Aberrant functional connectivity in depression as an index of state and trait rumination

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Supplemental Material

Detailed information on the depressed sample

Amongst the most frequently used medication in the MDD group were Selective Serotonin Reuptake Inhibitors (15% of the sample), Serotonin–Norepinephrine Reuptake Inhibitors (8.3%), Noradrenergic and Specific Serotonergic Antidepressants (5%), Tricyclic Antidepressants (3.4%), Melatonin Agonists (1.7%) and Hypericum perforatum (3.4%). Regarding life-time diagnoses, 8.33% were diagnosed each with PDD and Alcohol Abuse, 6.66% with Panic Disorder, 3.33% each with Social Phobia, Specific Phobia and Bulimia Nervosa and 1.66% had each diagnosis of Obsessive Compulsive Disorder, Posttraumatic Stress Disorder and Anorexia Nervosa.

Additional information on the computation of the state-rumination scale

VAS scales for assessing processes during the resting-state comprised the following items:

Mind-wandering:
1) I felt relaxed.
2) I let my mind flow.

Rumination:
3) I ruminated (in the sense of revolving thoughts).
4) I thought about things I have to do/ tried to make plans.
5) I tried to fight certain experiences.
6) I felt stressed.

Focus on sensations:
7) I felt body sensations.
8) I concentrated on things I hear.
   Fight against fatigue:
9) I thought about the duration of the measurement.
10) I needed to fight falling asleep.

Additional information on the rating of the self-report form

To validate the used VAS scales and for reasons of additional information on resting-state processes, we also used a qualitative self-report form. On a blank page, subjects were asked to note the experiences they had during the resting-state measurement. The instruction was as follows:

“Please describe in the following what you did during the resting state measurement and how you felt. You may answer the following questions: What did you feel and think during the measurement? How did you react to your thoughts and feelings? What consequences followed your reactions?"

The texts were screened and categorized by two independent raters to assess qualitative measures of processes during resting-state according to qualitative methods: First, self-report forms were analyzed and categories were built and defined until saturation was reached. The following categories were defined:

- Mind-wandering: The subject expressed to be in a relaxed mood and let his mind flow in an unconstrained way without any focus on a particular subject.
  Example: “I relaxed and let my mind flow.”
  Example: “I thought about things that matter to me, but I was not stuck in my thoughts. I liked to let my mind flow.”

- Rumination: The subject expressed a repetitive stressful style of thinking about an unfinished concern that leads to the urge of suppressing the inner experience.
  Examples: “I thought about a stressful meeting I had at work, which made me nervous, so I tried to distract myself from that memory.” “I thought about an argument with my boyfriend and asked myself what I am doing wrong.”

- Focus on body sensations: The subject expressed an attentional focus on their body.
  Examples: “I focused on my breathing.” “I felt my body and my heartbeat.”

- Mindfulness/Relaxation training: The subject expressed to be in a mindful state (detachment from cognition, concentration on breathing with detached mind) or
to perform some kind of relaxation technique (e.g. progressive muscle relaxation).
Example: “I focused on my breathing and watched my mind in a detached way.”
• Suppression: The subject expressed withdrawal from or suppression of unpleasant inner experiences.
• Boredom: The subject expressed that the resting-state was boring.
• Unfinished business: The subject expressed thoughts about things they will do. Examples: “I thought about what I would eat for dinner and decided to eat pizza.” “I thought about the homework I have to do.”
• Thinking about the measurement: The subject expressed thoughts about the given instructions or how their data might look like.
• Fight against fatigue: The subject expressed feeling sleepy or trying not to fall asleep.
• Thoughts about the duration of the measurement: The subject expressed thoughts about the duration of the measurement or counted the time.
Afterwards, the most common categories were used to categorize self-report forms by two independent psychologists.

