A body-mind map

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Symptom-specific effects of combined therapy versus psychotherapy in the treatment of mild to moderate depression: a network approach

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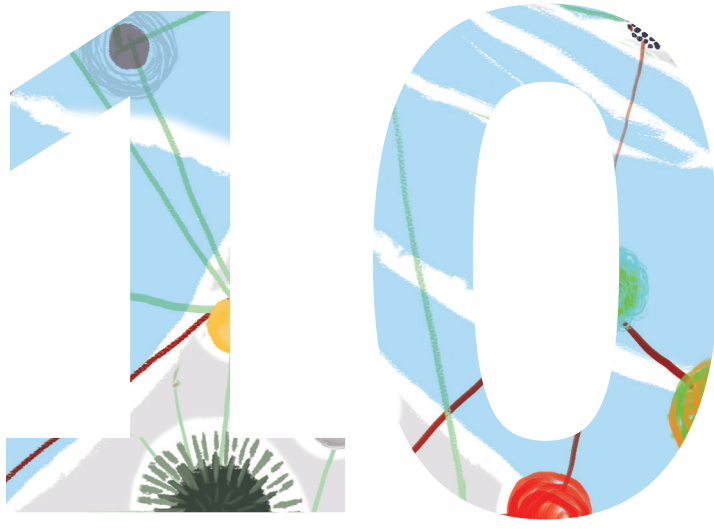


A number of studies have reported that adding pharmacotherapy to psychotherapy has no or only small advantages in the treatment of mild to moderate depression [364-366]. These studies have used sum scores of depression rating scales as effect parameters [364-366]. However, as individual items on these scales have recently been shown to respond differentially to pharmacotherapy compared to placebo [91], effects of an addition of pharmacotherapy to psychotherapy may only be detectable by focusing on individual depressive symptoms.

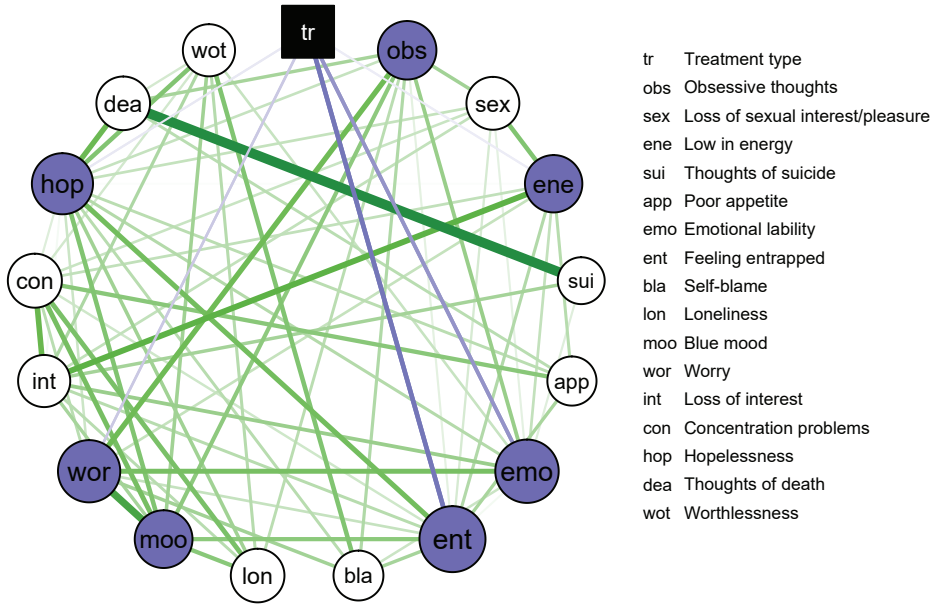
Previous studies investigating treatment responses of individual depressive symptoms did not take into account the potential interrelatedness of these symptoms. For example, patients who become less self-blaming in response to treatment may also be more likely to experience reductions in feelings of worthlessness or blue mood. Tools to consider symptom interrelatedness are offered by the network approach, which conceptualizes depression as a system of associated symptoms [94]. Earlier network studies have demonstrated that depressive symptoms are differentially related to one another [94,237,267]; however, it remains unknown if similar association patterns exist among changes in these symptoms during treatment. Taking into account these relations in a network structure provides the opportunity to determine effects of adjunctive pharmacotherapy on specific symptoms while adjusting for responses of other symptoms. This enables a differentiation between *direct* symptom-specific effects (i.e., those independent of changes in other symptoms) and *indirect* symptom-specific effects (i.e., those mediated by changes in other symptoms).

