Supplementary Material

Introducing Network Intervention Analysis to investigate sequential, symptom-specific treatment effects: A demonstration in co-occurring insomnia and depression.

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Supplementary Methods and Results

1. Sample characteristics and intervention

1.1. Sample characteristics

A total of 104 patients (82% female), with a mean±*SD* age of 45.99±12.32 years, fulfilled self-report DSM-5 criteria of insomnia, and at least subclinical depression (>4 on the PHQ-9). Participants suffered from insomnia for around 10 years (*M*±*SD* = 9.79±9.91). At baseline, depression scores ranged from 5-22 (*M*±*SD* = 10.19±3.90), from mild (PHQ-9>4) to severe (PHQ-9>19), see also Supplementary Table S1. The majority of participants (60%) were highly educated. Participants were recruited online and signed informed consent before randomisation to either CBTI (*N*=52) or a sleep diary monitoring control group (*N*=52).

1.2. Intervention

The online CBTI intervention i-Sleep encompasses five modules: (1) sleep hygiene/lifestyle advice, (2) stimulus control and sleep restriction therapy, (3) relaxation techniques, (4) cognitive exercises on dysfunctional thoughts about sleep, and (5) relapse prevention (Van der Zweerde et al., 2016). Participants received online guidance on a weekly basis from a coach (Master students clinical psychology). The study design is shown in Supplementary Figure S1. For details, please see Van der Zweerde et al., 2018.

2. Network estimation and LASSO regularization

2.1 Network estimation

For the Network Intervention Analysis (NIA) we selected a Mixed Graphical Model (MGM), implemented in the R-package mgm (Haslbeck & Waldorp, 2018a), in which we included all symptoms as continuous, and treatment as binary (0: no treatment, 1: treatment). Networks were estimated on the available data for each assessment, resulting in slightly varying sample size (100, 100, 97, 92, 90, 84, 90, 87, 86, 92). In estimating the networks, LASSO regularization was applied to reduce the inclusion of spurious edges, resulting in networks that are easier to interpret and have higher specificity (Epskamp & Fried, 2016; more details on the regularization in section 2.2). Because the network analyses require the estimation of many parameters, we performed robustness analyses

to assess the accuracy of the estimated edge weights (Epskamp, Borsboom, & Fried, 2017), see Supplementary Methods and Results 3.

In addition, we estimated the averaged networks for the pre-treatment assessments (T0-T1; Figure S2), for the treatment assessments (T2-T6; Figure S3), and for the post-treatment assessments (T7-T9; Figure S4).

2.2. LASSO regularization

The amount of regularization that is applied depends on the LASSO tuning parameter: a low tuning parameter omits only some edges from the network, likely resulting in the inclusion of some spurious edges; a high tuning parameter omits many edges, likely excluding some true edges from the network. Thus, there is a trade-off between the exclusion of edges and the number of false positive and false negative edges in the network – which is controlled by the tuning parameter. The tuning parameter can be selected using either cross-validation or by minimizing the Extended Bayesian Information Criterion (EBIC). For the regularized networks presented in the main text we adopted the default setting of *mgm* and used cross-validation to select the tuning parameter using a gamma hyperparameter of 0.25. We also estimated the networks using EBIC in selecting the tuning parameter. The resulting networks are shown in Supplementary Figures S5-S15.

Generally, using the EBIC to select the tuning parameter results in sparser networks compared to cross-validation. Our results show the same pattern, and sparser networks were estimated when using the EBIC. Importantly, the EBIC did retrieve conditional dependence relations between the binary treatment variable and the sleep problems *difficulty maintaining sleep* and *early morning awakenings*.

We additionally investigated the extent to which the use of LASSO regularization might have altered our interpretations of direct and indirect effects, by putting smaller effects to zero. We did so by estimating all networks using ridge regression. Unlike lasso regularization, ridge regression does not put parameters exactly to zero. Therefore, all estimated direct effects will be present in the network, which allows us to investigate whether there are direct treatment effects that were put to zero by the LASSO regularization. Due to size restrictions of the Supplementary Materials, we did not include the ten ridge regularized networks. We can provide these upon request. As expected, the ridge regularized networks include more direct treatment effects than are present in the LASSO regularized networks. While this indicates that some direct effects were indeed set to zero, it is important to note that during and after treatment (T2-T9), there are only three symptoms that were directly and negatively associated to the treatment allocation variable in the ridge regularized networks but were not in the LASSO regularized networks: *noticeability of impaired quality of life* (T6), *fatigue* (T8), and *feelings of worthlessness* (T4). During and after treatment, there were other symptoms that were directly and positively related to treatment, indicating favourable treatment "effects" for the control group: *loss of interest* (T2), *difficulty initiating sleep* (T2), *concentration problems* (T3, T4), *noticeability of impaired quality of life* (T3), *feelings of worthlessness* (T3, T6, T8), and *depressed mood* (T3, T7). Moreover, the ridge regularized networks included treatment "effects"

for the pre-treatment assessment weeks, whereas the LASSO regularized network rightfully did not include these effects.

In sum, the ridge regularized networks include direct treatment "effects" that were put to zero in the LASSO regularized networks. However, these associations more likely reflect slight mean differences between groups rather than actual treatment effects. Given the main objective of NIA to explore possible treatment targets, we would argue that LASSO regularization fits this purpose by selecting the most important edges in the network.

3. Edge weight accuracy

We used the *resample()* function implemented in the *mgm* package to evaluate the edge weight accuracy of the models reported in the main text. For each network model, we ran a hundred bootstrap samples for which we fitted the model. We subsequently plotted the resulting sampling distribution of all edges using the function *plotRes()*, also implemented in the *mgm* package. The plot shows the 5% and 95% quantiles of the sampling distribution and the proportion of estimates whose absolute values were larger than zero. Notably, because we used LASSO regularization in estimating the networks, the edge weights and their sampling distribution are biased towards zero. As a result, the 5% and 95% quantiles might include zero, whereas the corresponding 95% confidence interval does not. If the 5% and 95% quantiles do not contain zero, this ascertains that the 95% confidence interval does not either. For a more detailed explanation, see Epskamp, Borsboom, & Fried (2017). The resulting sampling distributions are shown in Supplementary Figures S15-S24. For example, in the estimated network of week 1, shown in Supplementary Figure S15, the edge weight between *depressed mood* and *feelings of worthlessness* was larger than zero in 100% of the bootstrap samples, and its 5% and 95% quantiles lie around 0.30 and 0.60.

4. Visualizing effect on symptom severity in node sizes

To visualize the differences in symptom severity between treatment and control condition, we first standardized the item-means for each assessment to the pooled baseline mean and standard deviation. After standardization, negative values indicate a decrease in symptom severity compared to baseline level, while positive values indicate an increase in symptom severity compared to baseline level. We computed the standardized item-means for the treatment and control group separately. Comparing the standardized item-means of the treatment group to the control group gives us an indication of the effect of CBTI on the severity of specific symptoms. Any reduction in symptom severity in the treatment group *over and above* the reduction in symptom severity in the control group is likely due to the CBTI treatment. Specifically, we visualized the improvement in symptom severity in the treatment group *compared with* the improvement in symptom severity in the control group. For example, on the post-assessment, the average *difficulty initiating sleep* was $M = 1.60$ in the control group and $M = 1.11$ in the treatment group, respectively. Standardized to the overall $M \pm SD$ of $2.25 \pm$

1.53 on difficulty initiating sleep during baseline, there is a reduction of -0.43 and -0.75, respectively. Thus, the treatment group improved -0.32 more than the control group, which is visualized in a smaller node size representing reduced symptom severity. Because we have accounted for the improvement in the control group, this improvement can be interpreted as induced by CBTI treatment. The raw item means are given in Supplementary Table S2 and the standardized scores and differences can be found in Supplementary Table S3.

5. Exploring the relation between predictability and variance of the symptoms

The predictability (i.e., proportion of explained variance; Haslbeck & Waldorp, 2018b) of the symptoms increased over the course of treatment, see Supplementary Table S4. We explored whether this increase might be explained by increased or decreased variability in the symptom scores over the course of treatment. To investigate this possibility, we first computed the observed variance in the symptoms for each week and evaluated its changes over time. The variance did not systematically increase or decrease over time. For example, compared to baseline, the variance at post-assessment increased for 8 symptoms (maximum increase of 0.50) and decreased for 7 symptoms (maximum decrease of 0.31), with an average difference of 0.04. Second, for each variable, we correlated the variance at each assessment to the observed predictability, which was, on average, only r=0.14 (range: -0.58 to 0.93). This correlation was significant for only three variables ('worry about sleep', 'loss of interest', and 'suicidal thoughts'; of which only the first two survived Bonferroni corrections). Thus, while the predictability consistently increased for all symptoms but two ('feelings of worthlessness' and 'depressed mood'), the observed variance did not show such a systematic pattern. Because the range of the correlation between the variance and predictability is quite large for some symptoms, we finally investigated whether this absolute correlation was related to the amount of increase in predictability. If this would be the case, then this would indicate that there might be a relationship between variance and predictability, but only for those variables that show the largest increase. The small correlation of r=0.14 (t(13)=0.53, p=0.60) indicated that this was not the case. Taken together, these results indicate that the increase in predictability does not simply reflect an increase or decrease in variance.

6. Baseline differences

There were no baseline differences in symptom severity between the treatment groups (all p>0.26) except for 'loss of interest' (t(98.3)=2.31, p=0.02; non-significant after Bonferroni corrections). It is important to note that for the current study the participants were randomly allocated to either the treatment or control condition. Group membership was thus not based on baseline severity. Nonetheless, to ensure that the treatment effect was not confounded by baseline differences between groups, we repeated the analyses excluding the symptom 'loss of interest', that differed between groups at baseline. Due to size restrictions of the Supplementary Materials, we did not include the ten

networks without *loss of interest* as Supplementary Figures. We can provide these upon request. None of the estimated treatment effects changed when omitting 'loss of interest' from the network estimations. In sum, because of randomization the two groups did not differ in baseline symptom severity, except for one symptom, but this difference did not affect the estimated treatment effects.

7. Exploring the effect of baseline symptom severity on the estimated treatment effects

Symptoms that are higher in severity at baseline have a higher probability to go down during treatment. In previous research (e.g., Hieronymous et al., 2016) it was seen that the treatment effects were larger for symptoms with higher baseline severity. We investigated whether baseline symptom severity explained the differential effects of cognitive behavioural therapy for insomnia (CBTI) on the insomnia symptoms. First, we correlated the average baseline insomnia symptom severity to the treatment effect (time*condition Cohen's d effect sizes, given in Supplementary Table S5), which was nonsignificant, r=0.63, t(5)=1.81, p=0.13. Second, we investigated, for each participant, which of the insomnia symptoms was reported to be most severe at baseline. We listed all symptoms that were indicated to be most severe, in case the highest severity score was given to multiple symptoms. For each of the insomnia symptoms, we then computed the proportion of participants for which this symptom was worst at baseline, shown in the Figure below. The rank-order of these proportions was not associated to the rank-order of the Cohen's d effect sizes (ρ=-0.14, S=64, p=0.78). Both results indicated that, although the symptom severity affects the probability of the symptom severity to go down during treatment, it seems unlikely that this explains the differential effect of treatment on the symptoms.

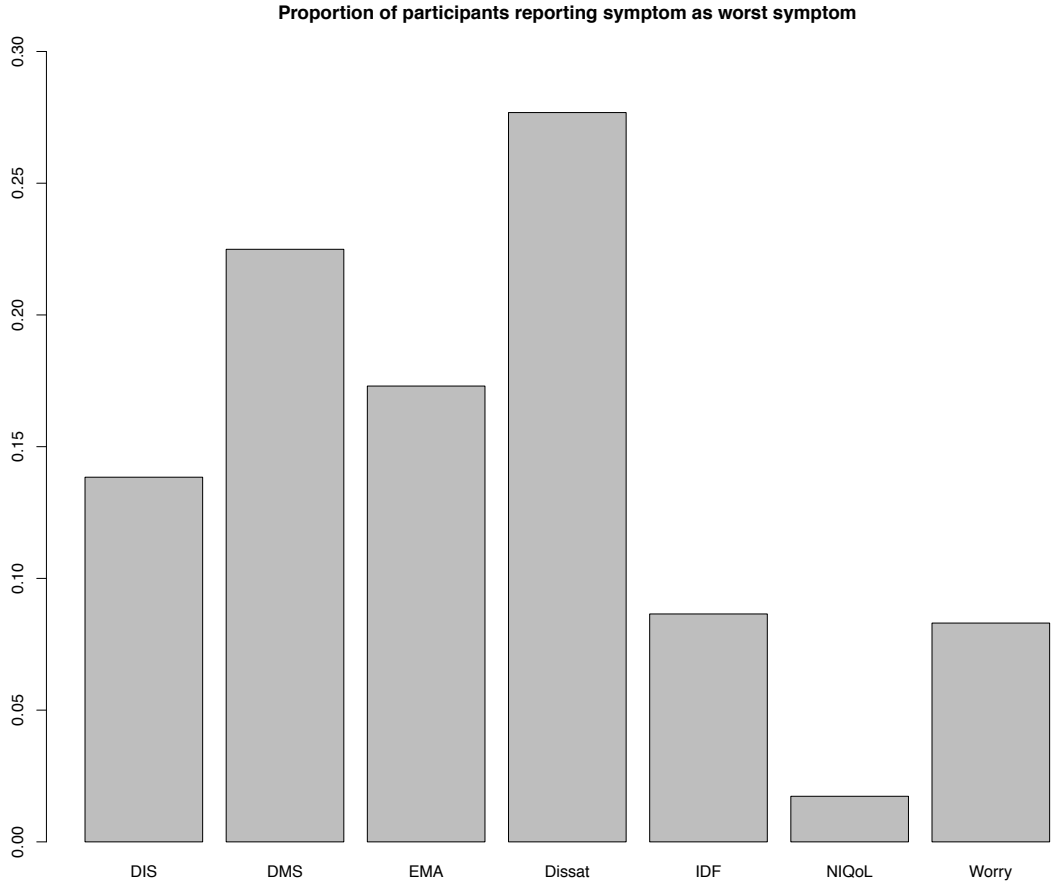

Figure. Proportion of participants that indicated a specific symptom to be most severe at baseline. For each participant, we listed the symptom(s) that were indicated to be most severe at baseline. For each symptom, we computed the proportion of participants that listed this symptom as most severe, which is shown in this Figure. The time*condition Cohen's *d* effect sizes of the symptoms were: 0.38, 1.59, 1.37, 1.28, 0.92, 0.84, 1.46, respectively. The rank-order correlation of the between the proportion of participants listing a symptom as most severe and the Cohen's *d* effect size was ρ=-0.14 (S=64, *p*=0.78).

8. Adjacency matrices

For reproducibility, the adjacency matrices of the regularized networks can be shared upon request.

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Supplementary Table 1

Table S3. Baseline and post-assessment M(±SD) in Treatment and Control group.

		N	Baseline *M(±SD)*	*N*	Post-assessment *M(±SD)*
PHQ-9	T	52	10.1 (4.19)	45	4.20 (3.57)
	C	52	9.54 (3.53)	47	7.89 (4.67)
PHQ-WS	T	52	7.58 (3.99)	45	3.07 (3.09)
	C	52	7.10 (3.44)	47	5.74 (4.22)
ISI	T	52	19.16 (3.76)	45	9.24 (5.41)
	C	52	18.83 (3.19)	47	17.09 (5.17)

Note. C = Control, sleep monitoring no treatment condition; T = Treatment; i-Sleep online CBTI condition; ISI = Insomnia Severity Index; PHQ-9 = Patient Health Questionnaire-9; PHQ-WS = Patient Health Questionnaire minus Sleep item.

Supplementary Table 2

Table S2. Item means for each week, for the control condition (upper panel) and treatment condition (lower panel) separately.

