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Supplementary material belonging to:

Indirect frontocingulate structural connectivity predicts clinical response to accelerated rTMS in major depressive disorder

D.C.W. Klooster, I.N. Vos, K. Caeyenberghs, A. Leemans, S. David, R.M.H. Besseling, A.P. Aldenkamp, C. Baeken

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Overview of aiTBS study protocol

Figure 1 shows an overview of the design of the aiTBS trial. To investigate the potential of dMRI data to predict the delayed clinical response to aiTBS, the stuctural connections, derived from the baseline measurements at T1, were correlated with $\Delta HDRS_{del}$ (derived from T_4 and T_1).

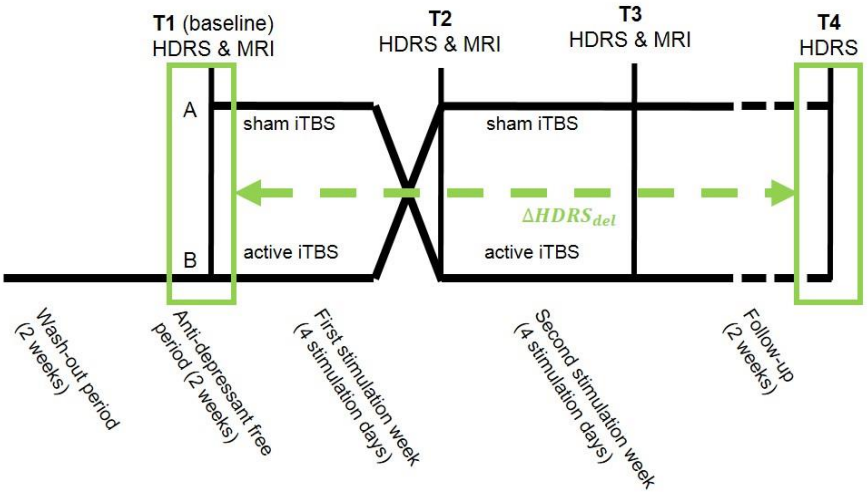

Figure 1: *Design of the aiTBS treatment procedure. After a wash-out period, all patients were at least two weeks anti-depressant free before they were randomized to receive active and sham aiTBS treatment. The green squares represent the parts of the study design that were used for analysis. At T_1, T_2, T_3 and additionally 2 weeks after the last stimulation (T_4), depression severity was assessed using the 17-item HDRS questionnaire [(18)] by an experienced psychiatrist not related to the study. Clinical data from T_1 and T_4 are used to determine the clinical effect of aiTBS. Clinical effects were correlated with baseline (T1) dMRI data.*