This is the first study to determine the relative efficacy of psychotherapy versus combined therapy on individual depressive symptoms. Data were derived from a randomized controlled trial comparing short-term psychodynamic supportive psychotherapy (SPSP) and this therapy combined with pharmacotherapy in patients with mild to moderate depression [364]. Participants consisted of newly registered patients at two outpatient facilities in Amsterdam (the Netherlands) of age 18-65 years with a DSM-IV defined major depressive disorder of mild to moderate severity. SPSP involves an open patient-therapist dialogue that uses supportive and insight-facilitating techniques to address the emotional background of depression and was delivered in 16 sessions of 45 minutes within a 24-week period. In the combined condition, antidepressants were provided for 24 weeks according to a protocol with several steps in case of intolerance or inefficacy: first venlafaxine, followed by fluoxetine and finally nortriptyline. Sixteen depressive symptoms were assessed at baseline and after 24 weeks with the depression subscale of the Symptom Checklist-90. Analyses were conducted in a sample consisting of all patients who started with the treatment they were allotted to (psychotherapy: N=103, combined therapy: N=83; see the online supplementary material for the sample characteristics) and the last outcome carried forward method was applied. First, we focus on the relative

efficacy of psychotherapy versus combined therapy by using individual symptoms as effect parameters and, then, differentiate between direct and indirect effects by taking into account symptom interrelatedness in a network model.

Symptom-specific efficacy of psychotherapy versus combined therapy was investigated using independent sample T-tests with change scores (post- minus pre-treatment) of depressive symptoms as dependent variables. Combined therapy was significantly more effective than psychotherapy in decreasing the symptoms feeling entrapped [ent] (Cohen's d=0.55, p<.001), emotional lability [emo] (Cohen's d=0.47, p=.002), worry [wor] (Cohen's d=0.44, p=.003), hopelessness [hop] (Cohen's d=0.41, p=.006), obsessive thoughts [obs] (Cohen's d=0.34, p=.02), blue mood [moo] (Cohen's d=0.32, p=.03) and low in energy [ene] (Cohen's d=0.31, p=.04). The remaining nine symptoms showed similar responses to psychotherapy and combined therapy (see **Figure 1**).

Figure 1. Symptom-specific effects of psychotherapy versus combined therapy.



The type of treatment is represented by the square and depressive symptoms by circles. Relative effect sizes of psychotherapy versus combined therapy on specific symptoms (all in favor of combined therapy) are indicated by the size of circles and their level of significance by circle color (violet=significant; white=non-significant). Connections in the network model are represented by lines, of which the thickness if proportional to the strength of associations. Direct associations between the type of treatment and change scores of symptoms (all in favor of combined therapy) are indicated by violet lines and associations between change scores of symptoms (all positive) by green lines.

Then, we took into account symptom interrelatedness to differentiate between direct and indirect effects of the addition of pharmacotherapy to psychotherapy. An L1-regularized partial correlation network of treatment type and change scores of all depressive symptoms was estimated (the network estimation procedure and tests for parameter estimate accuracy are described in the supplementary material). **Figure 1** shows that changes in depressive symptoms during treatment were strongly related. The strongest association was found between thoughts of death [dea] and thoughts of suicide [sui] (partial correlation=0.49), indicating that persons with an improvement in thoughts of death [dea] during treatment were more likely to experience an improvement in thoughts of suicide [sui] as well. Treatment type [tr] showed the strongest direct connections to feeling entrapped [ent] (partial correlation=0.16) and emotional lability [emo] (partial correlation=0.11), and was weakly connected to worry [wor] (partial correlation=0.04), low in energy [ene] (partial correlation=0.01) and hopelessness [hop] (partial correlation=0.01). All connections were in favor of combined therapy, suggesting that this therapy targeted these particular symptoms directly.

Despite their significant responses to the addition of pharmacotherapy to psychotherapy in our first analysis, obsessive thoughts [obs] and blue mood [moo] were not directly connected to treatment type in the network, and worry [wor], low in energy [ene] and hopelessness [hop] showed only weak direct associations to this variable. Interestingly, the network revealed that these symptoms were related to changes in feeling entrapped [ent] and emotional lability [emo], which in turn were more strongly connected to the type of treatment. This suggests that the effect of adjunctive pharmacotherapy on obsessive thoughts [obs], blue mood [moo], worry [wor], low in energy [ene] and hopelessness [hop] may largely have been indirect and could have been mediated by changes in feeling entrapped [ent] and emotional lability [emo].