		Insomnia Severity Index items							Patient Health Questionnaire items							
	Week	DIS	DMS	EMA	Dissat	IDF	NIQoL	Worry	LoI	Dep Mood	Fatigue	Appet	Worth	Con	Psych Mot	Sui
Control condition	T0	2.15	3.13	2.75	3.54	2.83	1.73	2.69	0.75	0.60	1.98	0.94	0.88	1.38	0.46	0.10
	T1	1.23	2.12	2.04	2.40	1.71	1.29	1.50	0.77	0.52	1.94	0.98	0.46	1.17	0.29	0.12
	T2	1.60	3.00	2.66	3.17	2.60	1.74	2.57	0.70	0.49	1.70	0.77	0.55	1.13	0.30	0.11
	T3	1.56	2.89	2.58	3.27	2.49	1.47	2.53	0.91	0.56	1.56	0.78	0.42	1.11	0.22	0.13
	T4	1.45	2.86	2.39	3.14	2.52	1.64	2.66	0.73	0.57	1.57	0.77	0.48	1.16	0.32	0.11
	T5	1.07	2.68	2.34	3.10	2.41	1.59	2.46	0.78	0.59	1.68	0.76	0.44	1.07	0.15	0.20
	T6	1.35	2.93	2.40	3.14	2.35	1.70	2.44	0.70	0.58	1.44	0.74	0.35	0.93	0.19	0.14
	T7	1.48	2.80	2.50	3.05	2.32	1.50	2.55	0.70	0.45	1.39	0.68	0.32	0.93	0.27	0.20
	T8	1.40	2.91	2.44	3.00	2.47	1.79	2.51	0.79	0.63	1.67	0.79	0.40	1.09	0.23	0.14
	T9	1.60	2.94	2.70	3.19	2.36	1.64	2.66	0.79	0.55	1.51	0.79	0.49	1.17	0.30	0.15
Treatment condition	T0	2.35	3.13	2.65	3.52	2.81	1.92	2.73	1.13	0.77	2.10	1.10	0.75	1.23	0.38	0.12
	T1	1.50	2.46	1.67	2.56	1.52	1.40	1.62	0.87	0.63	2.04	1.06	0.67	1.17	0.37	0.02
	T2 (T)	1.96	2.60	1.94	3.04	2.56	1.76	2.48	0.84	0.54	1.56	0.94	0.58	0.96	0.24	0.06
	T3 (T)	1.64	2.21	2.02	3.02	2.49	1.74	2.43	0.91	0.72	1.57	0.91	0.55	1.34	0.34	0.09
	T4 (T)	1.39	1.89	1.41	2.61	2.26	1.52	2.09	0.70	0.43	1.61	0.83	0.28	1.09	0.17	0.02
	T5 (T)	1.14	1.63	1.37	2.44	1.95	1.33	1.91	0.60	0.40	1.42	0.74	0.35	0.95	0.14	0.02
	T6 (T)	1.13	1.38	1.36	2.23	1.77	1.09	1.51	0.51	0.36	1.17	0.60	0.28	0.70	0.11	0.02
	T7	1.00	1.33	1.12	1.95	1.49	1.00	1.40	0.49	0.44	0.93	0.42	0.26	0.72	0.07	0.00
	T8	1.05	1.40	1.21	1.93	1.44	1.02	1.42	0.47	0.40	0.95	0.44	0.21	0.65	0.07	0.00
	T9	1.11	1.27	1.16	1.98	1.44	1.00	1.29	0.44	0.40	0.89	0.47	0.20	0.58	0.07	0.02

Note. DIS = difficulty initiating sleep; DMS = difficulty maintaining sleep; EMA = early morning awakenings; Dissat = dissatisfaction with sleep; IDF = interference with daily functioning; NIQoL = noticability of impaired quality of life; Worry = worry about sleep; LoI = loss of interest; Dep Mood = depressed mood; Appet = appetite change; Worth = feelings of worthlessness; Con = concentration problems; Psych Mot = psychomotor agitation; Sui = suicidal thoughts; (T) indicates that the participants received treatment in the week prior to this measurement.

Supplementary Table 3

Table S3. Item means, standardized to overall mean and standard deviation at baseline (T0). Differences indicate the standardized improvement of treatment condition over and above the improvement in the control condition.

		Insomnia Severity Index items							Patient Health Questionnaire items							
		DIS	DMS	EMA	Dissat	IDF	NIQoL	Worry	LoI	Dep Mood	Fatigue	Appet	Worth	Con	Psych Mot	Sui
Overall baseline (*M*±*SD*)		2.25 ± 1.52	3.13 ± 1.05	2.70 ± 1.37	3.53 ± 0.54	2.82 ± 0.68	1.83 ± 0.88	2.71 ± 0.86	0.94 ± 0.87	0.68 ± 0.79	2.04 ± 0.87	1.02 ± 0.94	0.82 ± 0.96	1.31 ± 0.98	0.42 ± 0.73	0.11 ± 0.31
T1	Control[a]	-0.67	-0.96	-0.48	-2.10	-1.63	-0.61	-1.42	-0.20	-0.20	-0.12	-0.04	-0.37	-0.14	-0.18	0.06
	Treatment[a]	-0.49	-0.64	-0.75	-1.80	-1.91	-0.48	-1.28	-0.09	-0.06	0.00	0.04	-0.15	-0.14	-0.08	-0.28
	Difference	0.18	0.32	-0.27	0.30	-0.28	0.13	0.13	0.11	0.14	0.12	0.08	0.22	0.01	0.10	-0.34
T2	Control[a]	-0.43	-0.13	-0.03	-0.67	-0.33	-0.09	-0.16	-0.28	-0.24	-0.39	-0.27	-0.27	-0.18	-0.17	0.00
	Treatment[a]	-0.49	-0.64	-0.75	-1.80	-1.91	-0.48	-1.28	-0.09	-0.06	0.00	0.04	-0.15	-0.14	-0.08	-0.28
	Difference	0.24	-0.38	-0.52	-0.24	-0.05	0.02	-0.11	0.16	0.06	-0.16	0.18	0.03	-0.17	-0.08	-0.15
T3	Control[a]	-0.46	-0.23	-0.09	-0.49	-0.48	-0.41	-0.21	-0.04	-0.16	-0.56	-0.26	-0.41	-0.20	-0.27	0.09
	Treatment[a]	-0.40	-0.88	-0.50	-0.94	-0.48	-0.09	-0.33	-0.03	0.05	-0.53	-0.11	-0.27	0.03	-0.11	-0.07
	Difference	0.05	-0.64	-0.41	-0.46	0.00	0.32	-0.13	0.00	0.21	0.02	0.15	0.14	0.23	0.16	-0.16
T4	Control[a]	-0.52	-0.26	-0.23	-0.73	-0.43	-0.22	-0.06	-0.25	-0.14	-0.54	-0.26	-0.35	-0.15	-0.14	0.03
	Treatment[a]	-0.56	-1.18	-0.94	-1.71	-0.82	-0.35	-0.73	-0.28	-0.31	-0.49	-0.2	-0.56	-0.23	-0.34	-0.27
	Difference	-0.04	-0.92	-0.71	-0.98	-0.39	-0.13	-0.67	-0.04	-0.17	0.05	0.06	-0.20	-0.07	-0.20	-0.30
T5	Control[a]	-0.77	-0.43	-0.26	-0.80	-0.59	-0.28	-0.29	-0.19	-0.12	-0.41	-0.28	-0.39	-0.24	-0.38	0.29
	Treatment[a]	-0.73	-1.43	-0.97	-2.02	-1.27	-0.57	-0.94	-0.39	-0.36	-0.71	-0.29	-0.49	-0.36	-0.39	-0.27
	Difference	0.04	-1.00	-0.71	-1.22	-0.68	-0.30	-0.65	-0.20	-0.24	-0.3	-0.01	-0.09	-0.12	-0.01	-0.56
T6	Control[a]	-0.59	-0.19	-0.22	-0.72	-0.69	-0.15	-0.32	-0.28	-0.13	-0.69	-0.29	-0.49	-0.39	-0.32	0.11
	Treatment[a]	-0.74	-1.66	-0.98	-2.40	-1.55	-0.85	-1.40	-0.50	-0.41	-1.00	-0.45	-0.56	-0.62	-0.43	-0.27
	Difference	-0.15	-1.47	-0.75	-1.68	-0.86	-0.70	-1.09	-0.22	-0.28	-0.31	-0.16	-0.08	-0.23	-0.11	-0.38
T7	Control[a]	-0.51	-0.32	-0.15	-0.90	-0.73	-0.37	-0.19	-0.27	-0.29	-0.75	-0.36	-0.52	-0.39	-0.21	0.32
	Treatment[a]	-0.82	-1.72	-1.16	-2.92	-1.96	-0.94	-1.54	-0.52	-0.30	-1.27	-0.64	-0.58	-0.60	-0.48	-0.34
	Difference	-0.31	-1.4	-1.01	-2.03	-1.22	-0.57	-1.34	-0.25	-0.02	-0.52	-0.28	-0.06	-0.22	-0.28	-0.66
T8	Control[a]	-0.56	-0.22	-0.19	-0.98	-0.52	-0.04	-0.23	-0.17	-0.07	-0.42	-0.24	-0.44	-0.22	-0.26	0.11
	Treatment[a]	-0.79	-1.65	-1.09	-2.97	-2.02	-0.92	-1.51	-0.55	-0.36	-1.25	-0.61	-0.63	-0.67	-0.48	-0.34
	Difference	-0.23	-1.44	-0.90	-1.99	-1.51	-0.88	-1.28	-0.37	-0.29	-0.83	-0.37	-0.19	-0.45	-0.22	-0.45
T9	Control[a]	-0.43	-0.19	0.00	-0.63	-0.67	-0.22	-0.06	-0.18	-0.16	-0.61	-0.25	-0.34	-0.14	-0.17	0.14
	Treatment[a]	-0.75	-1.77	-1.13	-2.88	-2.02	-0.94	-1.66	-0.57	-0.36	-1.32	-0.58	-0.64	-0.75	-0.49	-0.27
	Difference	-0.32	-1.59	-1.13	-2.25	-1.35	-0.73	-1.60	-0.39	-0.19	-0.72	-0.34	-0.30	-0.61	-0.32	-0.41

[a] Item mean standardized to baseline mean and standard deviation.

Note. DIS = difficulty initiating sleep; DMS = difficulty maintaining sleep; EMA = early morning awakenings; Dissat = dissatisfaction with sleep; IDF = interference with daily functioning; NIQoL = noticability of impaired quality of life; Worry = worry about sleep; LoI = loss of interest; Dep Mood = depressed mood; Appet = appetite change; Worth = feelings of worthlessness; Con = concentration problems; Psych Mot = psychomotor agitation; Sui = suicidal thoughts.

Supplementary Table 4

Table S4. Mean predictability.

	T0	T1	T2(T)	T3(T)	T4(T)	T5(T)	T6(T)	T7	T8	T9
Mean overall predictability	30%	20%	37%	45%	43%	46%	55%	58%	51%	53%
Mean predictability insomnia symptoms	29%	11%	38%	40%	47%	48%	58%	61%	60%	62%
Mean predictability depression symptoms	31%	27%	36%	48%	39%	45%	53%	55%	43%	46%

Note. We computed the mean predictability at each assessment and explored changes over time. Surprisingly, treatment seems to systematically and robustly increase predictability over time: from, on average, 30% explained variance at baseline to, on average, 53% at post-assessment. One explanation for the increase in predictability might be the direct associations that the treatment allocation variable has in the regularized network. To explore the effect of these direct effects on predictability, we re-estimated the networks without the treatment allocation variable. Even without the treatment allocation variable, the predictability increased over time from 31% at baseline to 53% at post-assessment. This indicates that the increase in predictability reflects something other than the direct associations of the treatment allocation variable. Possibly, treatment changes the regularized network structure of the symptoms, which would then be reflected in an increased predictability. In line with this possibility, it is important to note that the increase in predictability is especially pronounced in the insomnia symptoms – for which the treatment effect was largest: from, 29% at baseline to 62% at post-assessment; compared to an increase of the depression symptoms from 31% at baseline to 46% at post-assessment. We explored whether this increase might be associated to an in- or decrease in variability of the symptoms over time, but this was not the case (see Supplementary Methods and Results 4). However, alternative explanations like methodological artefacts as the result of repeated assessments should be explored.

Supplementary Table 5

Table S5. Effect sizes Time*Condition (Cohen's *d*[a]) per item of Insomnia Severity Index and Patient Health Questionnaire pre-assessment vs. week 1-9.

	Insomnia Severity Index							Patient Health Questionnaire								
	DIS	DMS	EMA	Dissat	IDF	NIQol	Worry	LoI	Dep Mood	Sleep[b]	Fatigue	Appet	Worth	Con	Psych Mot	Sui
T1	0.00	0.24	0.28	0.14	0.16	0.00	0.06	0.41	0.13	0.17	0.06	0.16	0.31	0.13	0.23	0.35
T2	0.16	0.39	0.64	0.17	0.00	0.11	0.18	0.29	0.14	0.36	0.29	0.00	0.17	0.00	0.14	0.17
T3	0.11	0.53	0.38	0.35	0.06	0.14	0.22	0.44	0.06	0.65	0.06	0.00	0.17	0.51	0.40	0.21
T4	0.37	0.97	0.90	0.64	0.18	0.19	0.77	0.45	0.33	0.77	0.06	0.00	0.00	0.22	0.09	0.21
T5	0.14	0.75	0.76	0.85	0.39	0.35	0.69	0.61	0.39	0.99	0.20	0.00	0.00	0.06	0.23	0.38
T6	0.34	1.52	0.85	1.03	0.40	0.75	1.15	0.60	0.45	1.01	0.29	0.23	0.00	0.11	0.00	0.31
T7	0.45	1.42	1.18	1.04	0.81	0.57	1.24	0.56	0.11	0.97	0.43	0.21	0.22	0.06	0.06	0.51
T8	0.40	1.32	0.98	1.11	0.97	0.84	1.35	0.60	0.38	1.11	0.69	0.42	0.06	0.26	0.06	0.37
T9	0.38	1.59	1.37	1.28	0.92	0.84	1.46	0.78	0.29	1.11	0.67	0.40	0.13	0.54	0.17	0.41

[a] Cohen's *d* converted from partial eta^2 using formula from Cohen (1988). Partial eta squares were obtained from the SPSS analysis and then recalculated into Cohen's *d*'s for interpretability as the distance between the two means expressed in standard deviations: $f^2=eta^2/(1-eta^2)$, f^2 being the square of the effect size, and therefore $f=sqrt(eta^2/(1-eta^2))$ and $d=2*f$.

[b] Sleep item taken out of effect analysis (PHQ-WS[21]). DIS = difficulty initiating sleep; DMS = difficulty maintaining sleep; EMA = early morning awakenings; Dissat = dissatisfaction with sleep; IDF = interference with daily functioning; NIQoL = noticeability of impaired quality of life; Worry = worry about sleep; LoI = loss of interest; Dep Mood = depressed mood; Appet = appetite change; Worth = feelings of worthlessness; Con = concentration problems; Psych Mot = psychomotor agitation; Sui = suicidal thoughts. Cohen's *d* is considered small (i.e. < 0.20), moderate (around 0.50) or large (≥ 0.80; Cohen, 1988)

Supplementary Figure 1.

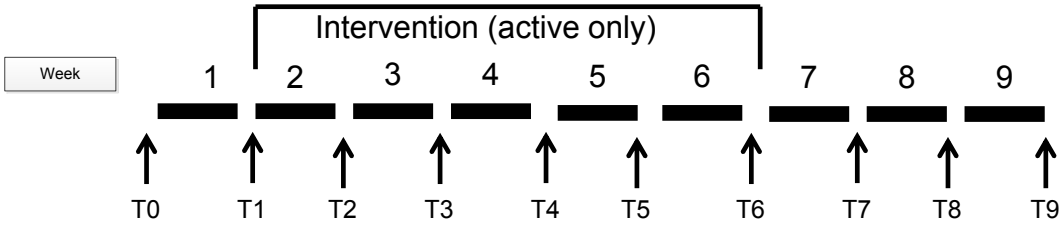

Figure S1. Study design. Data were collected in a randomised controlled trial on effects of online CBTI on insomnia and depression symptoms (Van der Zweerde et al., 2018). Participants (N=104) were asked to complete an online sleep diary daily and the Patient Health Questionnaire-9 (PHQ-9; Spitzer, Kroenke & Williams, 1999) and Insomnia Severity Index (ISI; Bastien, Vallieres & Morin, 2001) every week, for 10 weeks. Participants allocated to the CBTI condition received online treatment I-Sleep for five weeks. Nine weeks after randomisation the last post-assessment took place. Participants in the control condition were then offered the intervention. Most participants (N=41, 85%) completed the entire i-Sleep intervention, 7 participants completed one (N=3), two (N=1), or four sessions (N=3), 4 did not start. Further details and treatment effects are reported elsewhere (Van der Zweerde et al., 2018).

Supplementary Figure 2.