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Group-connectome generation

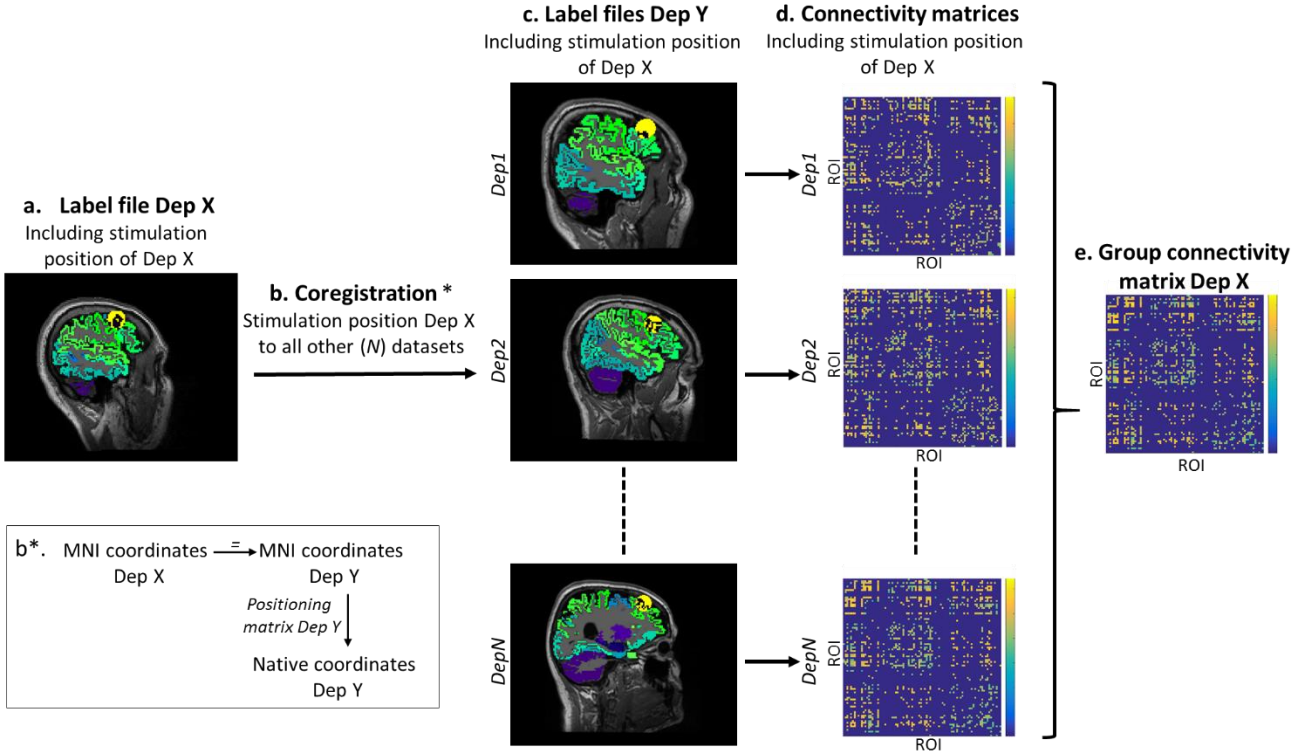

Figure 2: *Stepwise overview of the generation of the group connectivity matrix. Dep = depressed subject.*

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As stated before, it was not possible to average the connectivity matrices over all subjects to obtain an average structural group connectome. The stimulation position was manually defined as the center part of the midprefrontal gyrus (Brodmann area 9.46) based on anatomical MRI of each individual (Figure 1a). There is inter-individual variability in the exact coil position, and so also in the position of the stimulation node. As a result, simply averaging all the connectivity matrices would lead to inaccurate results of the stimulation position. Therefore, the subject-specific stimulation sites were coregistered to the native space of all other subjects. Coregistration was done by converting the MNI coordinates from the coil position in patient X to native coordinates in all other patients, using the 4x4 positioning matrix from any other patient (Figure 1b). So the specific coil position from patient X is mapped onto the brains of all other patients. In Figure c, specific label files are made for all patients and connectivity matrices are derived in d. In the final step, the connectivity matrices are averaged to obtain a 'patient-specific average connectivity matrix'. This procedure was repeated for every patient.

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Distribution of internodes connecting the stimulation position in the left DLPFC to any of the ROIs in the cingulate cortex

Figure 3 and 4 represent an overview of the internodes that are part of the indirect connections, with two internodes, between the stimulated left DLPFC and any of the ROIs in the cingulate cortex. Figure 3 shows the distribution of the first internodes, whereas Figure 4 shows the distribution of the second internode.