Influence of cofounders
Regarding effects of other resting-state process variables, there was no effect for the factors “focus on sensations” and “fighting against fatigue”. One reason for this finding may be that the variance for these scales was smaller, since many participants focused on body sensations and felt sleepy at some point of the resting-state measurement. In contrast to that, the scale for measuring mind-wandering was positively associated with FC in the DMN, as expected (see supplemental material Figure S2). NBS analysis of the factor revealed a significant (p=.026±0.0045) network with 28 nodes and 39 edges, reflecting higher FC in participants reporting high mind-wandering (see supplemental material Figure S3 and Table S1).
Medication status had no effect on FC-differences between depressed medicated and depressed non-medicated subjects (p>.1).
**FC properties in the probeset**

For the whole sample, FC coefficients in the used probeset showed an expected distribution with high connectivity within DMN regions of the middle parietal cortex and the supramarginal gyrus (SupG) and angular gyrus (AngG). These regions showed – as assumed – low to negative FC with the temporal cortex consisting of the superior temporal gyrus, fusiform gyrus and subcentral area (see figure S1). In addition, the self-reported amount of mind-wandering correlated positively with FC measures (see supplemental material Figure S2) and showed significant network differences between subjects reporting high vs. low mind-wandering within the DMN with hub nodes in the middle somatosensory cortex (SAC) and the SupG (see supplemental material: table S1 and Figure S3).

![Figure S1](image)

**Figure S1.** Mean FC of the sample in the different regions of the probeset
Figure S2. Correlations of trait rumination, state rumination and mind-wandering with FC.
Figure S3. NBS analysis of the main effect for mind-wandering. Left: Significantly hyperconnected network for “high mind-wanderers”. Right: FC maps for the contrast “high vs. low mind-wandering” in the seed region of the left supramarginal cortex. Results of the NBS analysis can be seen in table s1.
| Channel | Region | RSS $t$ | Rum $t$ | Mind-wandering $t$ |
|---------|--------|--------|--------|-------------------|
| 1       | PSC    | 0      | 2      | 0                 |
| 2       | SupG   | 1      | 9      | 5                 |
| 3       | SupG   | 10     | 0      | 8                 |
| 4       | SAC    | 10     | 1      | 3                 |
| 5       | SAC    | 6      | 2      | 4                 |
| 6       | SAC    | 10     | 3      | 6                 |
| 7       | SAC    | 1      | 0      | 1                 |
| 8       | SupG   | 1      | 0      | 2                 |
| 9       | SupG   | 0      | 0      | 1                 |
| 10      | SA     | 7      | 0      | 1                 |
| 11      | STG    | 1      | 3      | 0                 |
| 12      | SupG   | 2      | 13     | 10                |
| 13      | SupG   | 8      | 1      | 0                 |
| 14      | AngG   | 3      | 0      | 1                 |
| 15      | SAC    | 7      | 0      | 3                 |
| 16      | SAC    | 21     | 6      | 4                 |
| 17      | SAC    | 2      | 3      | 3                 |
| 18      | SupG   | 7      | 0      | 2                 |
| 19      | SupG   | 4      | 0      | 1                 |
| 20      | PSC    | 1      | 0      | 0                 |
| 21      | STG    | 2      | 0      | 2                 |
| 22      | STG    | 0      | 1      | 4                 |
| 24      | AngG   | 2      | 0      | 0                 |
| 26      | SAC    | 3      | 2      | 2                 |
| 27      | SAC    | 3      | 2      | 0                 |
| 28      | SAC    | 2      | 1      | 1                 |
| 29      | AngG   | 3      | 0      | 2                 |
| 30      | SupG   | 1      | 0      | 0                 |
| 31      | STG    | 0      | 0      | 1                 |
| 32      | MTG    | 0      | 0      | 1                 |
| 34      | AngG   | 1      | 0      | 0                 |
| 35      | SAC    | 0      | 1      | 0                 |
| 36      | SAC    | 2      | 1      | 2                 |
| 37      | SAC    | 7      | 1      | 4                 |
| 38      | V3     | 2      | 2      | 0                 |
| 39      | AngG   | 1      | 0      | 2                 |
| 40      | AngG   | 4      | 0      | 1                 |
| 45      | AngG   | 1      | 0      | 0                 |
| 46      | V3     | 2      | 1      | 0                 |
| 47      | V3     | 18     | 1      | 2                 |
| 48      | V3     | 3      | 1      | 1                 |
| 49      | V3     | 12     | 0      | 0                 |
| 50      | AngG   | 3      | 0      | 0                 |

|          | nodes  | edges | p-value  |
|----------|--------|-------|----------|
|          | 37     | 87    | 0.002±.0013 |
|          | 21     | 29    | 0.022±.0041 |
|          | 28     | 39    | 0.023±.0041 |