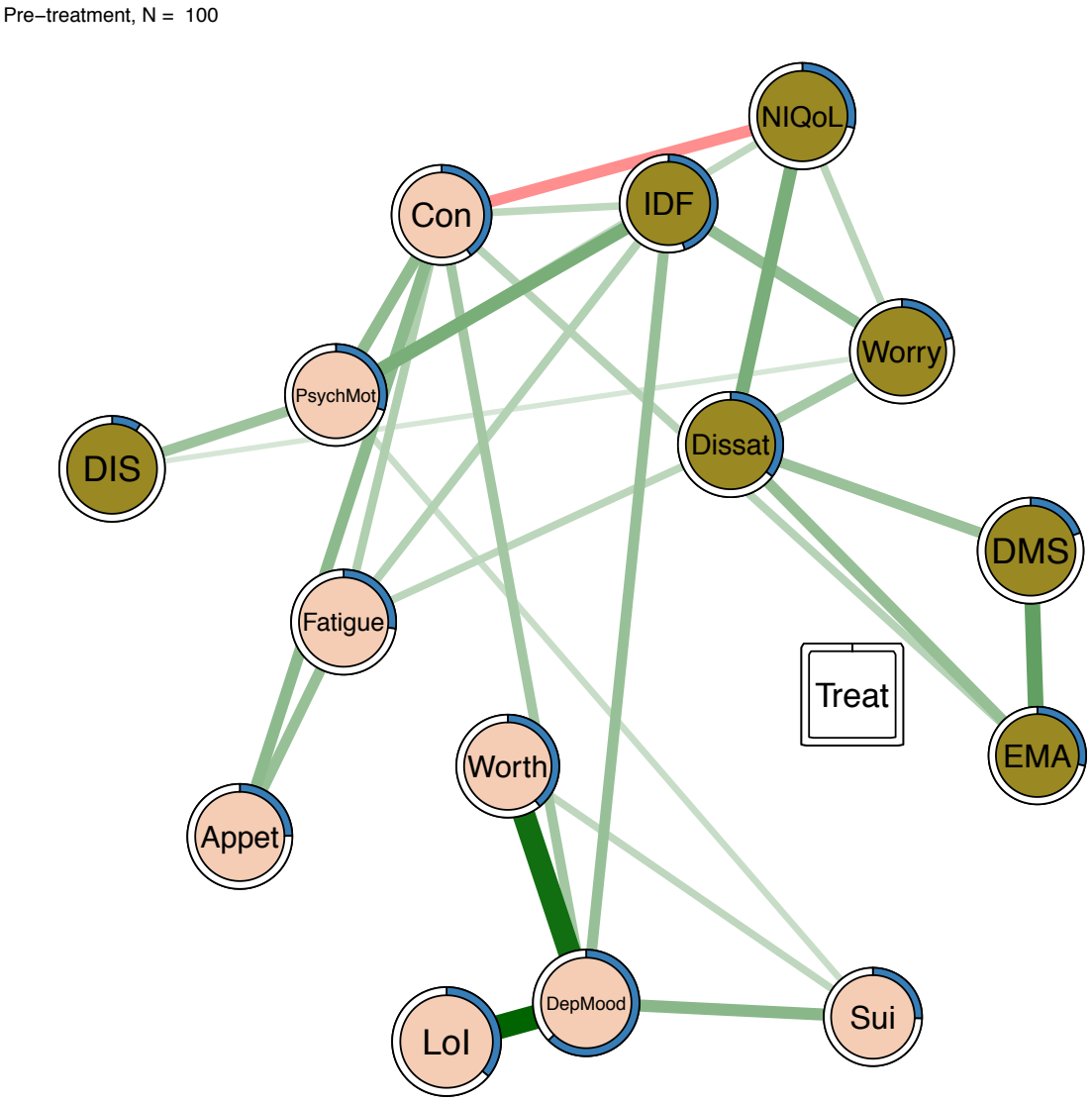

Figure S2. Regularized network averaged for the pre-treatment assessments (T0,T1). The network includes the ISI and PHQ-9 items (circles) and treatment (square). The edges represent the conditional dependence relations among the variables that capture the unique associations among the variables, while controlling for all the other variables in the network. Green edges represent positive associations, red edges represent negative associations, and the thickness and colour saturation of the edge is proportional to the strength of the association. For each node, the proportion of explained variance by the other nodes in the network, i.e., the predictability, is visualised by a ring around each node: a completely filled ring indicates that 100% of the variance is explained; a completely empty ring corresponds to an explained variance of 0%. Abbreviations: Appet = appetite change; Con = concentration problems; Dep Mood = depressed mood; DIS = difficulty initiating sleep; Dissat = dissatisfaction with sleep; DMS = difficulty maintaining sleep; EMA = early morning awakenings; IDF = interference with daily functioning; LoI = loss of interest; NIQoL = noticeability of impaired quality of life; Psych Mot = psychomotor agitation; Sui = suicidal thoughts; Worry = worry about sleep; Worth = feelings of worthlessness.

Supplementary Figure 3.

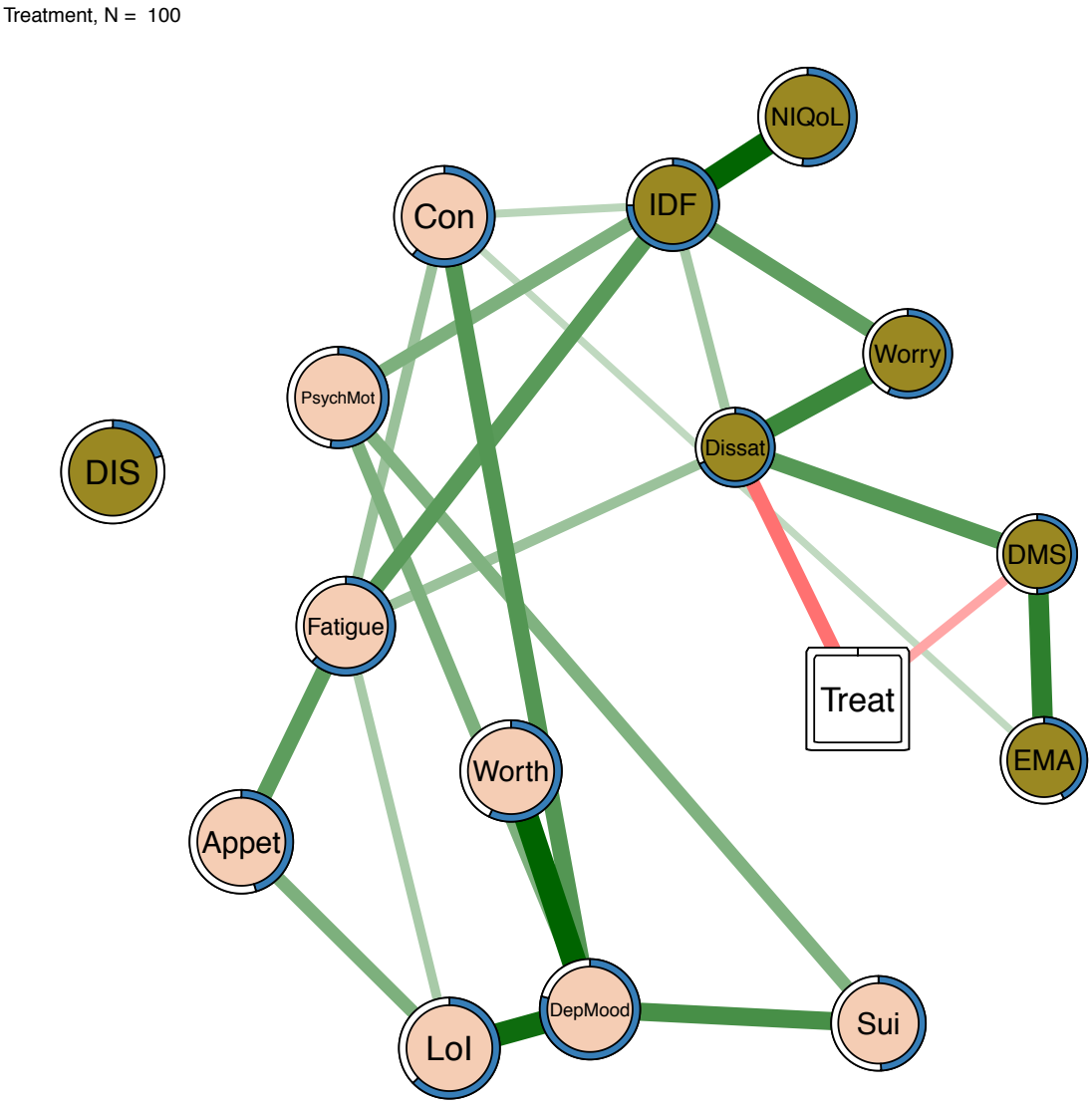

Figure S3. Regularized network averaged for the treatment assessments (T2-T6). The network includes the ISI and PHQ-9 items (circles) and treatment (square). The edges represent the conditional dependence relations among the variables that capture the unique associations among the variables, while controlling for all the other variables in the network. Green edges represent positive associations, red edges represent negative associations, and the thickness and colour saturation of the edge is proportional to the strength of the association. For each node, the proportion of explained variance by the other nodes in the network, i.e., the predictability, is visualised by a ring around each node: a completely filled ring indicates that 100% of the variance is explained; a completely empty ring corresponds to an explained variance of 0%. Abbreviations: Appet = appetite change; Con = concentration problems; Dep Mood = depressed mood; DIS = difficulty initiating sleep; Dissat = dissatisfaction with sleep; DMS = difficulty maintaining sleep; EMA = early morning awakenings; IDF = interference with daily functioning; LoI = loss of interest; NIQoL = noticeability of impaired quality of life; Psych Mot = psychomotor agitation; Sui = suicidal thoughts; Worry = worry about sleep; Worth = feelings of worthlessness.

Supplementary Figure 4.

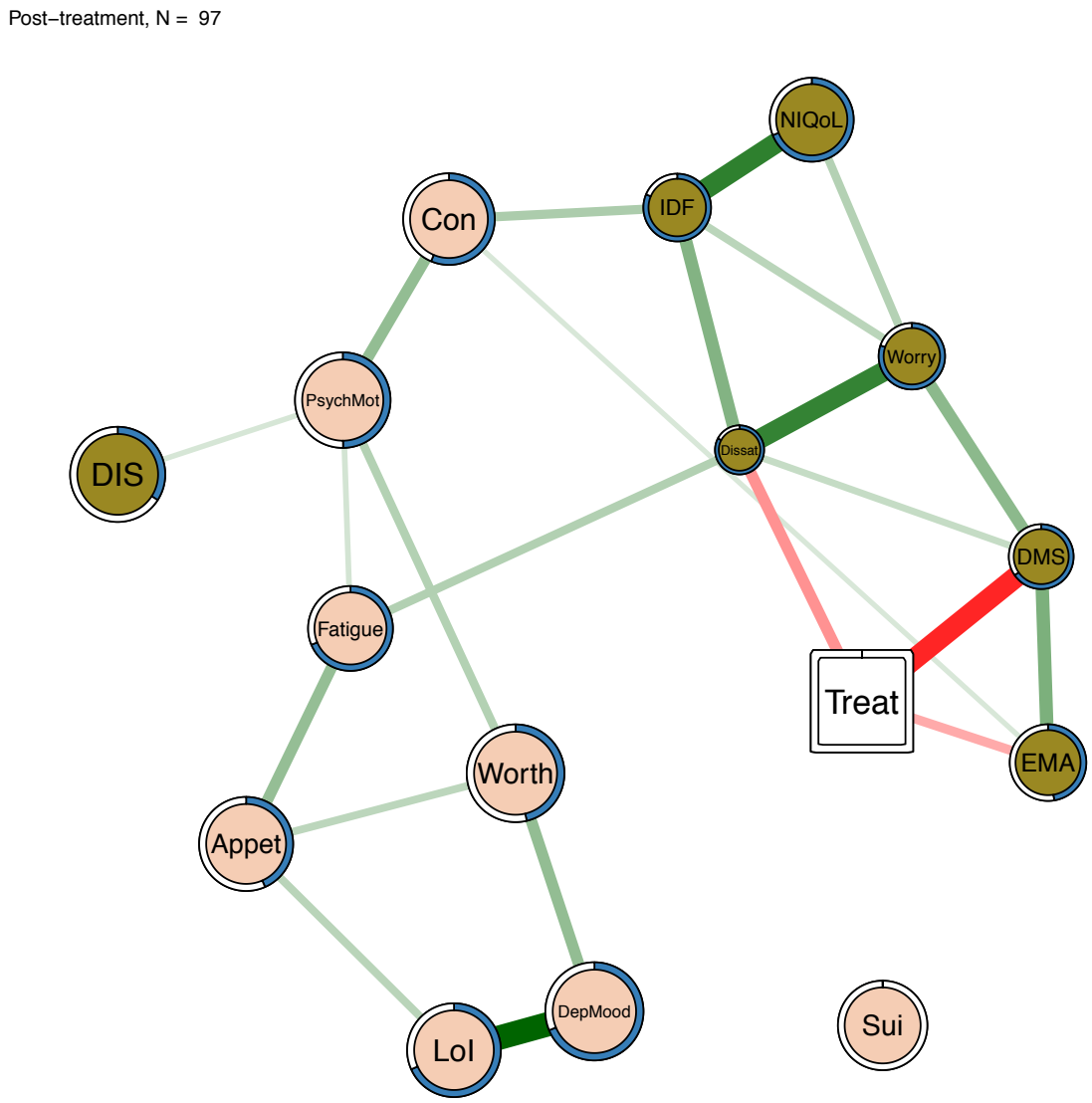

Figure S4. Regularized network averaged for the post-treatment assessments (T7-T9).The network includes the ISI and PHQ-9 items (circles) and treatment (square). The edges represent the conditional dependence relations among the variables that capture the unique associations among the variables, while controlling for all the other variables in the network. Green edges represent positive associations, red edges represent negative associations, and the thickness and colour saturation of the edge is proportional to the strength of the association. For each node, the proportion of explained variance by the other nodes in the network, i.e., the predictability, is visualised by a ring around each node: a completely filled ring indicates that 100% of the variance is explained; a completely empty ring corresponds to an explained variance of 0%. Abbreviations: Appet = appetite change; Con = concentration problems; Dep Mood = depressed mood; DIS = difficulty initiating sleep; Dissat = dissatisfaction with sleep; DMS = difficulty maintaining sleep; EMA = early morning awakenings; IDF = interference with daily functioning; LoI = loss of interest; NIQoL = noticeability of impaired quality of life; Psych Mot = psychomotor agitation; Sui = suicidal thoughts; Worry = worry about sleep; Worth = feelings of worthlessness.

Supplementary Figure 5.