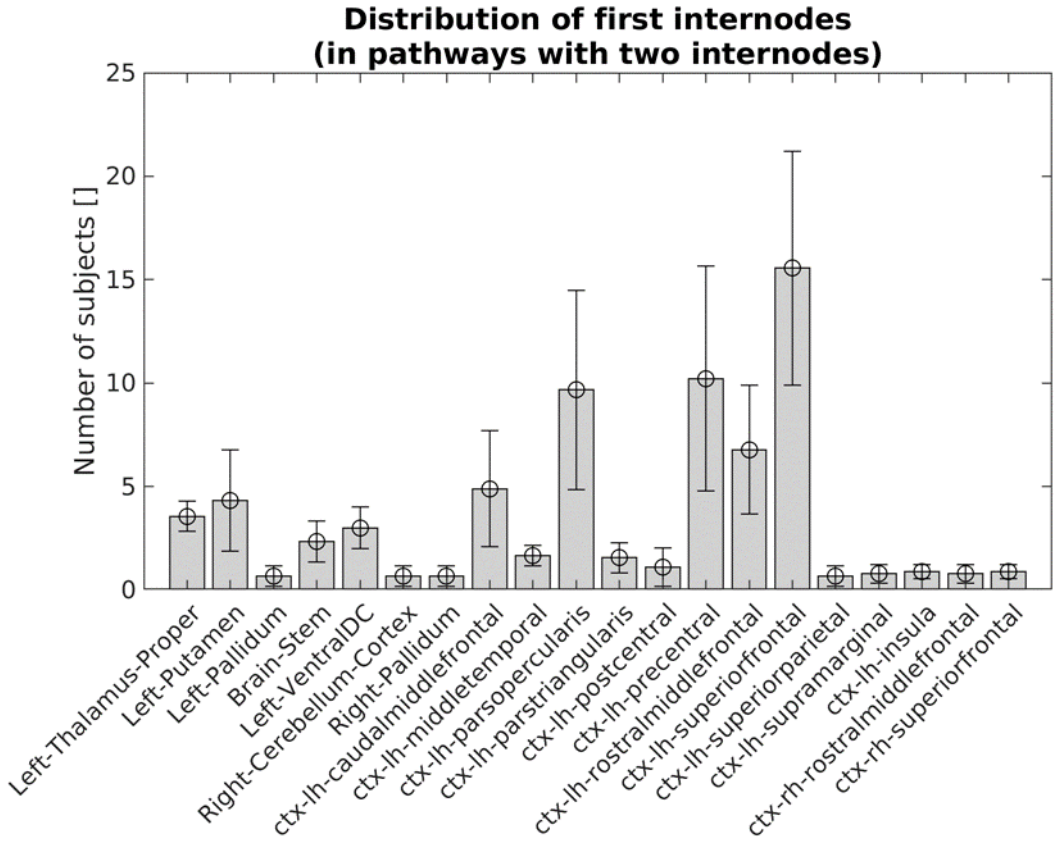

Figure 3: *Distribution of the first internodes. The first internodes are directly connected to the subject-specific stimulation node in the left DLPFC. The mean and standard deviation of the number of subjects using these nodes as first internode to connect the stimulation position to any of the ROIs are depicted. The nodes that are not shown in the figure were not included in any of the pathways between the stimulation node and the ROIs.*

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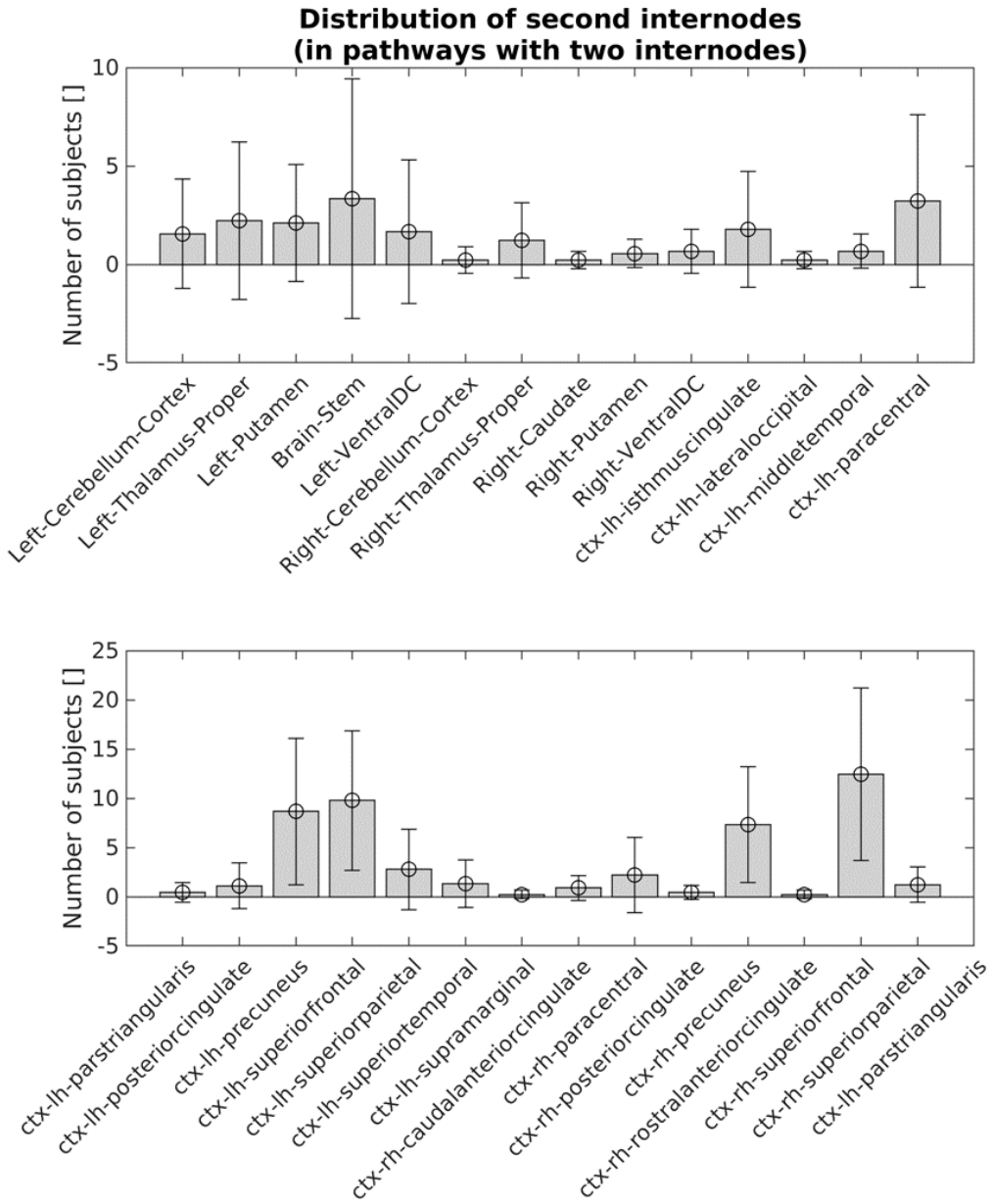

