# Supplemental Material

## Supplement 1: Choosing the participants

The second data freeze (26.04.2018) from the FOR2107 cohort was used comprising N=1 623 participants, of which N=629 patients suffered from MDD. N=567 patients suffering from MDD had an MRI scan, displayed no pathological variants in the T1 image and the DTI image survived quality control. Twelve participants were excluded due to a diagnosis of substance dependence or dysthymia without a depressive episode, craniocerebral injury, severe chronic illnesses or general study compliance (N=555). Lastly, N=531 participants suffering from MDD completely filled out the questionnaire and completed the clinical interview (current depressive episode: N=250, partial remission: N=141, complete remission: N=140).

**Supplement 2: Post-hoc associations with other measures of course of illness**

We argue that the number of previous hospitalizations is the most reliable measure of course of illness. Nonetheless, we tried to extend the association between number of hospitalizations and FA to other measures of course of illness (number of hospitalizations, time in inpatient treatment, month since first psychiatric treatment, number of depressive episodes). To this end, we calculated a principal component analysis (KMO: .579; Bartlett-test of sphericity: χ²(6)=599.27, *p*<.001, all anti-image matrices >.546). N=402 MDD patients provided all the necessary information and were used in the following analyses. Using the Kaiser rule (eigenvalue > 1) we found a single component (eigenvalue 2.12, Cronbach’s α=.658) which was confirmed in the scree-plot employing the elbow criteria. This factor was termed the “course of illness” factor explaining 52.93% of the variance. The factor loadings are .920 for the time in inpatient treatment, .915 for the number of hospitalizations, .577 for the month since the first psychiatric treatment and .316 for the number of depressive episodes. As expected, the number of depressive episodes showed the largest deviation from the other variables possibly due to its low reliability.

Using the mean extracted FA values from the significant cluster of the hospitalization association as dependent variable, age, sex, Marburg pre body-coil, Marburg post body-coil and TIV as nuisance variables, and the “course of illness” factor as independent variable confirmed the negative association between a more severe course of illness and reduced FA (*F*(1,395)=21.97, *p*<.001, *η²*=.053).

## Supplement 3: Checking for outliers in the first ANCOVA with disease state, course of illness and their interaction.

To check for the presence of influential data points the Cook’s distance for the regression with extracted mean MD and RD values as dependent variables, age, sex, TIV, Marburg pre body-coil, Marburg post body-coil as nuisance variables and disease state, number of hospitalizations and the disease state x number of hospitalizations interaction as regressors was calculated in SPSS (MD: *MCook*=.002, *SDCook*=.007, Range: ].000 - .123]; RD: *MCook*=.002, *SDCook*=.008, Range: ].000 - .122]). Five extreme values (*MCook* + 3\**SDCook*) for MD and 6 for RD were detected. Excluding extreme values, however, yielded similar results (MD: disease state: *β*=0.04, *p*=.236, number of hospitalizations: *β*=0.17, *p*< .001, disease state x number of hospitalizations: *β*=.01, *p*=.780; RD: disease state: *β*=-0.06, *p*=.116, number of hospitalizations: *β*=0.20, *p*< .001, disease state x number of hospitalizations: *β*<0.01, *p*=.976).

## Supplement 4: Checking for outliers in the first ANCOVA with symptom severity, course of illness and their interaction.

To check for the presence of influential data points the Cook’s distance for the regression with extracted mean FA, MD and RD values as dependent variable, age, sex, TIV, Marburg pre body-coil, Marburg post body-coil, BDI-score, number of hospitalizations and the BDI-score x number of hospitalizations interaction as regressors was calculated in SPSS (FA: *MCook*=.002, *SDCook*=.006, Range: ].000 - .120]; MD: *MCook*=.002, *SDCook*=.010, Range: ].000 - .199]; RD: *MCook*=.002, *SDCook*=.012, Range: ].000 - .250]). Two extreme values (*MCook* + 3\**SDCook*) were identified in FA and RD, 3 in MD. Excluding extreme values, however, yielded similar results (FA: BDI-score: *β*=0.01, *p*=.734, number of hospitalizations: *β*=-0.27, *p*<.001, BDI-score x number of hospitalizations interaction: *β*=0.01, *p*=.862; MD: BDI-score: *β*=0.02, *p*=.694, number of hospitalizations: *β*=0.22, *p*<.001, BDI-score x number of hospitalizations interaction: *β*=-0.04, *p*=.275; RD: BDI-score: *β*=0.02, *p*=.689, number of hospitalizations: *β*=0.24, *p*<.001, BDI-score x number of hospitalizations interaction: *β*=-0.02, *p*=.695).