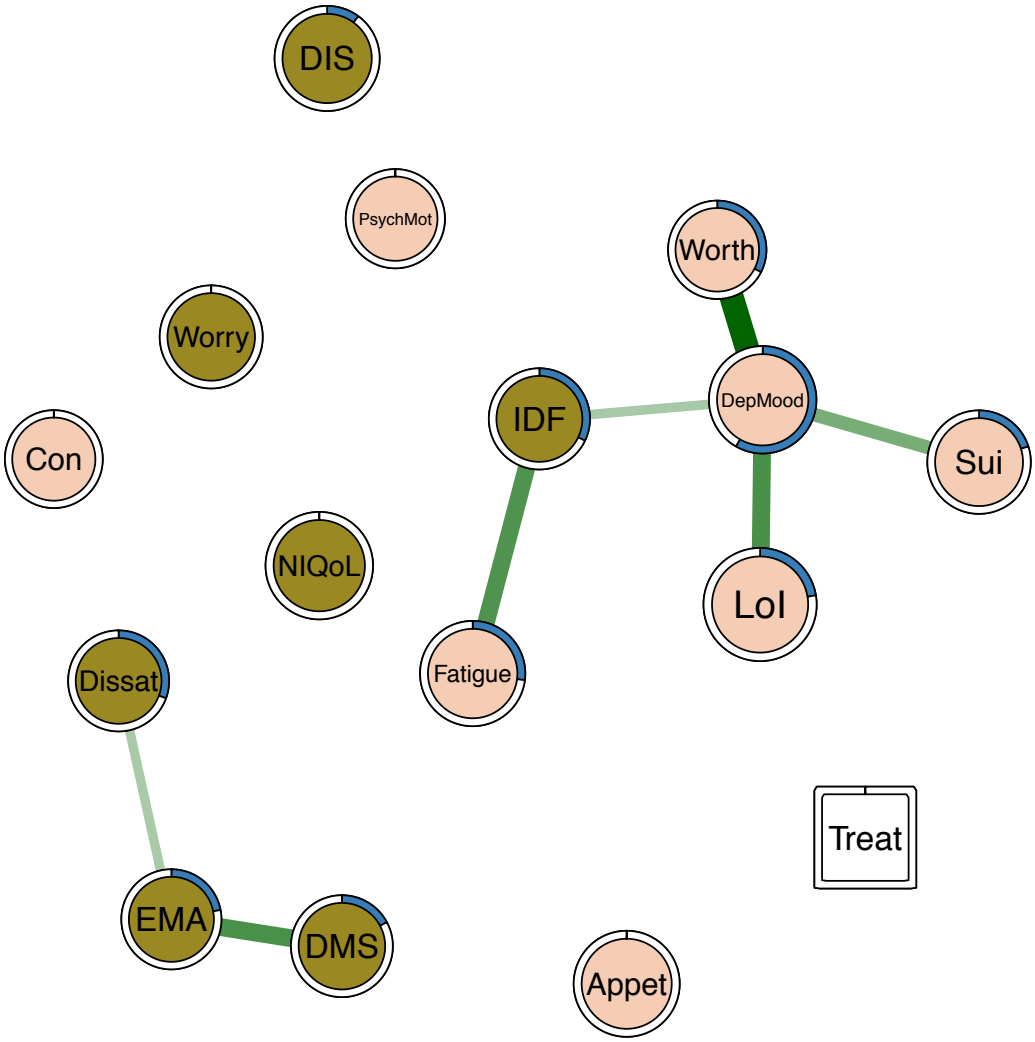

Figure S5. Regularized network at T0 using EBIC to select the tuning parameter. The network includes the ISI and PHQ-9 items (circles) and treatment (square). The edges represent the conditional dependence relations among the variables that capture the unique associations among the variables, while controlling for all the other variables in the network. Green edges represent positive associations, red edges represent negative associations, and the thickness and colour saturation of the edge is proportional to the strength of the association. For each node, the proportion of explained variance by the other nodes in the network, i.e., the predictability, is visualised by a ring around each node: a completely filled ring indicates that 100% of the variance is explained; a completely empty ring corresponds to an explained variance of 0%. Abbreviations: Appet = appetite change; Con = concentration problems; Dep Mood = depressed mood; DIS = difficulty initiating sleep; Dissat = dissatisfaction with sleep; DMS = difficulty maintaining sleep; EMA = early morning awakenings; IDF = interference with daily functioning; LoI = loss of interest; NIQoL = noticeability of impaired quality of life; Psych Mot = psychomotor agitation; Sui = suicidal thoughts; Worry = worry about sleep; Worth = feelings of worthlessness.

Supplementary Figure 6.

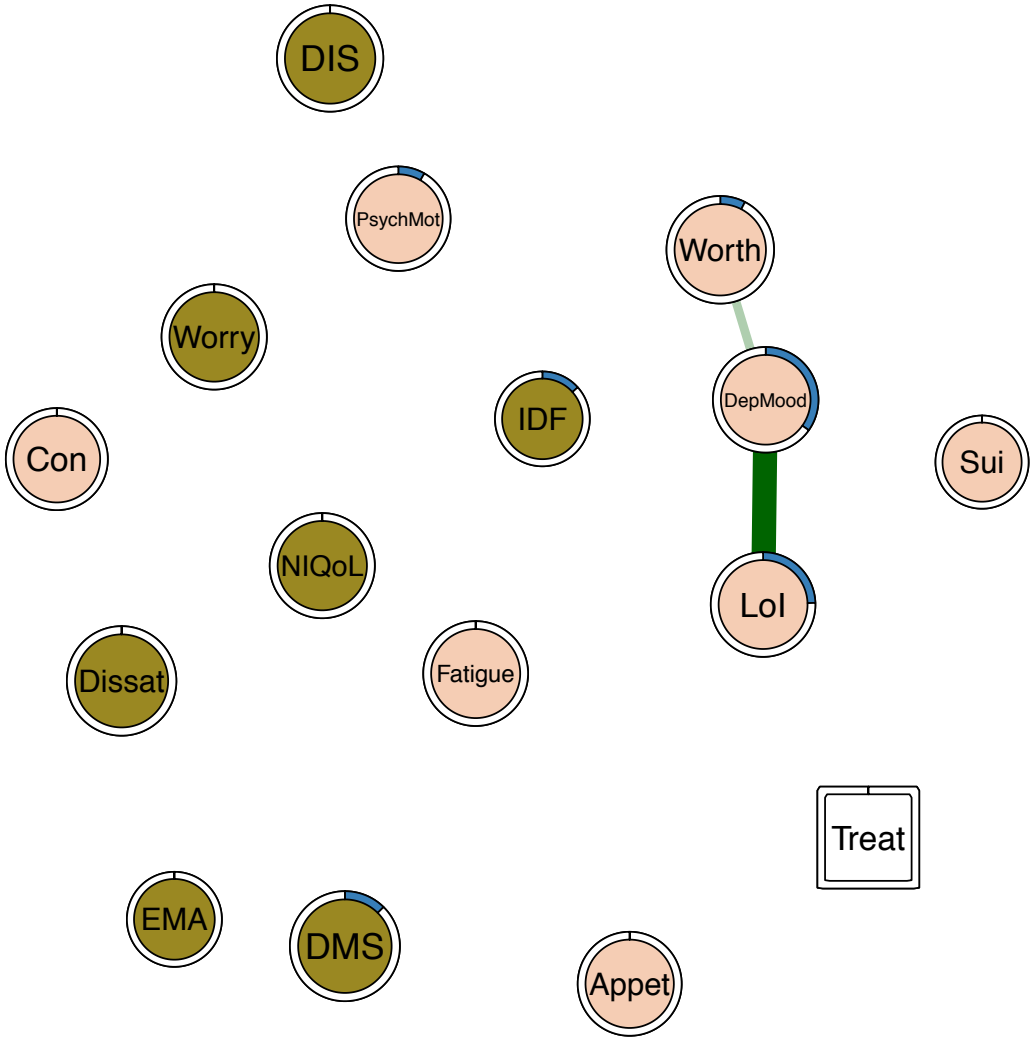

Figure S6. Regularized network at T1 using EBIC to select the tuning parameter. The network includes the ISI and PHQ-9 items (circles) and treatment (square). The edges represent the conditional dependence relations among the variables that capture the unique associations among the variables, while controlling for all the other variables in the network. Green edges represent positive associations, red edges represent negative associations, and the thickness and colour saturation of the edge is proportional to the strength of the association. For each node, the proportion of explained variance by the other nodes in the network, i.e., the predictability, is visualised by a ring around each node: a completely filled ring indicates that 100% of the variance is explained; a completely empty ring corresponds to an explained variance of 0%. Abbreviations: Appet = appetite change; Con = concentration problems; Dep Mood = depressed mood; DIS = difficulty initiating sleep; Dissat = dissatisfaction with sleep; DMS = difficulty maintaining sleep; EMA = early morning awakenings; IDF = interference with daily functioning; LoI = loss of interest; NIQoL = noticeability of impaired quality of life; Psych Mot = psychomotor agitation; Sui = suicidal thoughts; Worry = worry about sleep; Worth = feelings of worthlessness.

Supplementary Figure 7.

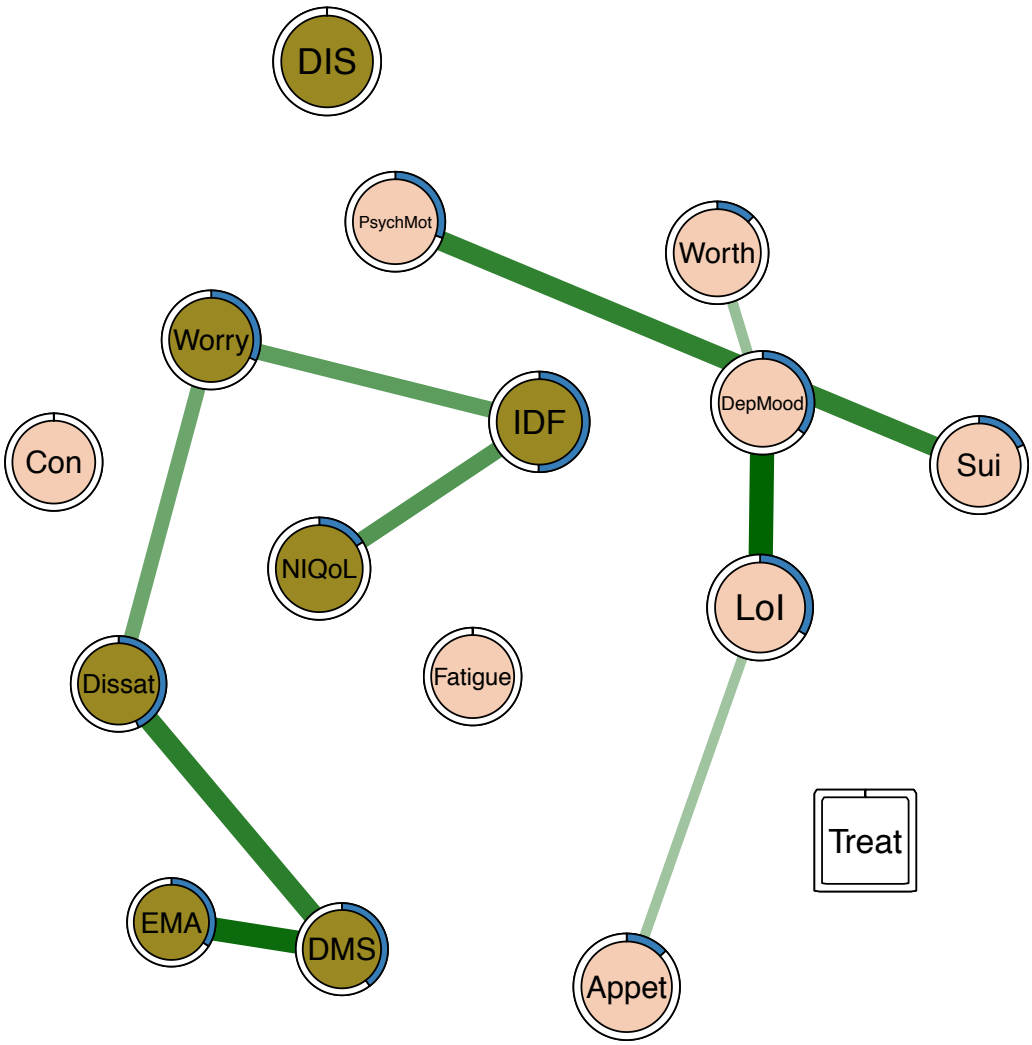

Figure S7. Regularized network at T2 using EBIC to select the tuning parameter. The network includes the ISI and PHQ-9 items (circles) and treatment (square). The edges represent the conditional dependence relations among the variables that capture the unique associations among the variables, while controlling for all the other variables in the network. Green edges represent positive associations, red edges represent negative associations, and the thickness and colour saturation of the edge is proportional to the strength of the association. For each node, the proportion of explained variance by the other nodes in the network, i.e., the predictability, is visualised by a ring around each node: a completely filled ring indicates that 100% of the variance is explained; a completely empty ring corresponds to an explained variance of 0%. Abbreviations: Appet = appetite change; Con = concentration problems; Dep Mood = depressed mood; DIS = difficulty initiating sleep; Dissat = dissatisfaction with sleep; DMS = difficulty maintaining sleep; EMA = early morning awakenings; IDF = interference with daily functioning; LoI = loss of interest; NIQoL = noticeability of impaired quality of life; Psych Mot = psychomotor agitation; Sui = suicidal thoughts; Worry = worry about sleep; Worth = feelings of worthlessness.

Supplementary Figure 8.

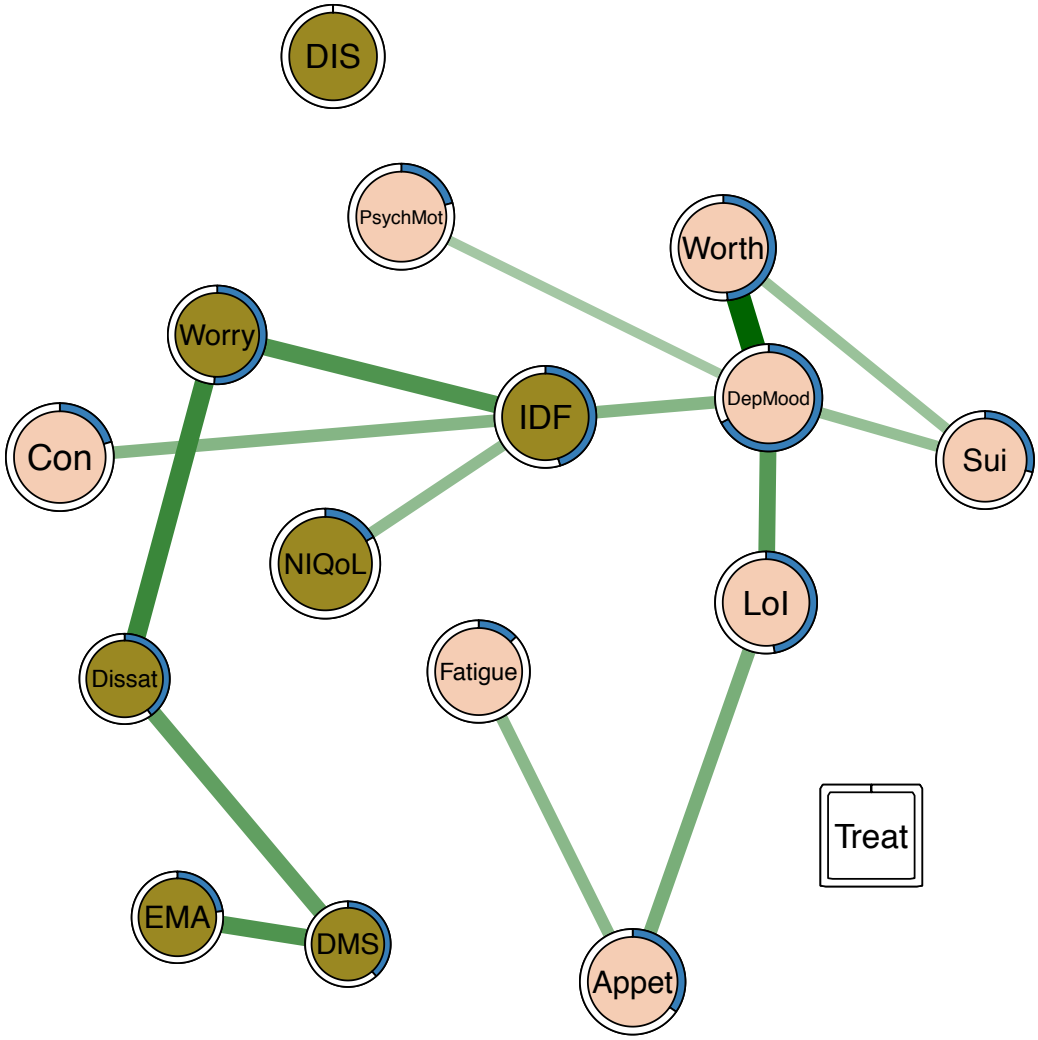

Figure S8. Regularized network at T3 using EBIC to select the tuning parameter. The network includes the ISI and PHQ-9 items (circles) and treatment (square). The edges represent the conditional dependence relations among the variables that capture the unique associations among the variables, while controlling for all the other variables in the network. Green edges represent positive associations, red edges represent negative associations, and the thickness and colour saturation of the edge is proportional to the strength of the association. For each node, the proportion of explained variance by the other nodes in the network, i.e., the predictability, is visualised by a ring around each node: a completely filled ring indicates that 100% of the variance is explained; a completely empty ring corresponds to an explained variance of 0%. Abbreviations: Appet = appetite change; Con = concentration problems; Dep Mood = depressed mood; DIS = difficulty initiating sleep; Dissat = dissatisfaction with sleep; DMS = difficulty maintaining sleep; EMA = early morning awakenings; IDF = interference with daily functioning; LoI = loss of interest; NIQoL = noticeability of impaired quality of life; Psych Mot = psychomotor agitation; Sui = suicidal thoughts; Worry = worry about sleep; Worth = feelings of worthlessness.

Supplementary Figure 6.