A strength of this study is that the trial included a fairly random and representative sample of patients with a mild to moderate depressive disorder in secondary care. Furthermore, we estimated the network structure using l1-regularization to prevent overfitting, which has been shown to adequately control for false positive associations. However, in our relatively small sample of 186 persons, small true positive associations could have been overlooked [238]. As baseline scores in our sample differed across symptoms, it is also important to note that higher baseline severity of symptoms was associated with stronger responses to adjunctive pharmacotherapy, which is in line with previous reports [365].

In conclusion, this study showed that combined therapy outperformed psychotherapy in the treatment of some depressive symptoms and not others. Although our results are exploratory rather than conclusive, they suggest that adjunctive pharmacotherapy targeted specific symptoms (e.g., feeling entrapped, emotional lability) directly and other symptoms (e.g., obsessive thoughts, hopelessness) indirectly. As direct effects

are independent of changes in other symptoms, our findings imply that adjunctive pharmacotherapy can effectuate improvements in directly targeted symptoms in all patients irrespective of changes in other symptoms. Indirectly targeted symptoms, in contrast, may respond to an addition of pharmacotherapy to psychotherapy, but only in patients improving on symptoms mediating these responses during treatment and, therefore, reporting these symptoms before treatment. If replicated, these insights may help clinicians to predict which patients could benefit from an addition of pharmacotherapy to psychotherapy [367].

Given the differential treatment responses across symptoms, we would like to encourage other researchers to analyze individual depressive symptoms as well as their interrelatedness. Network models are highly promising in this approach as they can be expanded with other psychiatric or physical symptoms (e.g., anxiety, nausea) to provide insight into secondary or side effects of a treatment independent of its effects on depressive symptoms. Furthermore, dynamic networks of depressive symptoms during various treatment stages could reveal that changes in specific symptoms are preceded by changes in other symptoms, which may inform on pathways underlying indirect responses of symptoms to a treatment [368].

SUPPLEMENTARY MATERIAL

Sample characteristics

A total of 186 patients were included in this study, of whom 103 received psychotherapy and 83 received combined therapy. Mean age of the sample was 35.4 (SD=10.8) years and 67.7% were female. No differences in sociodemographic or depression characteristics were found between the treatment groups (see **Supplementary Table 1**).

Network estimation method

An L1-regularized weighted network of the type of treatment (psychotherapy versus combined therapy) and change scores of all depressive symptoms was estimated and visualized with R-package qgraph (see **Supplementary Table 2** for the input correlation matrix) [241]. The network estimation technique calculated partial correlations for all pairs of variables, which indicate associations among symptoms while controlling for all other variables in the network. To prevent overfitting, an /1-penalty [239] was used to estimate possible networks with different levels of sparsity. The model with the best fit to the data was selected using the extended Bayesian information criterion (EBIC) [240] with hyperparameter y=0.5 [273]. This technique has been shown to yield adequate network structures [238,273,274].

Accuracy of the estimates in the network

To investigate the accuracy of estimated connections in the network, R-package bootnet [275] was used to calculate 95% confidence intervals around connection weights. Bootstrapped confidence intervals were calculated by drawing 10,000 bootstrap samples of the data and recalculating connection weights for each sample. Although these confidence intervals can inform on the precision of parameter estimates, it is important to stress that they should not be interpreted as a test for significance of a connection being different from zero as the /1-penalty already ensured that connections included in the network model were of sufficient strength [275]. **Supplementary Table 3** shows that the confidence intervals of associations in the network were rather wide and showed overlap, implying that connection weights should be interpreted with caution. Still, several connections were significantly stronger than others. The association between thoughts of suicide [sui] and thoughts of death [dea] (partial correlation coefficient=0.49, 95%CI=0.37-0.62), for example, was significantly stronger than all other associations in the network, except for the association between depressed mood [moo] and worry [wor] (partial correlation coefficient=0.33, 95%CI=0.23-0.44). This indicates that the association between thoughts of suicide [sui] and thoughts of death [dea] is reliably one of the strongest in the network.