## Supplement 5: Supplementary Tables

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| Supplementary Table 1*Anatomical regions for the significant effects of the analyses corrected for age, sex, TIV, site and scanner variables. Only values with a percentage larger than 1 in at least one DTI metric are depicted.* |
|  | Percentages |
| Region | MD | FA | RD |
| Disease state, alone |
| Corticospinal tract, L/R | 1.06 / 0.23 | - / 2.12 | 0.56 / 1.74 |
| Inferior fronto-occipital fasiculus, L/R | 0.05 / 0.24 | 2.57 / 2.74 | 2.37 / 0.70 |
| Inferior longitudinal fasciculus, L/R | 0.19 / 0.24 | 2.41 / 2.35 | 2.45 / 0.54 |
| Superior longitudinal fasciculus, L/R | 3.43 / 10.30 | 5.57 / 10.26 | 5.91 / 10.61 |
| Superior longitudinal fasciculus (temporal part), L/R | 1.72 / 3.41 | 2.86 / 3.35 | 3.10 / 3.65 |
| Number of hospitalizations, alone |
| Corticospinal tract, L/R | 0.01 / 3.25 | - / 1.18 | 0.39 / 1.21 |
| Forceps major, bilateral | 0.11 | 3.51 | 1.21 |
| Inferior fronto-occipital fasiculus, L/R | - / 2.93 | 3.51 / 5.53 | 1.58 / 3.60 |
| Inferior longitudinal fasciculus, L/R | - / 0.92 | 2.96 / 3.86 | 1.69 / 2.11 |
| Superior longitudinal fasciculus, L/R | 0.15 / 10.50 | 0.27 / 9.72 | 3.12 / 5.52 |
| Superior longitudinal fasciculus (temporal part), L/R | 0.09 / 3.30 | 0.16 / 3.15 | 1.30 / 1.77 |
| Number of hospitalizations, corrected for disease state |
| Anterior thalamic radiation, L/R | < 0.01 / 1.85 | - | - / 0.16 |
| Corticospinal tract, L/R | 0.02 / 4.33 | - | < 0.01 / 3.86 |
| Inferior fronto-occipital fasiculus, L/R | - / 2.95 | - | - / 0.11 |
| Superior longitudinal fasciculus, L/R | - / 11.83 | - | - / 17.30 |
| Superior longitudinal fasciculus (temporal part), L/R | - / 3.95 | - | - / 5.52 |
| Number of hospitalizations, corrected for BDI-score |
| Anterior thalamic radiation L/R | < 0.01 / 1.47 | <0.01 / 0.12 | < 0.01 / 0.14 |
| Corticospinal tract, L/R | < 0.01 / 3.04 | - / 1.80 | < 0.01 / 2.74 |
| Inferior fronto-occipital fasciculus, L/R | - / 2.89 | 0.10 / 0.13 | - / 0.38 |
| Superior longitudinal fasciculus, L/R | - / 11.40 | - / 22.59 | - / 16.21 |
| Superior longitudinal fasciculus (temporal part), L/R | - / 3.66 | - / 7.22 | - / 5.17 |
| *Abbreviations:* DTI = Diffusion Tensor Imaging, FA= fractional anisotropy, L = left, MD = mean diffusivity, R = right, RD = radial diffusivity, TIV = total intracranial volume |