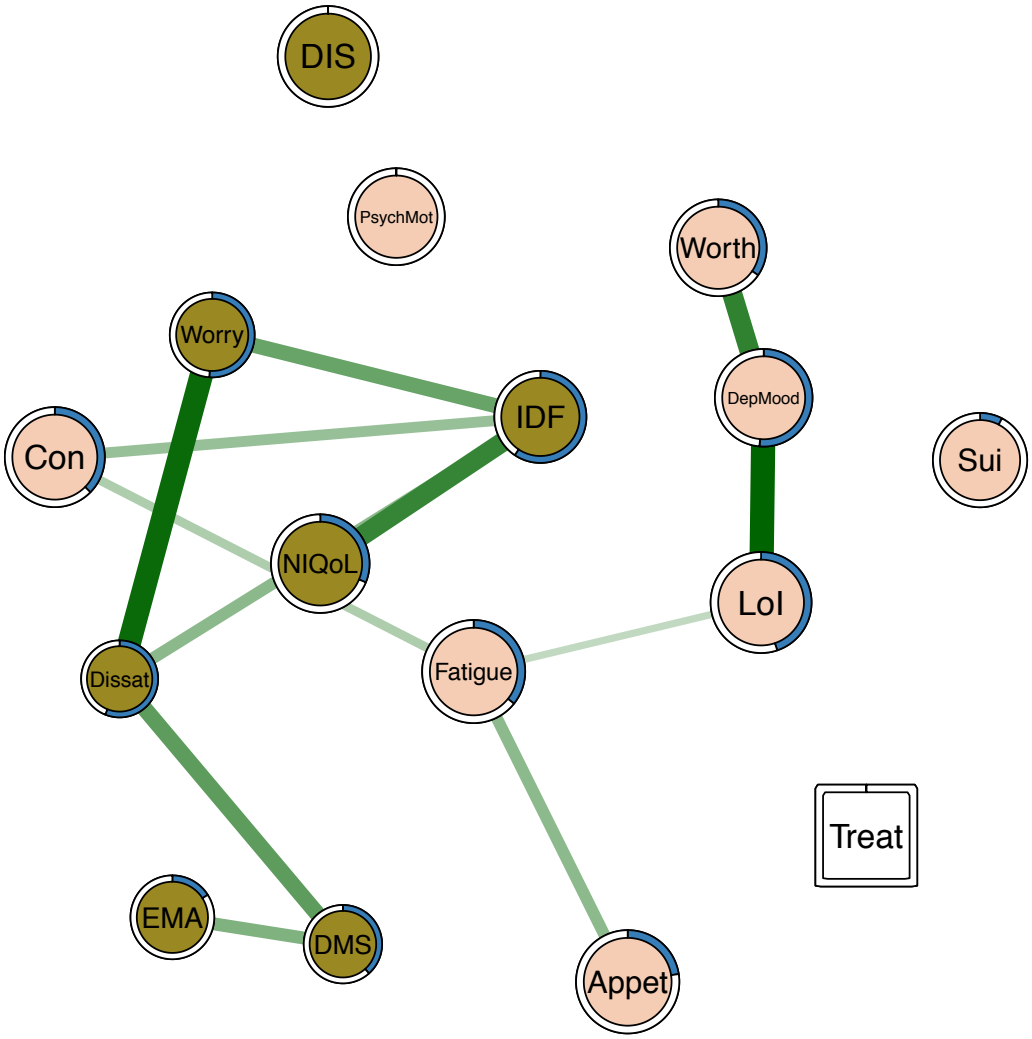

Figure S9. Regularized network at T4 using EBIC to select the tuning parameter. The network includes the ISI and PHQ-9 items (circles) and treatment (square). The edges represent the conditional dependence relations among the variables that capture the unique associations among the variables, while controlling for all the other variables in the network. Green edges represent positive associations, red edges represent negative associations, and the thickness and colour saturation of the edge is proportional to the strength of the association. For each node, the proportion of explained variance by the other nodes in the network, i.e., the predictability, is visualised by a ring around each node: a completely filled ring indicates that 100% of the variance is explained; a completely empty ring corresponds to an explained variance of 0%. Abbreviations: Appet = appetite change; Con = concentration problems; Dep Mood = depressed mood; DIS = difficulty initiating sleep; Dissat = dissatisfaction with sleep; DMS = difficulty maintaining sleep; EMA = early morning awakenings; IDF = interference with daily functioning; LoI = loss of interest; NIQoL = noticeability of impaired quality of life; Psych Mot = psychomotor agitation; Sui = suicidal thoughts; Worry = worry about sleep; Worth = feelings of worthlessness.

Supplementary Figure 10.

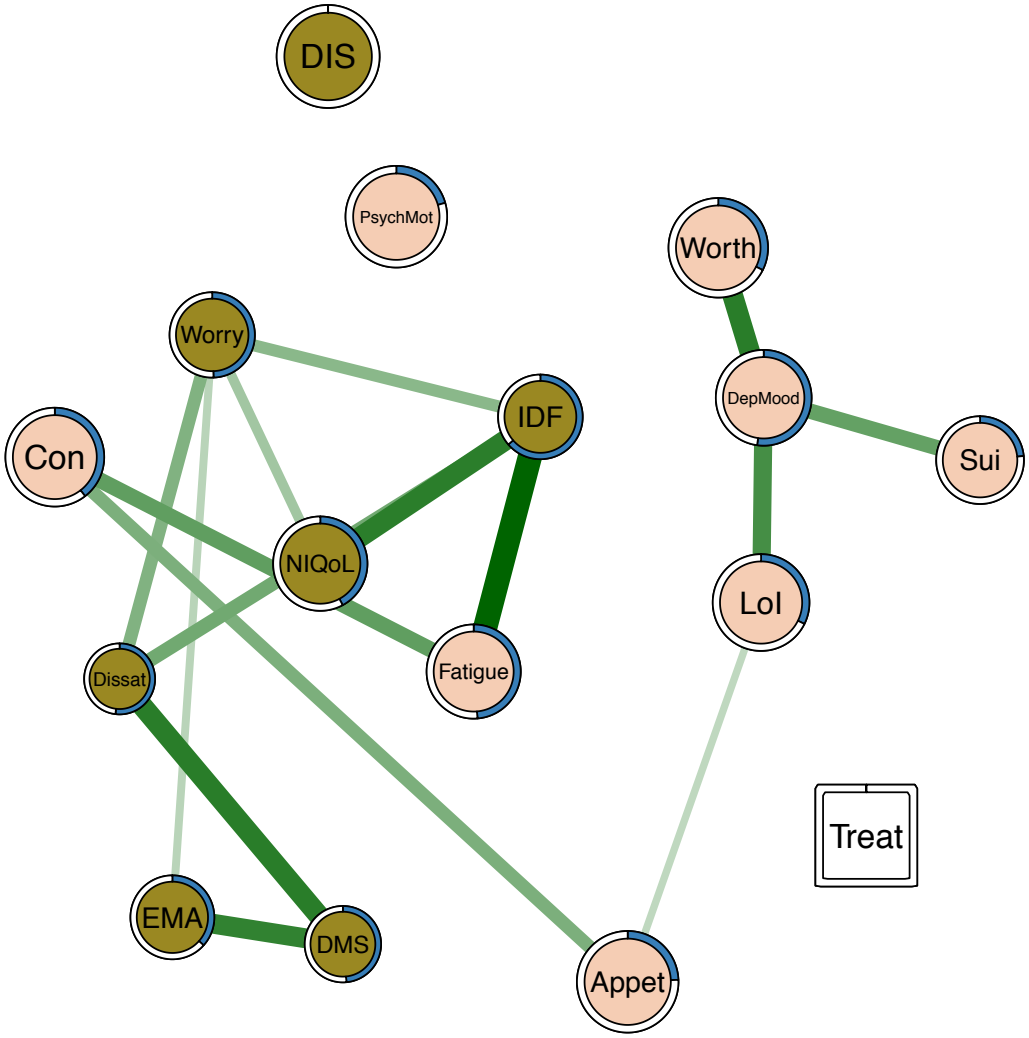

Figure S10. Regularized network at T5 using EBIC to select the tuning parameter. The network includes the ISI and PHQ-9 items (circles) and treatment (square). The edges represent the conditional dependence relations among the variables that capture the unique associations among the variables, while controlling for all the other variables in the network. Green edges represent positive associations, red edges represent negative associations, and the thickness and colour saturation of the edge is proportional to the strength of the association. For each node, the proportion of explained variance by the other nodes in the network, i.e., the predictability, is visualised by a ring around each node: a completely filled ring indicates that 100% of the variance is explained; a completely empty ring corresponds to an explained variance of 0%. Abbreviations: Appet = appetite change; Con = concentration problems; Dep Mood = depressed mood; DIS = difficulty initiating sleep; Dissat = dissatisfaction with sleep; DMS = difficulty maintaining sleep; EMA = early morning awakenings; IDF = interference with daily functioning; LoI = loss of interest; NIQoL = noticeability of impaired quality of life; Psych Mot = psychomotor agitation; Sui = suicidal thoughts; Worry = worry about sleep; Worth = feelings of worthlessness.

Supplementary Figure 11.

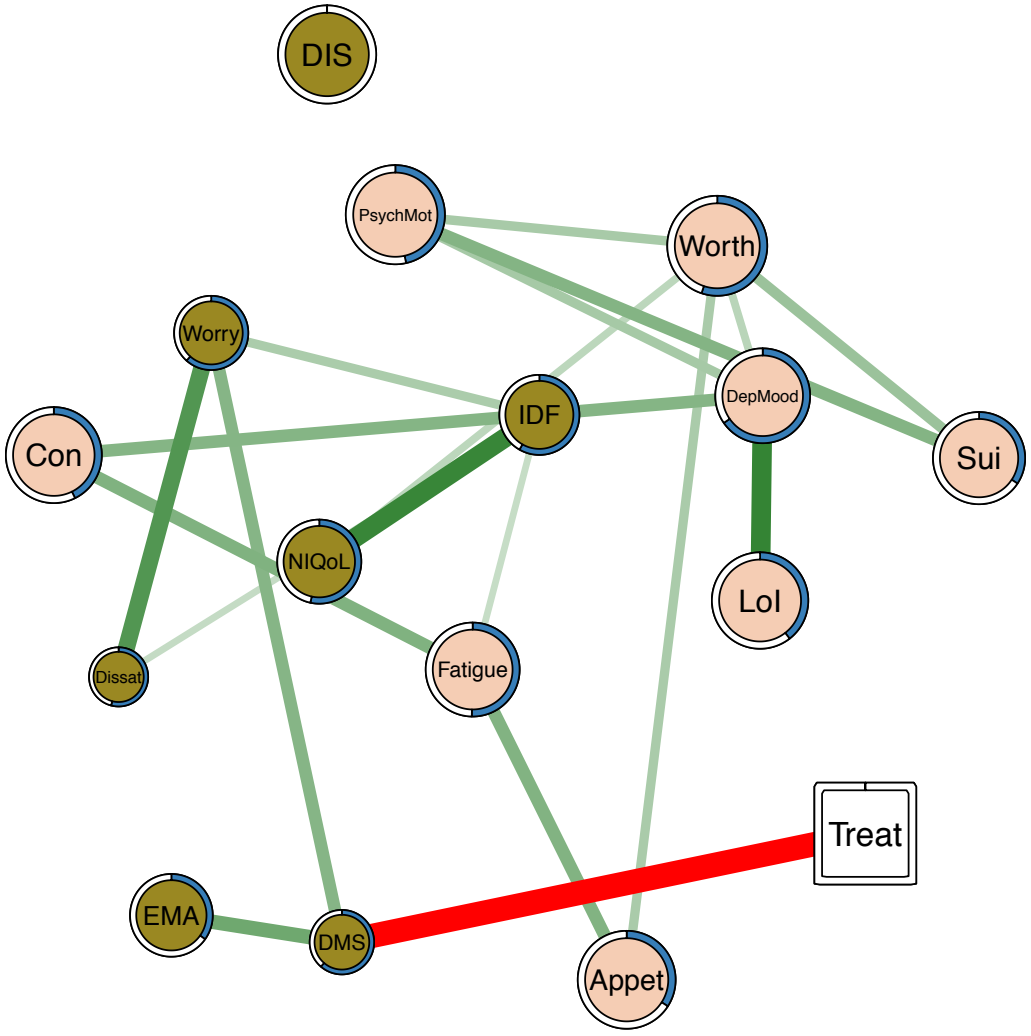

Figure S11. Regularized network at T6 using EBIC to select the tuning parameter. The network includes the ISI and PHQ-9 items (circles) and treatment (square). The edges represent the conditional dependence relations among the variables that capture the unique associations among the variables, while controlling for all the other variables in the network. Green edges represent positive associations, red edges represent negative associations, and the thickness and colour saturation of the edge is proportional to the strength of the association. For each node, the proportion of explained variance by the other nodes in the network, i.e., the predictability, is visualised by a ring around each node: a completely filled ring indicates that 100% of the variance is explained; a completely empty ring corresponds to an explained variance of 0%. Abbreviations: Appet = appetite change; Con = concentration problems; Dep Mood = depressed mood; DIS = difficulty initiating sleep; Dissat = dissatisfaction with sleep; DMS = difficulty maintaining sleep; EMA = early morning awakenings; IDF = interference with daily functioning; LoI = loss of interest; NIQoL = noticeability of impaired quality of life; Psych Mot = psychomotor agitation; Sui = suicidal thoughts; Worry = worry about sleep; Worth = feelings of worthlessness.

Supplementary Figure 12.

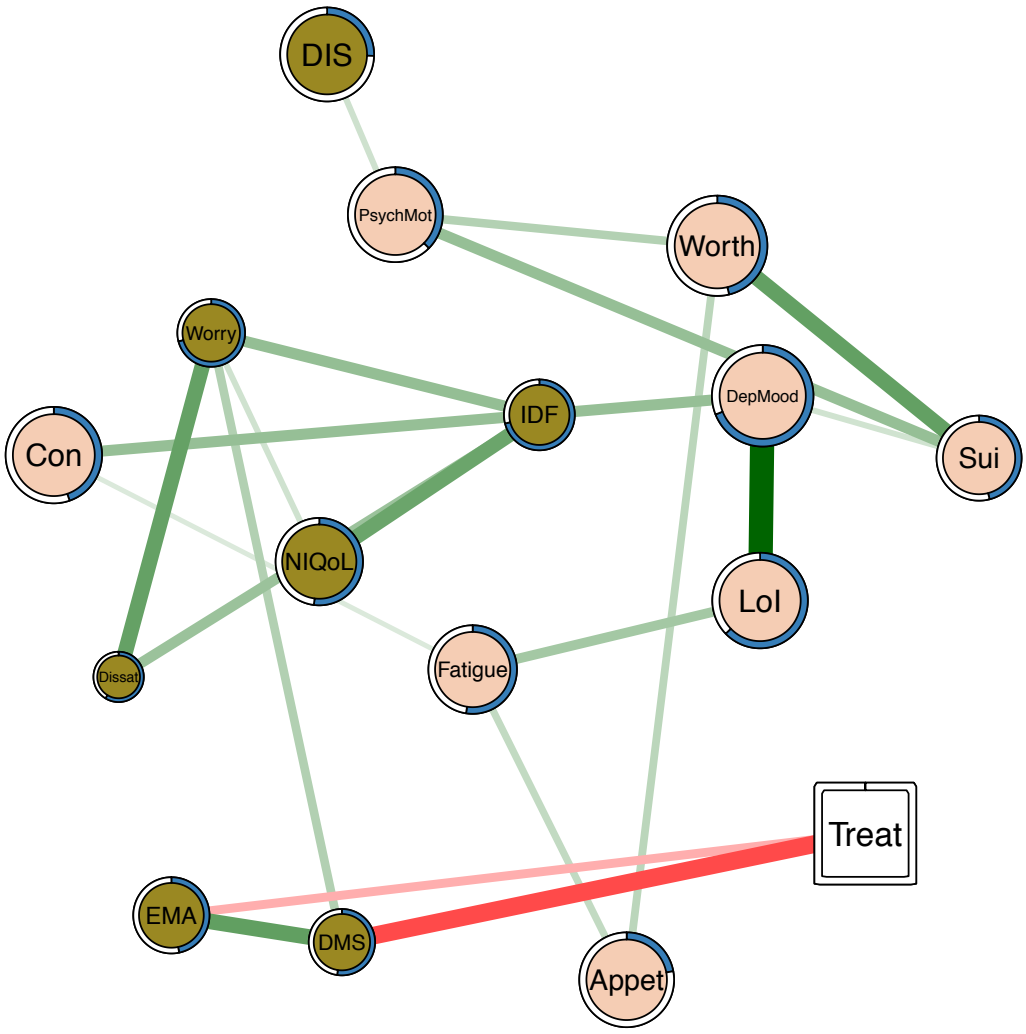

Figure S12. Regularized network at T7 using EBIC to select the tuning parameter. The network includes the ISI and PHQ-9 items (circles) and treatment (square). The edges represent the conditional dependence relations among the variables that capture the unique associations among the variables, while controlling for all the other variables in the network. Green edges represent positive associations, red edges represent negative associations, and the thickness and colour saturation of the edge is proportional to the strength of the association. For each node, the proportion of explained variance by the other nodes in the network, i.e., the predictability, is visualised by a ring around each node: a completely filled ring indicates that 100% of the variance is explained; a completely empty ring corresponds to an explained variance of 0%. Abbreviations: Appet = appetite change; Con = concentration problems; Dep Mood = depressed mood; DIS = difficulty initiating sleep; Dissat = dissatisfaction with sleep; DMS = difficulty maintaining sleep; EMA = early morning awakenings; IDF = interference with daily functioning; LoI = loss of interest; NIQoL = noticeability of impaired quality of life; Psych Mot = psychomotor agitation; Sui = suicidal thoughts; Worry = worry about sleep; Worth = feelings of worthlessness.