Figure 4: *Distribution of the second internodes. The second internodes are directly connected to any of the ROIs in the cingulate cortex. The mean and standard deviation of the number of subjects using these nodes as second internode to connect the stimulation position to any of the ROIs are depicted. The nodes that are not shown in the figure were not included in any of the pathways between the stimulation node and the cingulate ROIs.*

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Direct versus indirect structural connections between the stimulated area in the left DLPFC and the cingulate cortex

Direct connections

Table 1*: Overview of the number of patients with direct structural connections between the stimulated left DLPFC and any of the ROIs in the cingulate cortex.*

		Left				Right			
	sgACC	Rost	Caud	Post	Ist	Rost	Caud	Post	Ist
Number of patients	0	0	0	0	0	0	0	0	0

Indirect connections

One internode

Table 2*: Overview of the number of patients with indirect structural connections, with one internode, between the stimulated left DLPFC and any of the ROIs in the cingulate cortex. Also the mean and median number of connections are shown.*

		Left				Right			
	sgACC	Rost	Caud	Post	Ist	Rost	Caud	Post	Ist
Number of patients	0	4	13	11	16	4	9	3	6
Mean number of connections	-	1	1	1.18	1.25	1	1	1	1.33
Median number of connections	-	1	1	1	1	1	1	1	1

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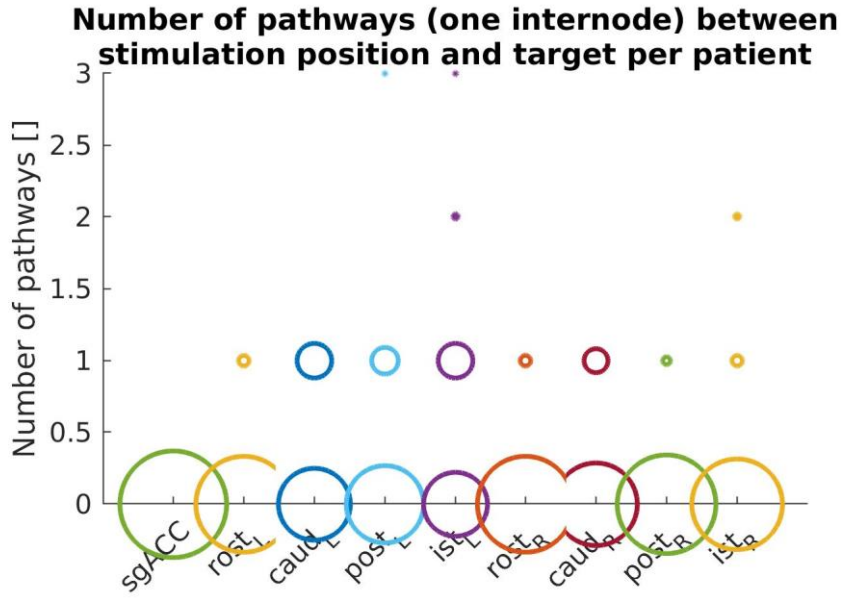

***Figure 5**: The number of pathways between the stimulated left DLPFC and any of the ROIs in the cingulate cortex. The size of the circles is proportional to the number of patients having that number of connections. Together with the Table 2, this figure shows that only few patients have indirect structural connections between the specific stimulation site in the left DLPFC and any of the ROIs in the cingulate cortex via one internode.*

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Two internodes

Table 3*: Overview of the number of patients with indirect structural connections, with two internodes, between the stimulated left DLPFC and any of the ROIs in the cingulate cortex. Also the mean and median number of connections are shown.*