Table S1.: Results of the NBS analysis for the main effects of trait-rumination (RSS), state-rumination (Rum) and mind-wandering. Bold numbers are hub nodes.
Figure S4. NBS analysis of the main effect for trait rumination. Left: Significantly disconnected network for “high trait-ruminators”. Right: FC maps for the contrast “high vs. low trait-ruminators” in the seed region of the middle SAC. Cold colours indicate higher FC for the low-rumination group. Results of the NBS analysis can be seen in table s1.
Figure S5. NBS analysis of the main effect for state-rumination. Left: Significantly disconnected network for “high state-ruminators”. Right: FC maps for the contrast “high vs. low state-ruminators” in the seed region of the middle SAC. Cold colours indicate higher FC for the low-rumination group. Results of the NBS analysis can be seen in table s1.
|       | Seed13 |   |   | Seed4 |   | Seed29 |   |   |
|-------|--------|---|---|-------|---|--------|---|---|
|       | RSS    |   |   | RSS   |   |        |   |   |
| Ch    | Rho    | p-value | rho | p-value | rho | p-value | rho | p-value |
| 1     | -0.08  | 0.469 | -0.14 | 0.197 | -0.05 | 0.653 | -0.20 | 0.062 |
| 2     | -0.25  | 0.020 | -0.09 | 0.008 | -0.31 | 0.004 | -0.22 | 0.047 |
| 3     | -0.23  | 0.034 | -0.17 | 0.126 | -0.27 | 0.014 | -0.09 | 0.429 |
| 4     | -0.35  | 0.001 | -0.14 | 0.191 | -0.25 | 0.022 | -0.17 | 0.122 |
| 5     | -0.40  | 0.000 | -0.15 | 0.160 | -0.28 | 0.009 | -0.25 | 0.023 |
| 6     | -0.41  | 0.000 | -0.22 | 0.040 | -0.28 | 0.019 | -0.17 | 0.122 |
| 7     | -0.40  | 0.000 | -0.14 | 0.211 | -0.22 | 0.041 | -0.20 | 0.066 |
| 8     | -0.25  | 0.022 | -0.05 | 0.648 | -0.26 | 0.019 | -0.17 | 0.122 |
| 9     | -0.20  | 0.065 | -0.05 | 0.664 | -0.19 | 0.076 | -0.15 | 0.170 |
| 10    | -0.36  | 0.011 | -0.17 | 0.118 | -0.14 | 0.191 | -0.20 | 0.369 |
| 11    | -0.12  | 0.259 | -0.21 | 0.057 | -0.13 | 0.253 | -0.06 | 0.571 |
| 12    | -0.02  | 0.830 | -0.01 | 0.964 | -0.27 | 0.012 | -0.12 | 0.260 |
| 13    | -0.29  | 0.007 | -0.08 | 0.467 | -0.27 | 0.012 | -0.11 | 0.303 |
| 14    | -0.25  | 0.022 | -0.11 | 0.315 | -0.30 | 0.006 | -0.10 | 0.371 |
| 15    | -0.42  | 0.000 | -0.29 | 0.007 | -0.28 | 0.009 | -0.08 | 0.447 |
| 16    | -0.23  | 0.034 | -0.16 | 0.134 | -0.28 | 0.009 | -0.21 | 0.051 |
| 17    | -0.33  | 0.002 | -0.02 | 0.891 | -0.31 | 0.004 | -0.11 | 0.306 |
| 18    | -0.21  | 0.053 | -0.04 | 0.749 | -0.28 | 0.010 | -0.09 | 0.432 |
| 19    | -0.07  | 0.500 | -0.17 | 0.124 | -0.19 | 0.083 | -0.12 | 0.258 |
| 20    | -0.25  | 0.023 | -0.04 | 0.692 | -0.15 | 0.176 | -0.25 | 0.021 |
| 21    | 0.01   | 0.916 | 0.10 | 0.365 | 0.07 | 0.534 | -0.13 | 0.236 |
| 22    | -0.10  | 0.372 | -0.02 | 0.872 | -0.07 | 0.527 | 0.07 | 0.548 |
| 23    | -0.19  | 0.087 | -0.14 | 0.212 | -0.25 | 0.020 | 0.01 | 0.933 |
| 24    | -0.13  | 0.240 | -0.08 | 0.496 | -0.24 | 0.027 | 0.01 | 0.952 |
| 25    | -0.18  | 0.111 | -0.08 | 0.453 | -0.20 | 0.068 | 0.00 | 0.190 |
| 26    | -0.16  | 0.143 | -0.11 | 0.327 | -0.22 | 0.045 | -0.05 | 0.677 |
| 27    | -0.20  | 0.064 | -0.01 | 0.923 | -0.28 | 0.011 | -0.16 | 0.157 |
| 28    | -0.30  | 0.006 | -0.02 | 0.836 | -0.36 | 0.001 | -0.17 | 0.132 |
| 29    | -0.22  | 0.048 | -0.07 | 0.551 | -0.21 | 0.050 | -0.02 | 0.867 |
| 30    | 0.03   | 0.774 | 0.07 | 0.548 | 0.03 | 0.774 | -0.06 | 0.578 |
| 31    | 0.23   | 0.038 | 0.05 | 0.620 | 0.18 | 0.097 | 0.04 | 0.738 |
| 32    | 0.04   | 0.730 | 0.12 | 0.271 | 0.01 | 0.958 | 0.08 | 0.467 |
| 33    | 0.02   | 0.882 | 0.00 | 0.987 | -0.13 | 0.235 | -0.12 | 0.283 |
| 34    | -0.17  | 0.133 | -0.13 | 0.249 | -0.27 | 0.014 | -0.04 | 0.706 |
| 35    | -0.19  | 0.080 | -0.06 | 0.618 | -0.20 | 0.067 | -0.06 | 0.580 |
| 36    | -0.25  | 0.022 | -0.08 | 0.047 | -0.28 | 0.010 | -0.01 | 0.896 |
| 37    | -0.20  | 0.074 | -0.18 | 0.104 | -0.26 | 0.017 | -0.17 | 0.134 |
| 38    | -0.21  | 0.054 | 0.00 | 0.989 | -0.28 | 0.011 | -0.15 | 0.163 |
| 39    | -0.23  | 0.032 | 0.03 | 0.792 | -0.34 | 0.001 | -0.18 | 0.101 |
| 40    | -0.02  | 0.852 | -0.13 | 0.226 | 0.06 | 0.608 | 0.01 | 0.932 |
| 41    | 0.00   | 0.000 | 0.00 | 0.000 | 0.00 | 0.000 | 0.00 | 0.000 |
Table S2. Korrelations between FC to the seed regions and state- and trait rumination for the whole sample (N=84). P-values are uncorrected, correlations greater .317 are significant after controlling for Type-I errors.
| Scale Mind Wandering | RRS | Scale Rum | Scale FAF | Scale Wandering | Scale Body |