Supplementary Figure 13.

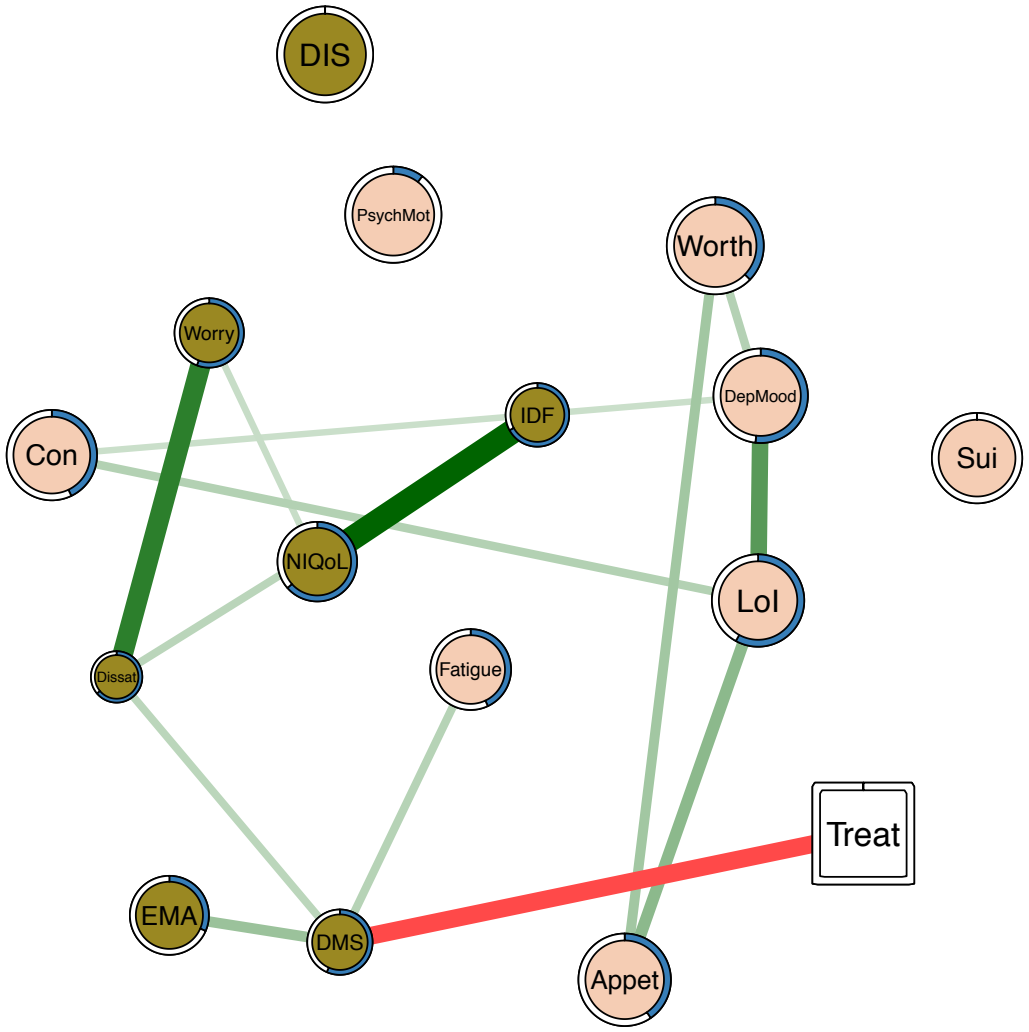

Figure S13. Regularized network at T8 using EBIC to select the tuning parameter. The network includes the ISI and PHQ-9 items (circles) and treatment (square). The edges represent the conditional dependence relations among the variables that capture the unique associations among the variables, while controlling for all the other variables in the network. Green edges represent positive associations, red edges represent negative associations, and the thickness and colour saturation of the edge is proportional to the strength of the association. For each node, the proportion of explained variance by the other nodes in the network, i.e., the predictability, is visualised by a ring around each node: a completely filled ring indicates that 100% of the variance is explained; a completely empty ring corresponds to an explained variance of 0%. Abbreviations: Appet = appetite change; Con = concentration problems; Dep Mood = depressed mood; DIS = difficulty initiating sleep; Dissat = dissatisfaction with sleep; DMS = difficulty maintaining sleep; EMA = early morning awakenings; IDF = interference with daily functioning; LoI = loss of interest; NIQoL = noticeability of impaired quality of life; Psych Mot = psychomotor agitation; Sui = suicidal thoughts; Worry = worry about sleep; Worth = feelings of worthlessness.

Supplementary Figure 14.

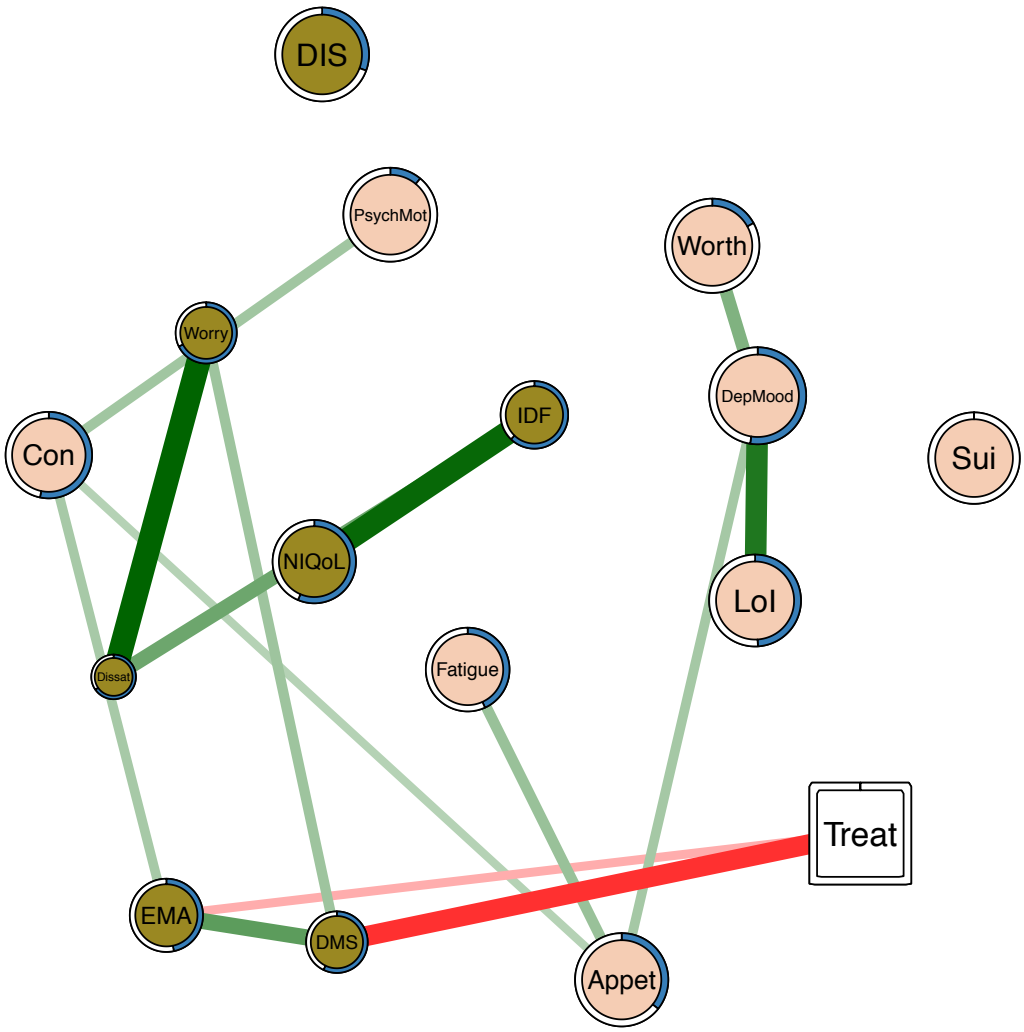

Figure S14. Regularized network at T9 using EBIC to select the tuning parameter. The network includes the ISI and PHQ-9 items (circles) and treatment (square). The edges represent the conditional dependence relations among the variables that capture the unique associations among the variables, while controlling for all the other variables in the network. Green edges represent positive associations, red edges represent negative associations, and the thickness and colour saturation of the edge is proportional to the strength of the association. For each node, the proportion of explained variance by the other nodes in the network, i.e., the predictability, is visualised by a ring around each node: a completely filled ring indicates that 100% of the variance is explained; a completely empty ring corresponds to an explained variance of 0%. Abbreviations: Appet = appetite change; Con = concentration problems; Dep Mood = depressed mood; DIS = difficulty initiating sleep; Dissat = dissatisfaction with sleep; DMS = difficulty maintaining sleep; EMA = early morning awakenings; IDF = interference with daily functioning; LoI = loss of interest; NIQoL = noticeability of impaired quality of life; Psych Mot = psychomotor agitation; Sui = suicidal thoughts; Worry = worry about sleep; Worth = feelings of worthlessness.

Supplementary Figure S15.

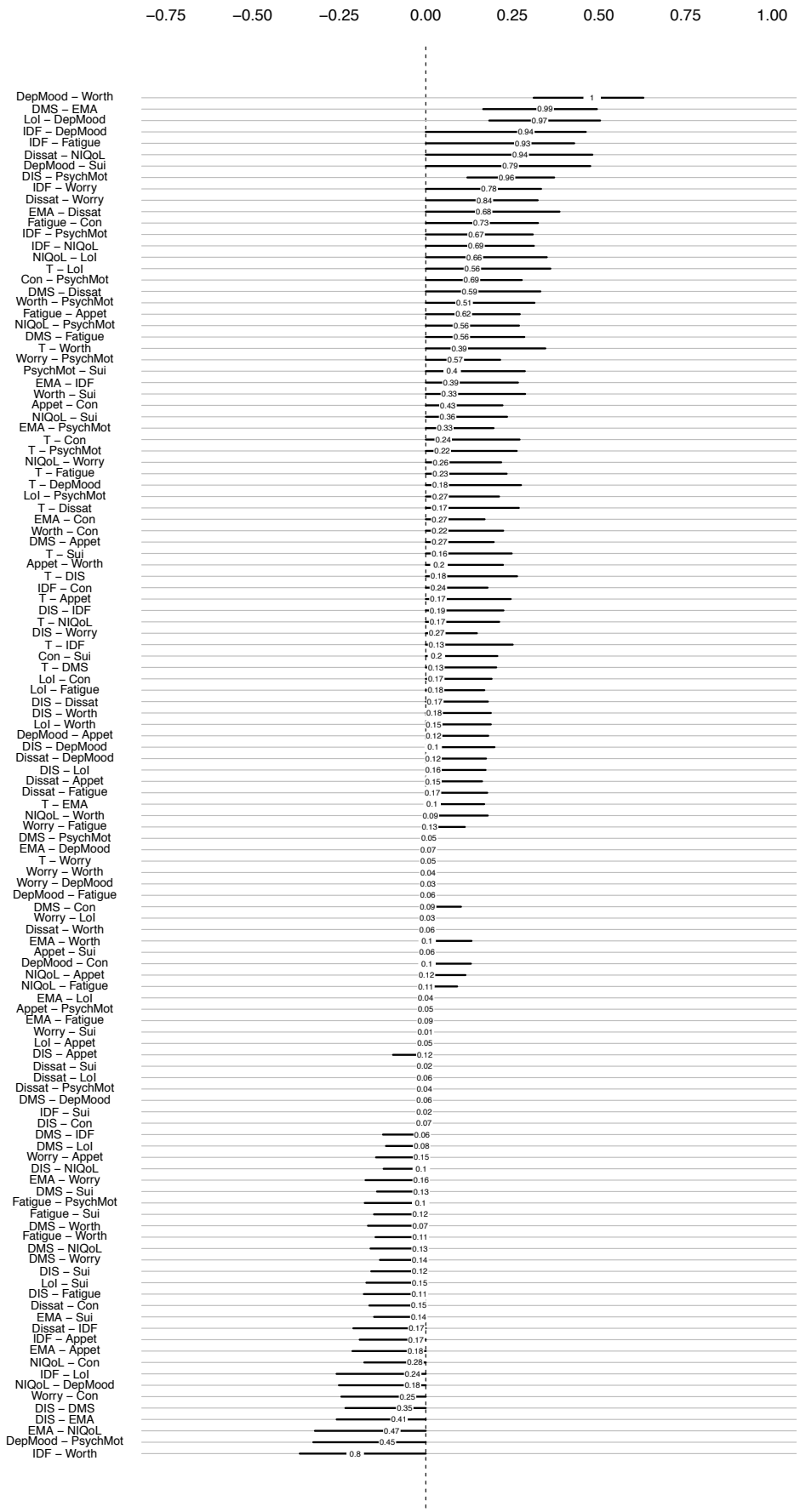

Figure S15. Bootstrapped sampling distribution of the edge weights of the regularized network of T0.

Supplementary Figure 16.

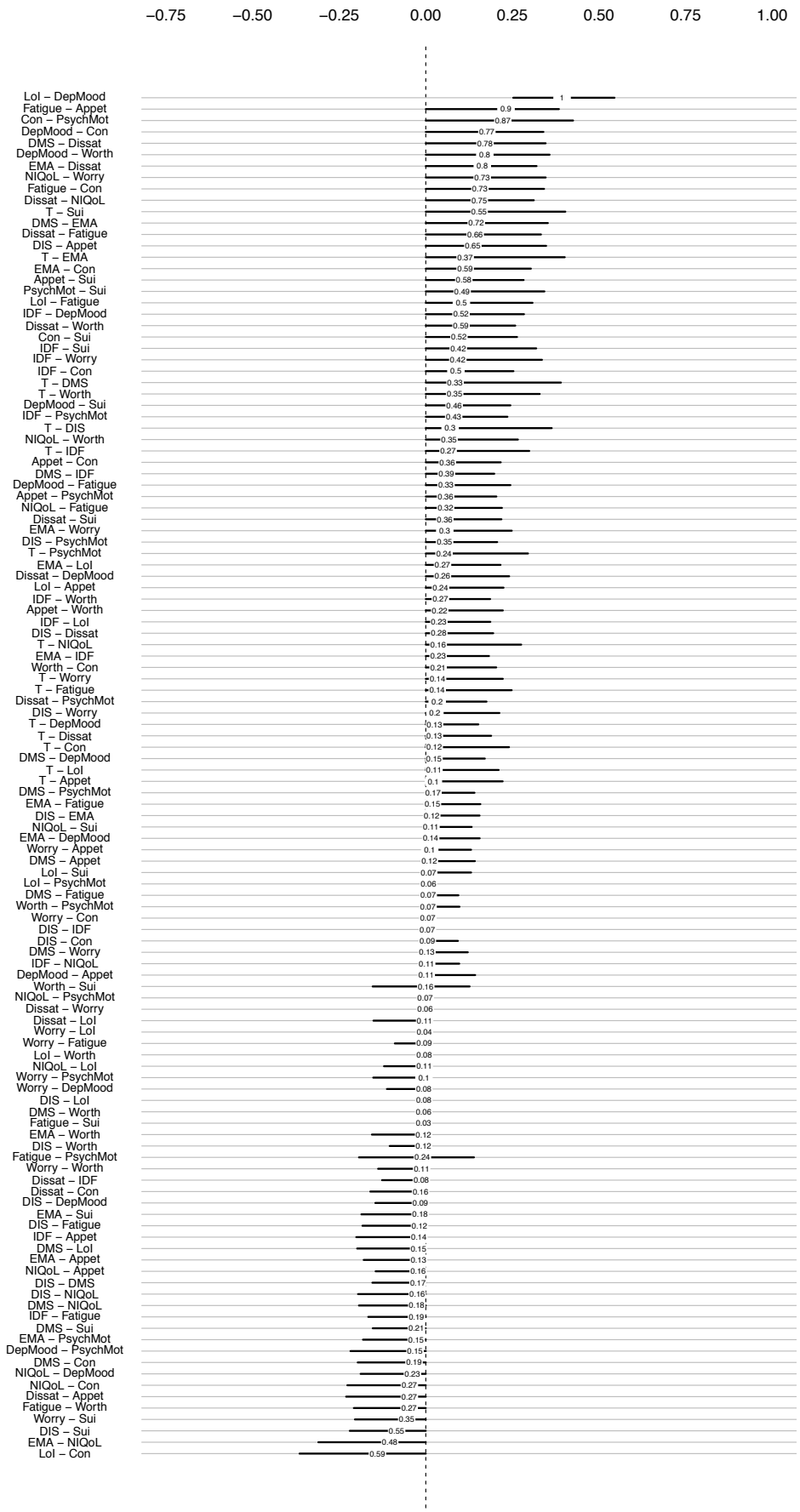

Figure S16. Bootstrapped sampling distribution of the edge weights of the regularized network of T1.