Supplementary Table 1. Sample characteristics at baseline

	Psychotherapy N=103	Combined therapy N=83	p
	N (%)/mean (SD)	N (%)/mean (SD)	
Sociodemographics			
Age	35.5 (11.0)	35.3 (10.6)	.94
Female	70 (68.0%)	56 (67.5%)	1.00
Education			.54
Low	13 (12.6%)	11 (13.3%)	
Middle	36 (35.0%)	35 (42.2%)	
High	54 (52.4%)	37 (44.6%)	
Depression characteristics			
Sum score of all symptoms	49.9 (8.9)	49.0 (9.5)	.49
Individual depressive symptoms			
Obsessive thoughts [obs]	3.6 (0.9)	3.5 (1.0)	.25
Loss of sexual interest/pleasure [sex]	2.6 (1.4)	2.7 (1.4)	.83
Low in energy [ene]	3.8 (1.1)	3.9 (1.0)	.44
Thoughts of suicide [sui]	1.7 (0.9)	1.6 (0.9)	.44
Poor appetite [app]	1.9 (1.2)	2.0 (1.2)	.68
Emotional lability [emo]	3.0 (1.3)	3.2 (1.4)	.47
Feeling entrapped [ent]	3.2 (1.2)	3.3 (1.2)	.49
Self-blame [bla]	3.2 (1.2)	2.9 (1.3)	.08
Loneliness [lon]	3.3 (1.2)	3.1 (1.2)	.20
Blue mood [moo]	3.8 (0.9)	3.8 (1.0)	.96
Worry [wor]	4.1 (0.8)	4.1 (0.9)	.58
Loss of interest [int]	3.3 (1.1)	3.1 (1.2)	.30
Concentration problems [con]	3.4 (1.1)	3.3 (1.1)	.44
Hopelessness [hop]	3.6 (1.1)	3.5 (1.1)	.62
Thoughts of death [dea]	2.1 (1.2)	2.1 (1.2)	.63
Worthlessness [wot]	3.3 (1.2)	3.2 (1.2)	.64

P-values are based on chi square analyses for categorical variables and independent t-tests for continuous variables.

Supplementary Table 2. Correlations between the type of treatment and change scores of depressive symptoms

	Treatment type [tr]	Obsessive thoughts [obs]	Loss of sexual interest/ pleasure [sex]	Low in energy [ene]	Thoughts of suicide [sui]	Poor appetite [app]	Emotional lability [emo]	Feeling entrapped [ent]
Treatment type [tr]	1.00	0.21	0.12	0.19	0.02	0.06	0.28	0.33
Obsessive thoughts [obs]	0.21	1.00	0.32	0.32	0.26	0.24	0.46	0.42
Loss of sexual interest/ pleasure [sex]	0.12	0.32	1.00	0.35	0.09	0.10	0.25	0.28
Low in energy [ene]	0.19	0.32	0.35	1.00	0.13	0.28	0.35	0.39
Thoughts of suicide [sui]	0.02	0.26	0.09	0.13	1.00	0.09	0.24	0.22
Poor appetite [app]	0.06	0.24	0.10	0.28	0.09	1.00	0.20	0.33
Emotional lability [emo]	0.28	0.46	0.25	0.35	0.24	0.20	1.00	0.38
Feeling entrapped [ent]	0.33	0.42	0.28	0.39	0.22	0.33	0.38	1.00
Self-blame [bla]	0.07	0.40	0.20	0.21	0.20	0.18	0.34	0.40
Loneliness [lon]	0.13	0.43	0.16	0.28	0.21	0.26	0.34	0.39
Blue mood [moo]	0.20	0.59	0.29	0.37	0.29	0.29	0.46	0.58
Worry [wor]	0.27	0.60	0.28	0.39	0.15	0.20	0.53	0.50
Loss of interest [int]	0.11	0.34	0.32	0.52	0.33	0.25	0.44	0.46
Concentration problems [con]	0.14	0.44	0.30	0.42	0.19	0.37	0.35	0.46
Hopelessness [hop]	0.25	0.50	0.30	0.37	0.33	0.34	0.45	0.57
Thoughts of death [dea]	0.13	0.38	0.10	0.19	0.62	0.27	0.25	0.22
Worthlessness [wot]	0.11	0.36	0.21	0.34	0.24	0.14	0.36	0.39

The correlation matrix consists of polyserial correlations between Treatment [tr] and change scores of depressive symptoms and Pearson correlations between change scores of depressive symptoms.