|---------------------|-----|-----------|----------|----------------|------------|
| Spearman’s Rho      | 1.000 | 0.317** | 0.169 | -0.431** | 0.074 |
| Sig. (2-seitig)     | 84   | 84        | 84      | 84            | 84         |
| N                   | 84   | 84        | 84      | 84            | 84         |
| Scale Rum           | 0.317* | 1.000     | -0.063 | -0.516** | -0.287** |
| Sig. (2-seitig)     | 84   | 84        | 84      | 84            | 84         |
| N                   | 84   | 84        | 84      | 84            | 84         |
| Scale FAF           | 0.169 | -0.063    | 1.000   | -0.391* | -0.225* |
| Sig. (2-seitig)     | 84   | 84        | 84      | 84            | 84         |
| N                   | 84   | 84        | 84      | 84            | 84         |
| Scale Body          | 0.074 | 0.074     | 0.074   | 0.074         | 0.074     |
| Spearman’s Rho      | -0.431** | -0.516**  | -0.391* | 1.000         | -0.249** |
| Sig. (2-seitig)     | 84   | 84        | 84      | 84            | 84         |
| N                   | 84   | 84        | 84      | 84            | 84         |
| Scale Wandering     | 0.000 | 0.000     | 0.000   | 0.000         | 0.000     |
| Sig. (2-seitig)     | 84   | 84        | 84      | 84            | 84         |
| N                   | 84   | 84        | 84      | 84            | 84         |
| Scale Body          | 0.221* | 0.070      | -0.180 | 0.535** | -0.316** |
| Spearman’s Rho      | 0.444 | 0.528      | 0.100  | 0.000         | 0.000     |
| Sig. (2-seitig)     | 84   | 84        | 84      | 84            | 84         |
| N                   | 84   | 84        | 84      | 84            | 84         |
| Relaxing            | 0.105 | 0.683**    | -0.048 | -0.263* | -0.251* |
| Spearman’s Rho      | 0.342 | 0.000      | 0.662  | 0.015         | 0.021     |
| Sig. (2-seitig)     | 84   | 84        | 84      | 84            | 84         |
| N                   | 84   | 84        | 84      | 84            | 84         |
| Mindflow            | 0.313* | 0.801**    | 0.125  | -0.533** | -0.195 |
| Spearman’s Rho      | 0.004 | 0.000      | 0.257  | 0.000         | 0.003     |
| Sig. (2-seitig)     | 84   | 84        | 84      | 84            | 84         |
| N                   | 84   | 84        | 84      | 84            | 84         |
| Body Sensation      | 0.090 | -0.125    | -0.136 | -0.316* | 0.815* |
| Spearman’s Rho      | 0.415 | 0.256      | 0.218  | 0.003         | 0.000     |
| Sig. (2-seitig)     | 84   | 84        | 84      | 84            | 84         |
| N                   | 84   | 84        | 84      | 84            | 84         |
| Control Myself      | 0.253 | 0.071      | 0.276  | -0.578* | 0.148 |
| Spearman’s Rho      | 0.020 | 0.519      | 0.011  | 0.000         | 0.000     |
| Sig. (2-seitig)     | 84   | 84        | 84      | 84            | 84         |
| N                   | 84   | 84        | 84      | 84            | 84         |
| Supression          | 0.193 | -0.110    | 0.038  | -0.431* | 0.718 |** |
| Spearman’s Rho      | 0.079 | 0.319      | 0.731  | 0.000         | 0.000     |
| Sig. (2-seitig)     | 84   | 84        | 84      | 84            | 84         |
| N                   | 84   | 84        | 84      | 84            | 84         |
| Feeling Stressed    | 0.387** | 0.646**    | -0.140 | 0.465** | 0.333 |
| Spearman’s Rho      | 0.000 | 0.000      | 0.205  | 0.000         | 0.000     |
| Sig. (2-seitig)     | 84   | 84        | 84      | 84            | 84         |
| N                   | 84   | 84        | 84      | 84            | 84         |
| Thinking about the duration of the measurement | 0.313* | 0.534** | 0.250 | -0.649** | -0.035 |
| Spearman’s Rho      | 0.044 | 0.000      | 0.022  | 0.000         | 0.749     |
| Sig. (2-seitig)     | 84   | 84        | 84      | 84            | 84         |
| N                   | 84   | 84        | 84      | 84            | 84         |
| Supression          | 0.369** | 0.149      | 0.692** | -0.582** | 0.070 |
| Spearman’s Rho      | 0.001 | 0.176      | 0.000  | 0.000         | 0.526     |
| Sig. (2-seitig)     | 84   | 84        | 84      | 84            | 84         |
| N                   | 84   | 84        | 84      | 84            | 84         |
| Feeling Stressed    | 0.147 | 0.032      | 0.864** | -0.382* | -0.217* |
| Spearman’s Rho      | 0.182 | 0.772      | 0.000  | 0.000         | 0.047     |
| Sig. (2-seitig)     | 84   | 84        | 84      | 84            | 84         |