Supplementary Figure 17.

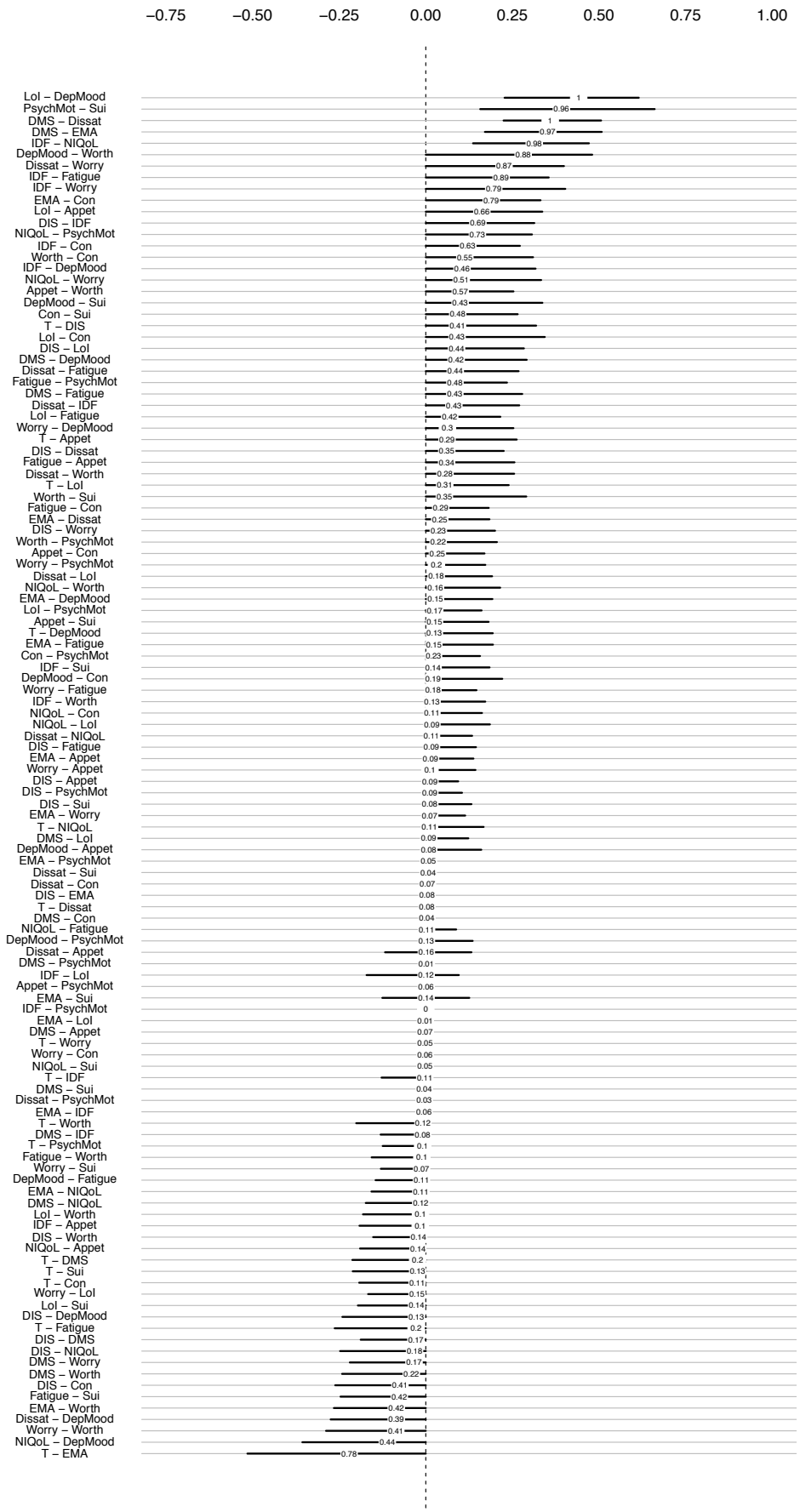

Figure S17. Bootstrapped sampling distribution of the edge weights of the regularized network of T2.

Supplementary Figure 18.

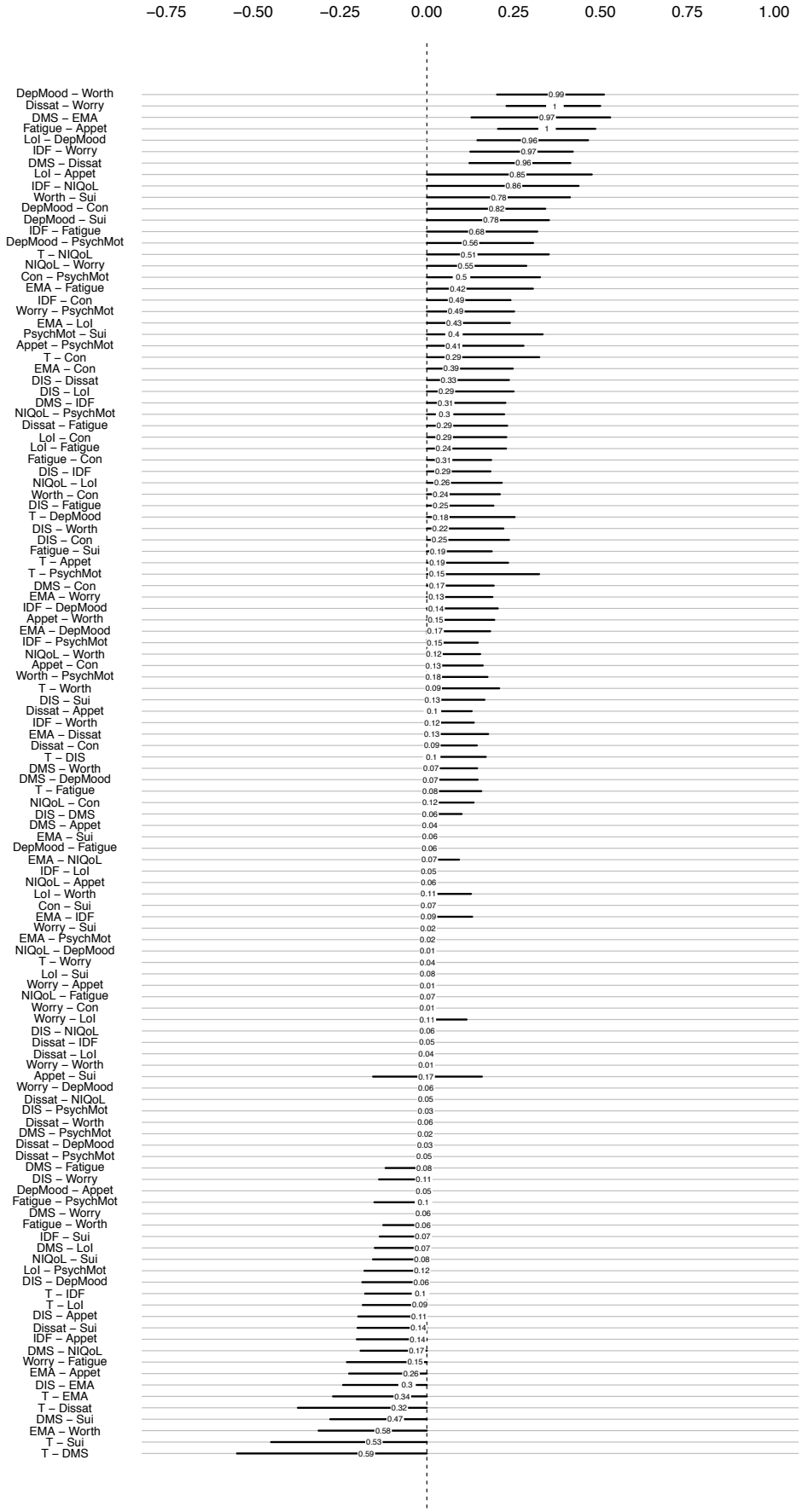

Figure S18. Bootstrapped sampling distribution of the edge weights of the regularized network of T3.

Supplementary Figure 19.

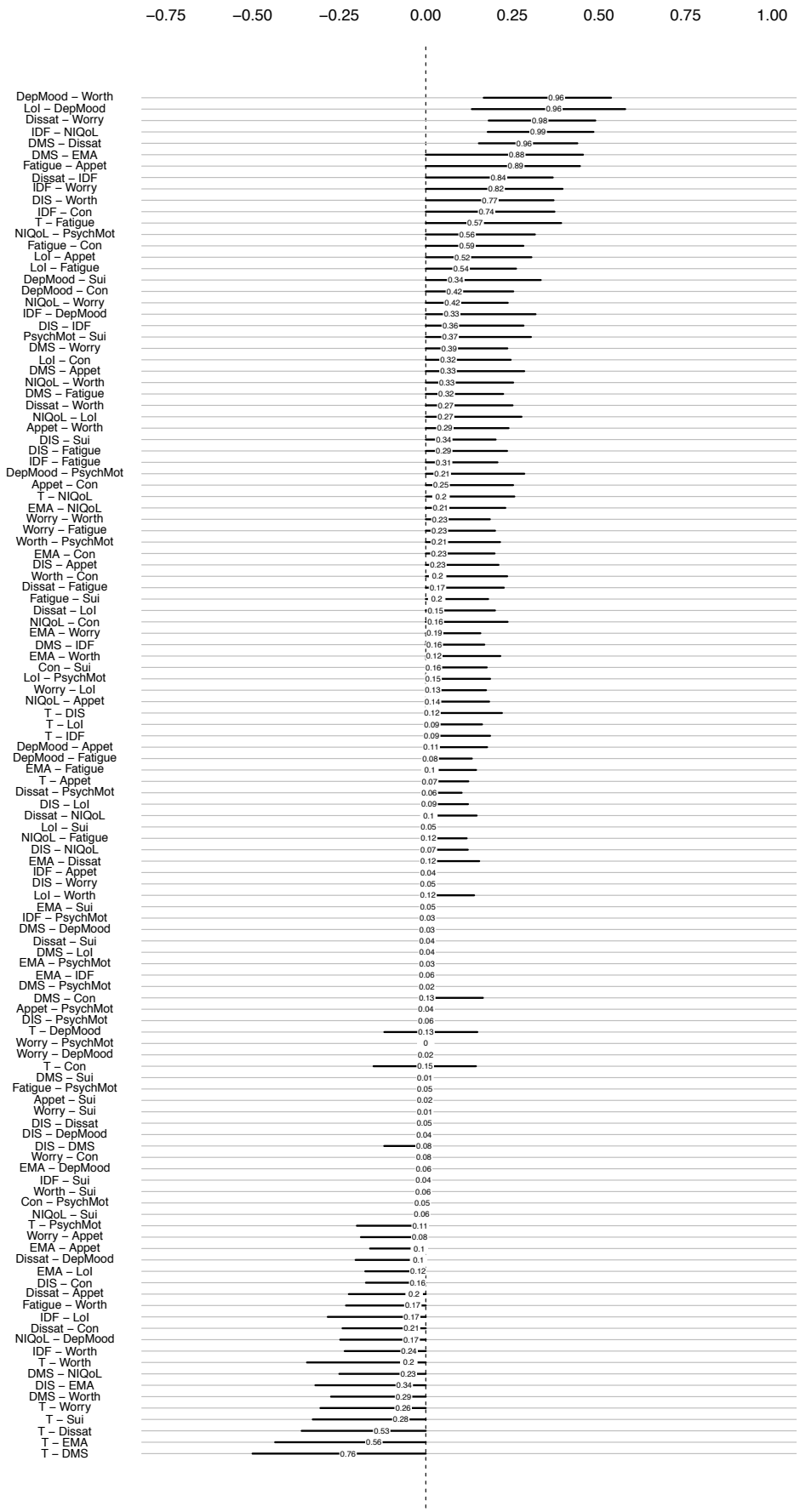

Figure S19. Bootstrapped sampling distribution of the edge weights of the regularized network of T4.

Supplementary Figure 20.

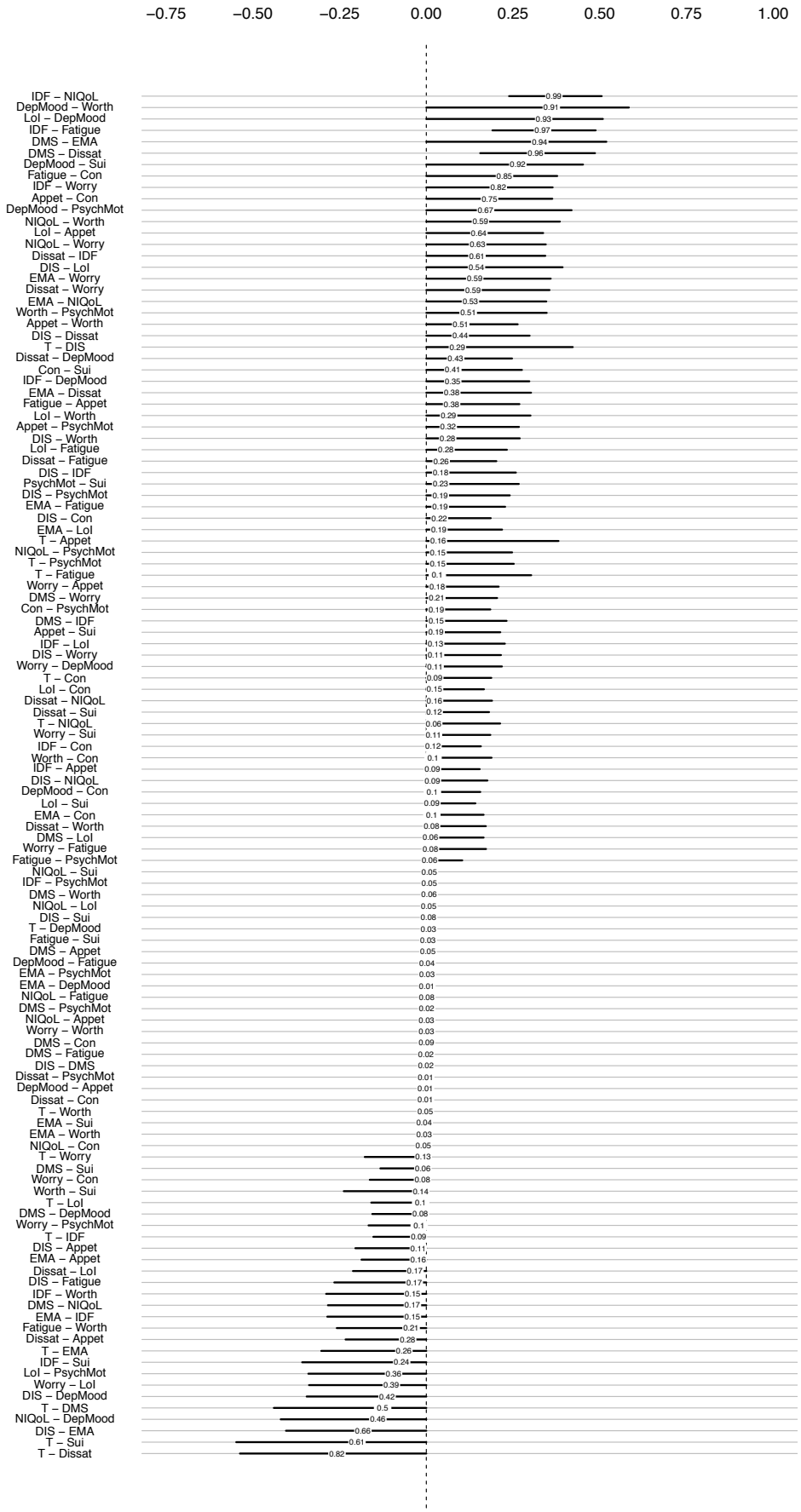

Figure S20. Bootstrapped sampling distribution of the edge weights of the regularized network of T5.

