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Data supplement

Analyses for prediction of response

Response rate was defined as a $\geqslant$50% decrease in $HRSD_{17}$ score from baseline to week 8 and was analysed as a secondary outcome in the study. Demographic and clinical details for the responders and non-responders group are summarised in Table DS1.

Results

Predictors of treatment response

As for the remission data (see Method section in the article), a backward logistic regression analysis was performed to identify white matter predictors of response. This analysis converged on a model with only the fornix white matter tract ($P = 0.017$; Table DS2). Overall accuracy in predicting response was 59.5% (sensitivity: 77.8%, specificity: 31.0%). The participants in the MDD group who had a lower fornix fractional anisotropy were more likely to respond to treatment (fractional anisotropy fornix responders, 0.519 (s.d. = 0.011); fractional anisotropy fornix non-responders, 0.562 (s.d. = 0.014)). Model parameters are listed in Table DS2. A whole brain backward logistic analysis (as described above for remission) also identified this tract in the most parsimonious model, a result that further validates the role of the fornix in response prediction.

The LDA cross-validation analysis confirmed the fornix as the primary predictor of response. The weighted scores for all five preselected tracts were: CgC, 0.095; CgH, 0.120; stria terminalis, 0.088; fornix, 0.627; and uncinate fasciculus, 0.126. The fornix was identified as the sole predictor for 48 out of the 100 LDA runs, with an average cross-validated prediction accuracy of 62.4% (range: 60.4–70.3%).

Additional effect of demographic and clinical variables in treatment prediction

The previous analysis excluded the effects of age, baseline depressive severity, age at onset and duration of illness on white matter fractional anisotropy measures prior to analysis (see Method). We therefore investigated the additional effect of adding these clinical and demographic variables for the predictive model (Table DS2). Age at onset, duration of MDD and baseline severity were significant additional elements (in addition to the significance of the existing fornix fractional anisotropy measure) for the response prediction model. Prediction accuracy improved to an overall accuracy of 70.3% (sensitivity: 82.2%, specificity 51.7%).

Analysis of mean, axial and radial diffusivity DTI measures for the significant tracts identified

We compared mean, axial and radial diffusivity measures for the tracts identified in the treatment prediction analysis for both remission and response, i.e. the cingulate portion of the cingulate gyrus (CgC) and stria terminalis for remission and fornix for response. We performed an independent sample *t*-test to compare remitters *v.* non-remitters and responders *v.* non-responders for these measures.

For remission, only radial diffusivity for the CgC was found to be significantly different between the remitter and non-remitter groups ($t = 2.06$, $P = 0.043$; non-remitters > remitters).

No significant difference in mean, axial and radial diffusivity for the fornix was found between responders and non-responders. The means for the measures are summarised in Table DS3.

Table DS1 Demographics and clinical measures summary

			Response	
	Control group	MDD group	Yes	No
n (%)	34	80	48/80 (60)	32/80 (40)
Age, years: mean (s.d.)[b]	31.5 (12.4)	33.8 (13.1)	29.7 (9.5)	37.4 (14.9)
Females, *n* (%)	16 (47.0)	40 (50.0)	24 (60)	16 (40)
Hamilton Rating Scale for Depression (17-item) score, mean (s.d.)				
Baseline[b,d]	1.0 (1.2)	21.0 (3.9)	21.9 (4.1)	20.1 (3.3)
Week 8[c,d]	1.1 (1.5)	9.3 (4.8)	5.6 (2.5)	14.7 (3.4)
% change[c]	–	54.4 (24.9)	74.0 (11.8)	26.1 (17.7)
Age at onset, years: mean (s.d.)[a]	–	22.1 (12.2)	18.7 (7.7)	23.2 (14.3)
Disease duration, years: mean (s.d.)	–	11.3 (11.8)	10.5 (10.6)	13.8 (13.1)

MDD, Major depressive disorder.
a. Difference between responders and non-responders at $P < 0.1$.
b. Difference between responders and non-responders at $P < 0.05$.
c. Difference between responders and non-responders at $P < 0.001$.
d. Difference between MDD and control groups at $P < 0.001$.

Table DS2 Prediction models for response

	Overall model summary		Model parameters		Prediction accuracy		
	Nagelkerke R^2	*P*	β	*P*	% overall	% sensitivity	% specificity
Anterior cingulate–limbic white matter tracts	0.127	0.007			59.5	77.8	31.0
Fornix			−11.34	0.017			
Constant			0.59	0.027			
Anterior cingulate–limbic white matter tracts + demographic and clinical measures	0.306	0.001			70.3	82.2	51.7
Fornix			−11.00	0.033			
Hamilton Rating Scale for Depression (17-item) baseline			0.15	0.05			
Age at onset			−0.07	0.024			
Constant			−0.55	0.745			

Table DS3 Comparison of mean, axial and radial diffusivity measures based on treatment outcome

White matter tract	Mean diffusivity ($\times 10^{-3}$)			Axial diffusivity ($\times 10^{-3}$)			Radial diffusivity ($\times 10^{-3}$)		
	Mean (s.d.)	*t*-test	*P*	Mean (s.d.)	*t*-test	*P*	Mean (s.d.)	*t*-test	*P*
Remission									
Cingulum portion of the cingulate		0.70	0.48		0.91	0.37		**2.06**	**0.043***
Remitters	0.730 (0.039)			1.313 (0.077)			**0.439 (0.037)**		
Non-remitters	0.737 (0.047)			1.297 (0.076)			**0.458 (0.041)**		
Stria terminalis		0.76	0.45		0.77	0.45		0.46	0.65
Remitters	0.811 (0.031)			1.388 (0.055)			0.522 (0.038)		
Non-remitters	0.804 (0.042)			1.378 (0.060)			0.517 (0.052)		
Response									
Fornix		0.69	0.49		0.34	0.73		0.81	0.42
Responders	1.291 (0.288)			2.077 (0.241)			0.898 (0.316)		
Non-responders	1.291 (0.288)			2.059 (0.179)			0.845 (0.199)		

Results in bold are significant.
*Significant difference at $P<0.05$.