Table S3. Correlations of the scales and between the scales and the Items of the Resting State Questionnaire.
| Item                                      | Mean  | SD    | Median | Min | Max |
|-------------------------------------------|-------|-------|--------|-----|-----|
|                                            | HC    | MDE   | HC     | MDE |     | HC  | MDE |
| I felt relaxed                            | 86.46 | 68.08 | 11.46  | 24.17 | 90.00 | 70.00 | 60   | 5   | 100 | 100 |
| I let my mind flow                        | 71.88 | 71.08 | 26.777 | 24.32 | 80.00 | 80.00 | 10   | 10  | 100 | 100 |
| I thought about things I have to do       | 32.29 | 38.02 | 28.589 | 30.68 | 27.50 | 30.00 | 0    | 0   | 90  | 100 |
| I ruminated                               | 14.33 | 34.58 | 17.166 | 31.21 | 10.00 | 22.50 | 0    | 0   | 50  | 100 |
| I felt sensations of my body              | 56.67 | 37.68 | 31.021 | 28.13 | 60.00 | 30.00 | 0    | 0   | 100 | 100 |
| I needed to control myself                | 23.29 | 33.18 | 25.506 | 30.58 | 15.00 | 20.00 | 0    | 0   | 80  | 100 |
| I heard sounds                            | 32.92 | 25.32 | 30.321 | 24.63 | 22.50 | 20.00 | 0    | 0   | 100 | 100 |
| I needed to suppress inner experiences    | 4.79  | 19.62 | 7.442  | 22.76 | 0.00  | 10.00 | 0    | 0   | 30  | 80  |
| I felt stressed                           | 7.71  | 16.90 | 15.250 | 21.88 | 0.00  | 10.00 | 0    | 0   | 60  | 96  |
| I thought about how long the measurement  | 24.75 | 36.70 | 31.489 | 26.77 | 10.00 | 30.00 | 0    | 0   | 100 | 98  |
| will last                                 |       |       |        |      |      |      |      |     |     |     |
| I fought against falling asleep           | 32.29 | 42.07 | 35.201 | 32.71 | 20.00 | 33.50 | 0    | 0   | 100 | 100 |