Supplementary Figure 21.

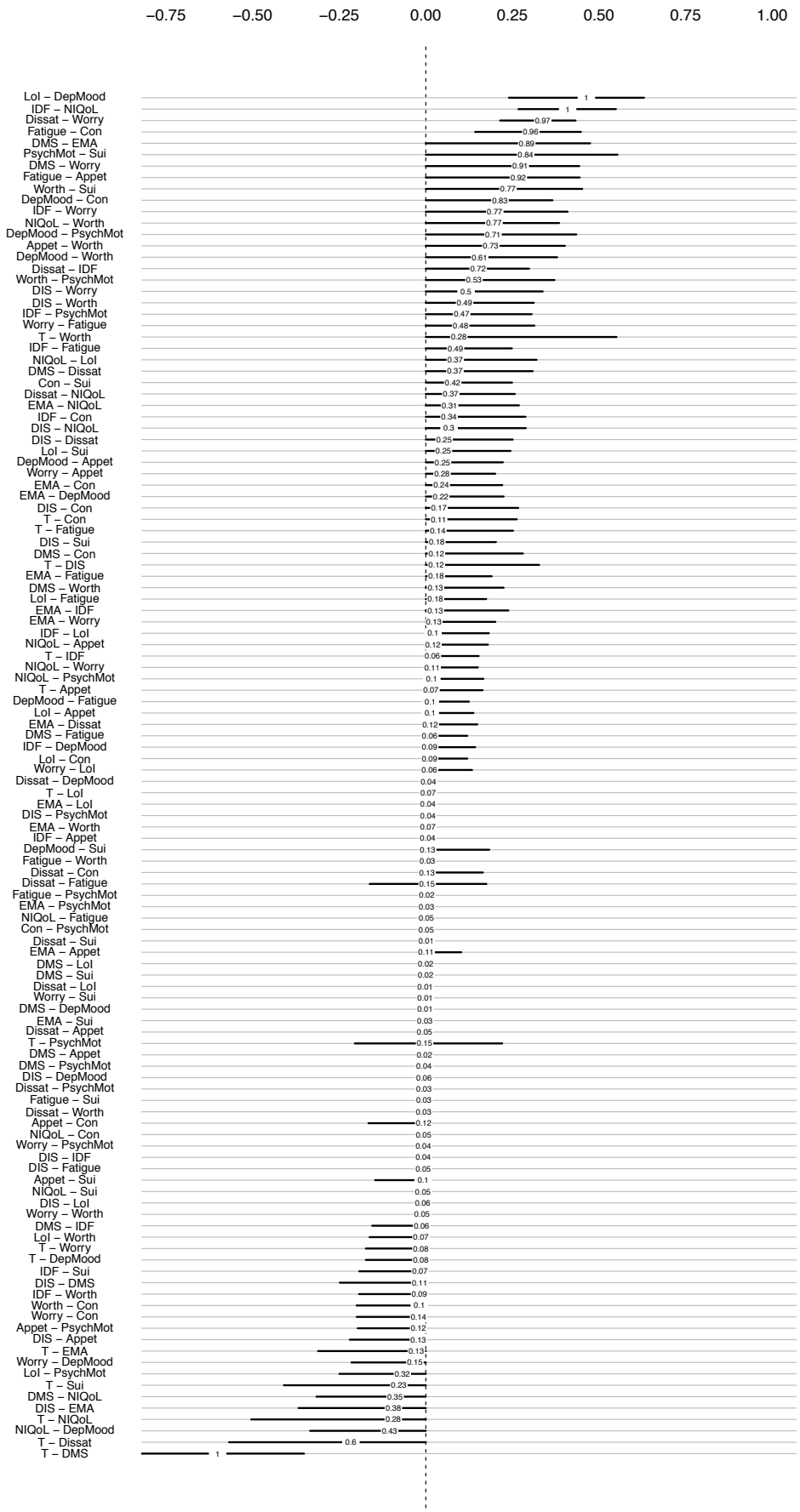

Figure S21. Bootstrapped sampling distribution of the edge weights of the regularized network of T6.

Supplementary Figure 22.

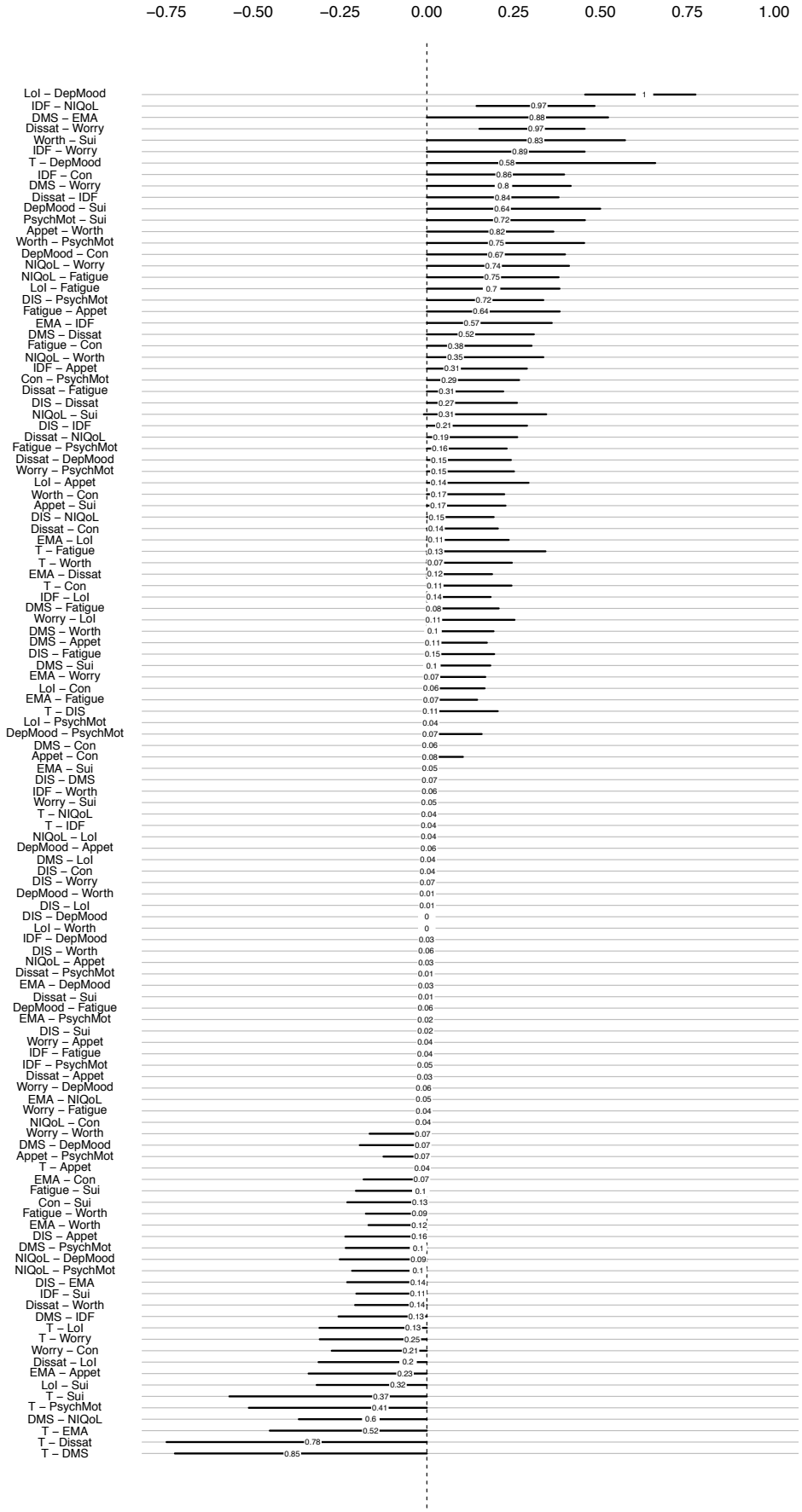

Figure S22. Bootstrapped sampling distribution of the edge weights of the regularized network of T7.

Supplementary Figure 23.

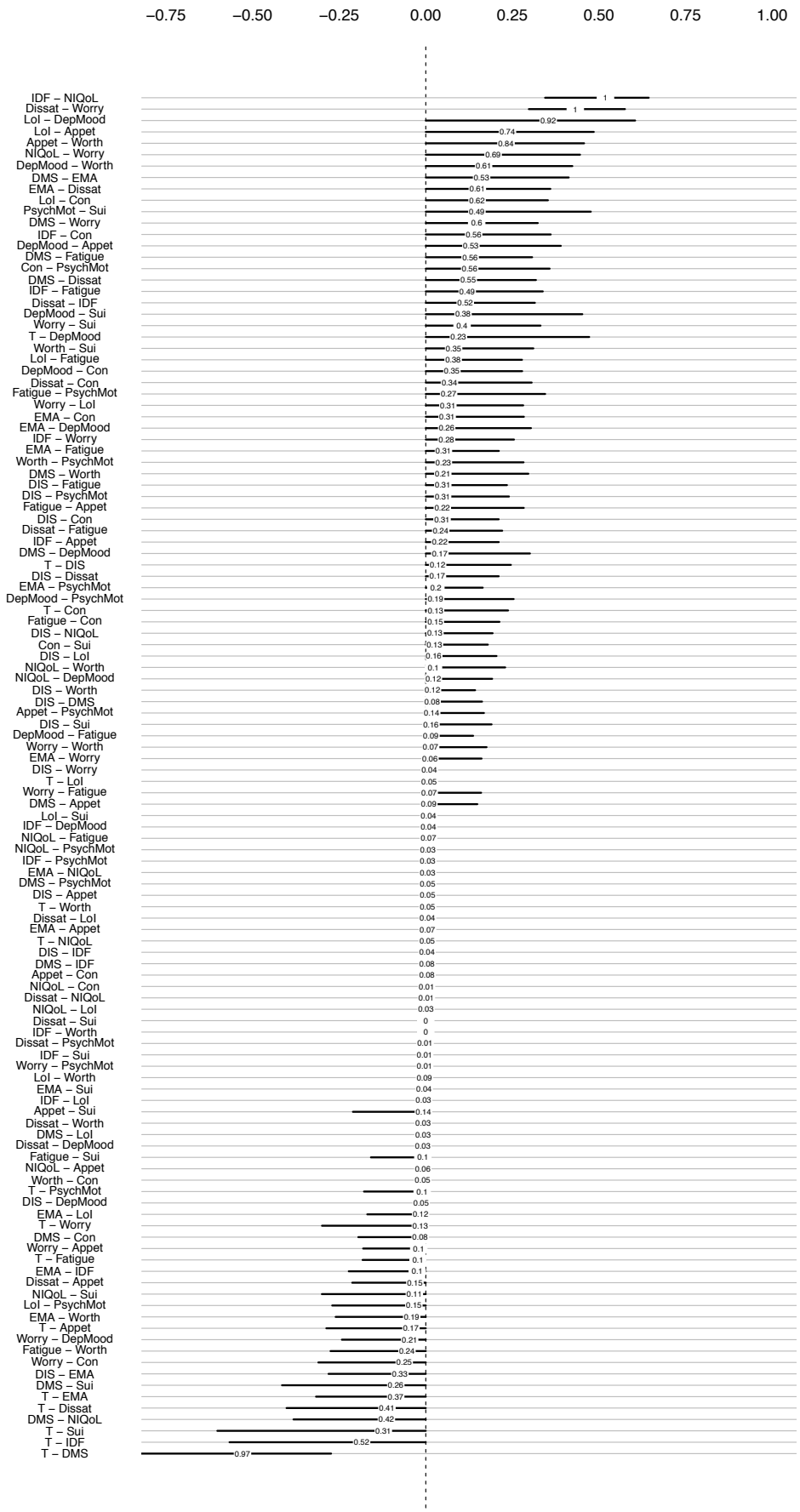

Figure S23. Bootstrapped sampling distribution of the edge weights of the regularized network of T8.

Supplementary Figure 24.

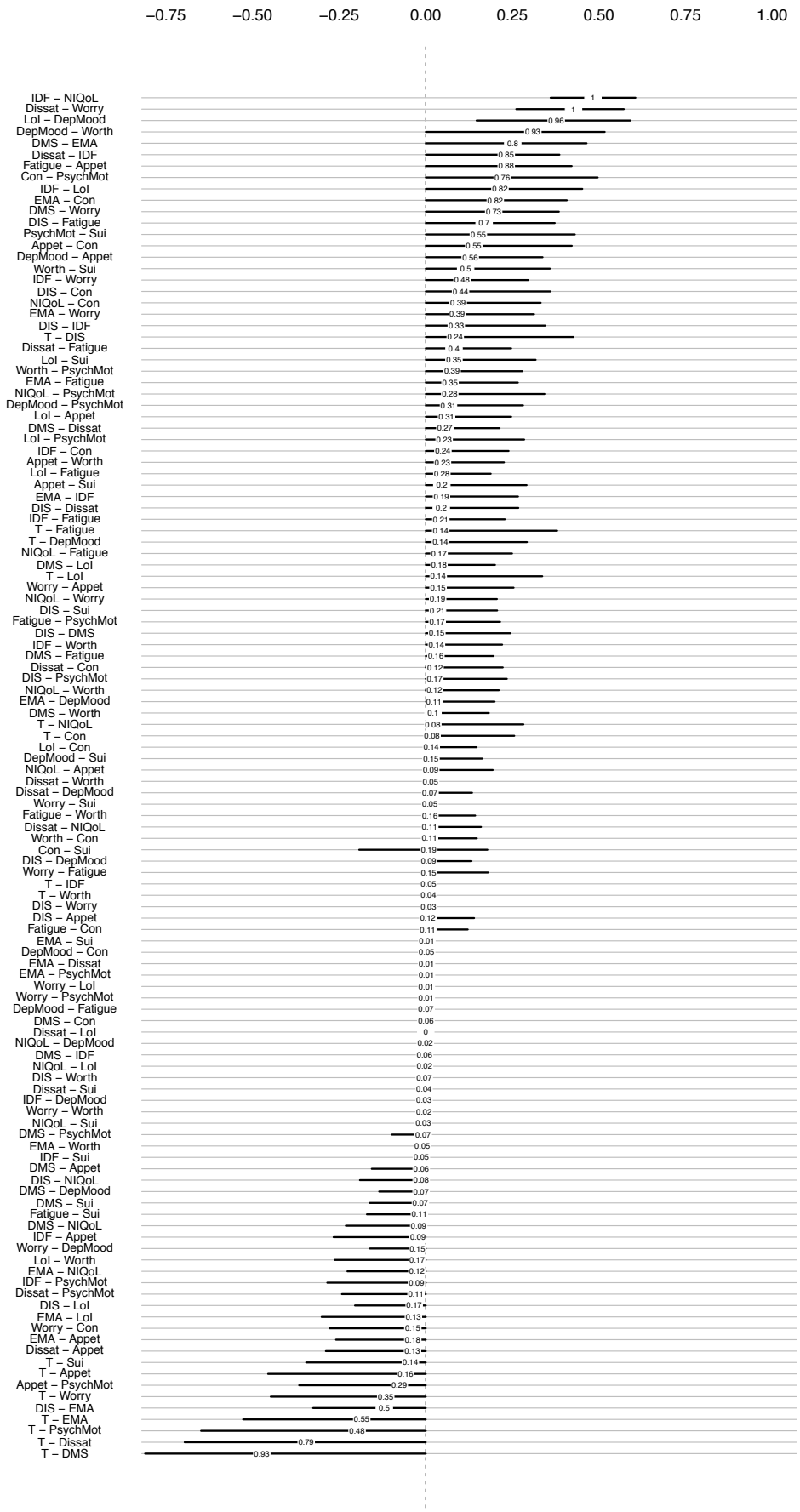

Figure S24. Bootstrapped sampling distribution of the edge weights of the regularized network of T9.