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| Supplementary Table 2*ANOCVA for the number of hospitalizations and mean extracted MD and RD values from the significant cluster corrected for disease state with additional variables for medication intake, the socioeconomic status and the presence of comorbid disorders.* |
|  | Mean diffusivity |  | Radial diffusivity |
| Factor | *F*(1,412)1 | *p*-value | *η²* |  | *F*(1,412)1 | *p*-value | *η²* |
| Age | 1.93 | .166 | .005 |  | 26.22 | < .001 | .060 |
| Sex | <0.01 | >.999 | <.001 |  | <0.01 | >.999 | < .001 |
| Total intracranial volume | <0.01 | >.999 | < .001 |  | 5.65 | .018 | .014 |
| Marburg pre body-coil | 90.07 | < .001 | .179 |  | 35.36 | <.001 | .079 |
| Marburg post body-coil | 40.52 | < .001 | .090 |  | 28.90 | <.001 | .066 |
| Disease state, acute vs. remitted | 1.62 | .204 | .004 |  | 1.20 | .274 | .003 |
| Number of hospitalizations | 12.03 | < .001 | .028 |  | 16.11 | <.001 | .038 |
| Disease state x number of hospitalizations | 1.77 | .184 | .004 |  | 0.387 | .534 | .001 |
| Medication Load Index | 2.89 | .090 | .007 |  | 2.51 | .114 | .006 |
| Socioeconomic status | 0.39 | .531 | .001 |  | 1.01 | .315 | .002 |
| Comorbid disorder, yes vs. no | 1.06 | .304 | .003 |  | 0.04 | .833 | <.001 |
| Month since first psychiatric treatment | 0.14 | .704 | <.001 |  | 0.72 | .397 | .002 |
| *Notes:* 1107 MDD patients were excluded due to missing data. *Abbreviations:* ANCOVA = Analysis of Covariance, MD = mean diffusivity, RD = radial diffusivity |

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| Supplementary Table 3*ANOCVA for the number of hospitalizations and mean extracted FA, MD and RD values from the significant cluster corrected for BDI-scores with additional variables for medication intake, the socioeconomic status and the presence of comorbid disorders.* |
|  | Fractional anisotropy |  | Mean diffusivity |  | Radial diffusivity |
| Factor | *F*(1,412)1 | *p*-value | *η²* |  | *F*(1,412)1 | *p*-value | *η²* |  | *F*(1,412) | *p*-value | *η²* |
| Age | 60.34 | <.001 | .128 |  | 2.16 | .142 | .005 |  | 28.54 | <.001 | .065 |
| Sex | 0.13 | .722 | <.001 |  | 0.26 | .613 | .001 |  | 0.28 | .595 | .001 |
| Total intracranial volume | 18.34 | <.001 | .043 |  | 0.10 | .750 | <.001 |  | 4.92 | .027 | .012 |
| Marburg pre body-coil | 11.29 | .001 | .027 |  | 87.52 | <.001 | .175 |  | 42.52 | <.001 | .094 |
| Marburg post body-coil | 15.82 | <.001 | .037 |  | 36.07 | <.001 | .080 |  | 25.07 | <.001 | .057 |
| BDI-score | 0.05 | .827 | <.001 |  | 0.32 | .570 | .001 |  | 0.02 | .881 | <.001 |
| Number of hospitalizations | 10.65 | .001 | .025 |  | 7.24 | .007 | .017 |  | 7.89 | .005 | .019 |
| BDI-score x number of hospitalization | 0.49 | .484 | .001 |  | 1.27 | .261 | .003 |  | 1.09 | .297 | .003 |
| Medication Load Index | 2.66 | .104 | .006 |  | 2.56 | .110 | .006 |  | 4.30 | .039 | .010 |
| Socioeconomic status | 3.05 | .081 | .007 |  | 0.78 | .376 | .002 |  | 2.19 | .140 | .005 |
| Comorbid disorder, yes vs. no | 0.21 | .649 | .001 |  | 0.86 | .355 | .002 |  | .351 | .554 | .001 |
| Month since first psychiatric treatment | 2.83 | .093 | .007 |  | 0.11 | .744 | <.001 |  | .916 | .339 | .002 |
| *Notes:* 1107 MDD patients had to be excluded due to missing data. *Abbreviations:* ANCOVA = Analysis of Covariance, BDI = Beck Depression Inventory, FA = fractional anisotropy, MD = mean diffusivity, RD = radial diffusivity |