Table S4. Item characteristics of the resting-state VAS scales.
**Supplementary Analysis:**

As supplementary exploratory analysis, we performed two different analyses that were not directly related to the research question, but gave additional information for the interpretation of the results:

1) We performed a rumination subgroup analysis as defined by the qualitative rumination rating (based on the self-report form) in the MDD group only. To this end, the 40% of the MDD subjects reporting rumination in the self-report form during resting-state were compared with the 60% which did not report rumination in the self-report form.

2) In the main analysis, the RRS total score was used. In a third analysis, we also correlated sub-scores of the questionnaire (brooding and reflection) with the FC scores in the whole sample.

**Supplementary Analysis of the qualitative rumination rating in the MDD group only.**

The analysis of the 40% of the depressed subjects that reported rumination in the self-report form as compared to the 60% of the depressed subjects that did not report rumination revealed a significant disconnected network (with 36 nodes and 67 edges, \( t_{(58)} = 2.7, p = .003 \)).

The network – which showed lower FC in high ruminating subjects – was bilaterally organized and had hubs in the bilateral fusiform gyri and somatosensory association cortex. However, inter-hemispheric disconnections were rare and mediated over central hubs. Effect sizes ranged between \( d = -0.44 \) to \( d = -0.96 \) within FC to the seed channel in the somatosensory association cortex and between \( d = -0.56 \) to \( d = -0.94 \) in the right fusiform gyrus.

![Brain Network Images](image)

Figure S6. Differences between the subgroup depressed high ruminators and depressed low ruminators according to the qualitative self-report forms. Blue colors indicate reduced FC in high ruminators.
Supplementary Analysis of RRS subscales Rumination and Reflection

As in the analysis of the total RRS score, correlations between FC and the subscale brooding showed negative associations ranging from $\rho = -.21$ to $\rho = -.36$ ($p<.05$ to $p<.001$). The negative relationship between brooding and FC covered areas including the supramarginal gyrus, angular gyrus, somatosensory association cortex, primary somatosensory cortex and the fusiform gyrus. Only the correlation to the right angular gyrus remained significant after controlling for multiple comparisons. In contrast to that, reflection only showed negative correlations with the seed channel 29 and 13. Here, correlations were sparse and located in the somatosensory association cortex and the right supramarginal gyrus. No correlation remained significant after controlling for multiple comparisons.

Figure S7. Correlations between seed-channel FC in the depression-related network and subscales of the RRS