxious' (mean symptom score (SD) at baseline; escitalopram 1.47 (1.04), placebo 2.07 (1.40) on the 7-point scale). The rest of the baseline scores were quite similar. With regard to centrality, there were also a few baseline differences, that is total network connectivity (escitalopram 9.79, placebo 6.41, $p = 0.28$). Additionally, node strength of 'relaxed' differed significantly at baseline (escitalopram 1.97, placebo 0.73, $p = 0.021$). Only 1 out of 100 connections was significantly different at baseline, namely happy-irritated (escitalopram 0.30, placebo -0.02 , $p = 0.029$). Unfortunately, in network analyses it is not possible to correct for baseline differences, because network analysis consists of multiple regression coefficients within a study group per timepoint. Comparisons between timepoints or between study groups are performed using permutations which are univariate. When all baseline values and connections would have been similar, we would expect to find similar results. Because we evaluated general patterns, we do not expect baseline differences on individual connections or individual node centrality measures to have influenced the results. The difference in total network connectivity at baseline required more caution with interpretation of the present results. However, we do not expect that absence of this baseline difference would have changed the pattern between 3 and 6 months showing an increase in total connectivity for the escitalopram group opposed to a decrease in the placebo group. Nevertheless, replication of the present results is needed. A third limitation was that there was multiple testing. In the network analysis, 600 regression coefficients were calculated and 300 differences between groups were tested. Therefore, there is multiple testing and the networks

and statistical significances should be cautiously interpreted. An option is to correct for multiple testing (e.g., using Bonferroni), but these, in turn, would lead to too many false negatives [47,48]. In our case, with a total of 990 tests (600 connections, 300 differences, 30 node strengths, 30 outdegrees and 30 indegrees) this would result in an alpha of $0.05/990 = 0.000051$. For which permutation analysis with 3000 permutations is not accurate enough.

4.2. Conclusion

To our knowledge, this is the first study in IBS patients with comorbid panic disorder, that assesses symptom interrelations and centrality after 6 months of SSRI treatment, compared to placebo. The present results suggest SSRI's impact on emotion regulation networks compared with placebo, foremost influencing anxiety centrality in the symptom network. The differences in the networks did not evidently consist of changes in the connections between negative affect and physical symptoms. However, physical symptom scores ameliorated after treatment, possibly as a result of healthier emotion regulation. Additionally, our findings add to previous research reporting increased symptom network connectivity after symptom severity decreased in individual patients. Finally, this study shows a potential role of ESM to evaluate the effect of momentary factors that possibly modulate symptom formation and treatment response. This study demonstrates the potential of ESM and network analysis in studying symptom dynamics in the field of psychosomatics, calling for further research with larger study populations using ESM. Additionally, to investigate if present findings are reproducible in a general IBS population, which may help identify in what subgroups there might be benefit from SSRI treatment. Furthermore, comparative studies (e.g. psychological therapy vs. SSRI) could further improve our understanding of symptom networks in IBS and the effect of different treatments.

Disclosure statement

AM has received a ZON MW, The Netherlands Organization for Health Research and Development, health care efficiency grant to evaluate efficacy of peppermint oil in IBS. AM has received an unrestricted research grant from Will Pharma S.A. and research funding from Allegan and Grünenthal on IBS topics. AM has given scientific advice to Bayer (topic: IBS) to Kyowa Kirin (topic: constipation) and to Takeda (topic: gastroparesis). AM received funding from Pentax Europe GmbH. AM has received funding from the Dutch Cancer Society related to endoscopy and to colorectal polyps.

Funding sources

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

Author contributions

CL, JK, AM, JO, BR conceptualized this study. ZM, LV, JK and CL collected the data and constructed the database. DK and MD performed the statistical analyses. DK drafted the manuscript under supervision of JK, CL and MD. All authors critically reviewed, provided feedback and approved the manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jpsychores.2020.110351>.

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