Self-blame [bla]	Loneliness [lon]	Blue mood [moo]	Worry [wor]	Loss of interest [int]	Concentration problems [con]	Hopelessness [hop]	Thoughts of death [dea]	Worthlessness [wot]
0.07	0.13	0.20	0.27	0.11	0.14	0.25	0.13	0.11
0.40	0.43	0.59	0.60	0.34	0.44	0.50	0.38	0.36
0.20	0.16	0.29	0.28	0.32	0.30	0.30	0.10	0.21
0.21	0.28	0.37	0.39	0.52	0.42	0.37	0.19	0.34
0.20	0.21	0.29	0.15	0.33	0.19	0.33	0.62	0.24
0.18	0.26	0.29	0.20	0.25	0.37	0.34	0.27	0.14
0.34	0.34	0.46	0.53	0.44	0.35	0.45	0.25	0.36
0.40	0.39	0.58	0.50	0.46	0.46	0.57	0.22	0.39
1.00	0.40	0.43	0.44	0.32	0.34	0.43	0.20	0.43
0.40	1.00	0.57	0.44	0.45	0.53	0.50	0.25	0.42
0.43	0.57	1.00	0.72	0.56	0.63	0.64	0.37	0.52
0.44	0.44	0.72	1.00	0.48	0.53	0.55	0.24	0.43
0.32	0.45	0.56	0.48	1.00	0.59	0.48	0.35	0.43
0.34	0.53	0.63	0.53	0.59	1.00	0.50	0.30	0.42
0.43	0.50	0.64	0.55	0.48	0.50	1.00	0.50	0.52
0.20	0.25	0.37	0.24	0.35	0.30	0.50	1.00	0.32
0.43	0.42	0.52	0.43	0.43	0.42	0.52	0.32	1.00

Supplementary Table 3. Partial correlations and their 95% confidence intervals between the type of treatment and change scores of depressive symptoms

	Treatment type [tr]	Obsessive thoughts [obs]	Loss of sexual interest/ pleasure [sex]	Low in energy [ene]	Thoughts of suicide [sui]	Poor appetite [app]	Emotional lability [emo]	Feeling entrapped [ent]
Treatment type [tr]	-	0.00 (-0.08-0.08)	0.00 (-0.08-0.08)	0.00 (-0.09-0.10)	0.00 (0.08-0.08)	0.00 (0.07-0.07)	0.11 (-0.03-0.25)	0.16 (0.01-0.31)
Obsessive thoughts [obs]	0.00 (-0.08-0.08)	-	0.10 (0.00-0.21)	0.00 (-0.07-0.07)	0.00 (-0.04-0.04)	0.00 (-0.07-0.07)	0.12 (-0.01-0.25)	0.01 (-0.07-0.10)
Loss of sexual interest/ pleasure [sex]	0.00 (-0.08-0.08)	0.10 (0.00-0.21)	-	0.16 (0.04-0.29)	0.00 (-0.02-0.02)	0.00 (-0.04-0.04)	0.01 (-0.07-0.09)	0.02 (-0.06-0.11)
Low in energy [ene]	0.01 (-0.09-0.10)	0.00 (-0.07-0.07)	0.16 (0.04-0.29)	-	0.00 (-0.02-0.02)	0.07 (-0.06-0.20)	0.05 (-0.05-0.15)	0.07 (-0.02-0.17)
Thoughts of suicide [sui]	0.00 (-0.08-0.08)	0.00 (-0.04-0.04)	0.00 (-0.02-0.02)	0.00 (-0.02-0.02)	-	0.00 (-0.04-0.04)	0.02 (-0.05-0.08)	0.00 (-0.03-0.03)
Poor appetite [app]	0.00 (0.07-0.07)	0.00 (-0.07-0.07)	0.00 (-0.04-0.04)	0.07 (-0.06-0.20)	0.00 (-0.04-0.04)	-	0.00 (-0.05-0.05)	0.09 (-0.01-0.19)
Emotional lability [emo]	0.11 (-0.03-0.25)	0.12 (-0.01-0.25)	0.01 (-0.07-0.09)	0.05 (-0.05-0.15)	0.02 (-0.05-0.08)	0.00 (-0.05-0.05)	-	0.00 (-0.07-0.08)
Feeling entrapped [ent]	0.16 (0.01-0.31)	0.01 (-0.07-0.10)	0.02 (-0.06-0.11)	0.07 (-0.02-0.17)	0.00 (-0.03-0.03)	0.09 (-0.01-0.19)	0.00 (-0.07-0.08)	-
Self-blame [bla]	0.00 (-0.08-0.08)	0.08 (-0.03-0.18)	0.00 (-0.07-0.07)	0.00 (-0.03-0.03)	0.00 (-0.06-0.06)	0.00 (-0.05-0.05)	0.04 (-0.05-0.13)	0.09 (-0.02-0.21)
Loneliness [lon]	0.00 (-0.05-0.05)	0.06 (-0.04-0.16)	0.00 (-0.03-0.03)	0.00 (-0.03-0.03)	0.00 (-0.04-0.04)	0.00 (-0.08-0.08)	0.00 (-0.06-0.06)	0.00 (-0.06-0.06)
Blue mood [moo]	0.00 (-0.03-0.03)	0.14 (0.03-0.25)	0.00 (-0.04-0.04)	0.00 (-0.02-0.02)	0.00 (-0.04-0.04)	0.00 (-0.04-0.04)	0.00 (-0.05-0.05)	0.14 (0.03-0.26)
Worry [wor]	0.04 (-0.06-0.14)	0.21 (0.08-0.35)	0.00 (-0.06-0.06)	0.05 (-0.02-0.12)	0.00 (-0.04-0.04)	0.00 (-0.02-0.02)	0.19 (0.07-0.31)	0.05 (-0.04-0.13)
Loss of interest [int]	0.00 (-0.06-0.06)	0.00 (-0.02-0.02)	0.05 (-0.05-0.15)	0.25 (0.14-0.37)	0.10 (0.01-0.19)	0.00 (-0.04-0.04)	0.12 (-0.01-0.24)	0.07 (-0.05-0.19)
Concentration problems [con]	0.00 (-0.04-0.04)	0.01 (-0.07-0.08)	0.04 (-0.05-0.13)	0.05 (-0.06-0.17)	0.00 (-0.01-0.01)	0.15 (0.03-0.27)	0.00 (-0.03-0.03)	0.03 (-0.06-0.13)
Hopelessness [hop]	0.01 (-0.08-0.09)	0.04 (-0.04-0.13)	0.05 (-0.03-0.12)	0.00 (-0.07-0.07)	0.00 (-0.04-0.04)	0.06 (-0.03-0.16)	0.07 (-0.03-0.17)	0.20 (0.10-0.30)
Thoughts of death [dea]	0.00 (-0.06-0.06)	0.09 (0.00-0.18)	0.00 (-0.03-0.03)	0.00 (-0.02-0.02)	0.49 (0.37-0.62)	0.06 (-0.03-0.16)	0.00 (-0.03-0.03)	0.00 (-0.03-0.03)
Worthlessness [wot]	0.00 (-0.05-0.05)	0.00 (-0.06-0.06)	0.00 (-0.04-0.04)	0.05 (-0.04-0.14)	0.00 (-0.05-0.05)	0.00 (-0.06-0.06)	0.04 (-0.06-0.15)	0.00 (-0.06-0.06)

Self-blame [bla]	Loneliness [lon]	Blue mood [moo]	Worry [wor]	Loss of interest [int]	Concentration problems [con]	Hopelessness [hop]	Thoughts of death [dea]	Worthlessness [wot]
0.00 (-0.08-0.08)	0.00 (-0.05-0.05)	0.00 (-0.03-0.03)	0.04 (-0.06-0.14)	0.00 (-0.06-0.06)	0.00 (-0.04-0.04)	0.01 (-0.08-0.09)	0.00 (-0.06-0.06)	0.00 (-0.05-0.05)
0.08 (-0.03-0.18)	0.06 (-0.04-0.16)	0.14 (0.03-0.25)	0.21 (0.08-0.35)	0.00 (-0.02-0.02)	0.01 (-0.07-0.08)	0.04 (-0.04-0.13)	0.09 (0.00-0.18)	0.00 (-0.06-0.06)
0.00 (-0.07-0.07)	0.00 (-0.03-0.03)	0.00 (-0.04-0.04)	0.00 (-0.06-0.06)	0.05 (-0.05-0.15)	0.04 (-0.05-0.13)	0.05 (-0.03-0.12)	0.00 (-0.03-0.03)	0.00 (-0.04-0.04)
0.00 (-0.03-0.03)	0.00 (-0.03-0.03)	0.00 (-0.02-0.02)	0.05 (-0.02-0.12)	0.25 (0.14-0.37)	0.05 (-0.06-0.17)	0.00 (-0.07-0.07)	0.00 (-0.02-0.02)	0.05 (-0.04-0.14)
0.00 (-0.06-0.06)	0.00 (-0.04-0.04)	0.00 (-0.04-0.04)	0.00 (-0.04-0.04)	0.10 (0.01-0.19)	0.00 (-0.01-0.01)	0.00 (-0.04-0.04)	0.49 (0.37-0.62)	0.00 (-0.05-0.05)
0.00 (-0.05-0.05)	0.00 (-0.08-0.08)	0.00 (-0.04-0.04)	0.00 (-0.02-0.02)	0.00 (-0.04-0.04)	0.15 (0.03-0.27)	0.06 (-0.03-0.16)	0.06 (-0.03-0.16)	0.00 (-0.06-0.06)
0.04 (-0.05-0.13)	0.00 (-0.06-0.06)	0.00 (-0.05-0.05)	0.19 (0.07-0.31)	0.12 (-0.01-0.24)	0.00 (-0.03-0.03)	0.07 (-0.03-0.17)	0.00 (-0.03-0.03)	0.04 (-0.06-0.15)
0.09 (-0.02-0.21)	0.00 (-0.06-0.06)	0.14 (0.03-0.26)	0.05 (-0.04-0.13)	0.07 (-0.05-0.19)	0.03 (-0.06-0.13)	0.20 (0.10-0.30)	0.00 (-0.03-0.03)	0.00 (-0.06-0.06)
-	0.10 (-0.01-0.21)	0.00 (-0.05-0.05)	0.10 (-0.01-0.21)	0.00 (-0.05-0.05)	0.00 (-0.05-0.05)	0.07 (-0.04-0.18)	0.00 (-0.03-0.03)	0.17 (0.05-0.28)
0.10 (-0.01-0.21)	-	0.15 (0.03-0.26)	0.00 (-0.04-0.04)	0.06 (-0.05-0.18)	0.18 (0.04-0.32)	0.10 (-0.02-0.23)	0.00 (-0.02-0.02)	0.07 (-0.05-0.19)
0.00 (-0.05-0.05)	0.15 (0.03-0.26)	-	0.33 (0.22-0.44)	0.09 (-0.01-0.20)	0.19 (0.06-0.32)	0.17 (0.06-0.27)	0.00 (-0.04-0.04)	0.10 (-0.01-0.22)
0.10 (-0.01-0.21)	0.00 (-0.04-0.04)	0.33 (0.22-0.44)	-	0.00 (-0.07-0.07)	0.06 (-0.03-0.15)	0.04 (-0.05-0.12)	0.00 (-0.02-0.02)	0.00 (-0.06-0.06)
0.00 (-0.05-0.05)	0.06 (-0.05-0.18)	0.09 (-0.01-0.20)	0.00 (-0.07-0.07)	-	0.23 (0.10-0.36)	0.00 (-0.05-0.06)	0.02 (-0.05-0.08)	0.08 (-0.03-0.19)
0.00 (-0.05-0.05)	0.18 (0.04-0.32)	0.19 (0.06-0.32)	0.06 (-0.03-0.15)	0.23 (0.10-0.36)	-	0.02 (-0.06-0.09)	0.00 (-0.04-0.04)	0.03 (-0.06-0.12)
0.07 (-0.04-0.18)	0.10 (-0.02-0.23)	0.17 (0.06-0.27)	0.04 (-0.05-0.12)	0.00 (-0.05-0.06)	0.02 (-0.06-0.09)	-	0.22 (0.12-0.31)	0.16 (0.05-0.27)
0.00 (-0.03-0.03)	0.00 (-0.02-0.02)	0.00 (-0.04-0.04)	0.00 (-0.02-0.02)	0.02 (-0.05-0.08)	0.00 (-0.04-0.04)	0.22 (0.12-0.31)	-	0.03 (-0.04-0.10)
0.17 (0.05-0.28)	0.07 (-0.05-0.19)	0.10 (-0.01-0.22)	0.00 (-0.06-0.06)	0.08 (-0.03-0.19)	0.03 (-0.06-0.12)	0.16 (0.05-0.27)	0.03 (-0.04-0.10)	-