		Left				Right			
	sgACC	Rost	Caud	Post	Ist	Rost	Caud	Post	Ist
Number of patients	9	20	34	34	38	24	33	33	37
Mean number of connections	1.56	3.25	4.15	4.74	7.74	3.13	3.12	3.91	6.86
Median number of connections	1	3	3	3	6	2	2	3	4

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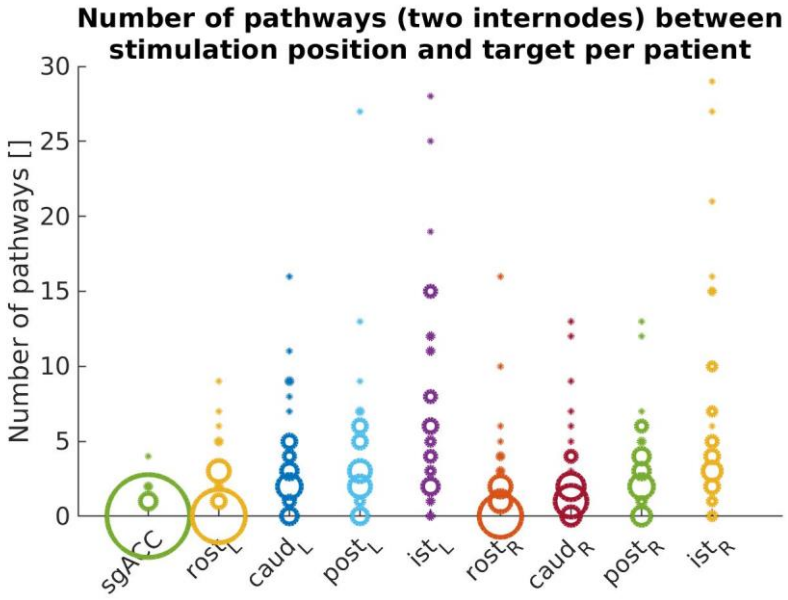

***Figure 6**: The number of pathways with two internodes between the stimulated left DLPFC and any of the ROIs in the cingulate cortex. The size of the circles is proportional to the number of patients having that number of connections. This figure, and also Table 3, shows that most patients have indirect structural connections between the specific stimulation site in the left DLPFC and any of the ROIs in the cingulate cortex, when two internodes are considered.*

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Prediction of the immediate clinical effects

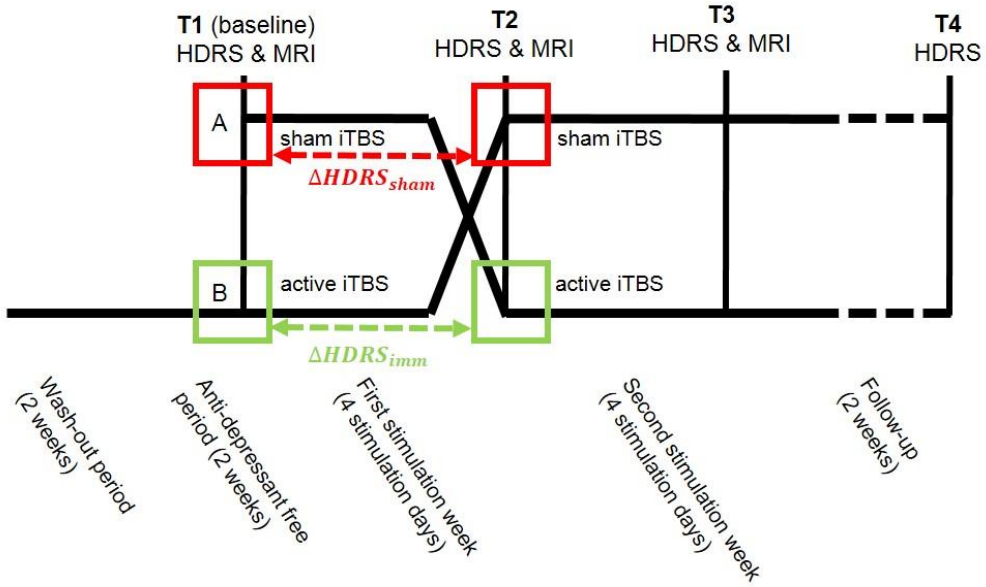

***Figure 7**: Overview of the stimulation protocol. Parts of the data that are used to compute the predictive effects of baseline structural connectivity on sham and active immediate clinical responses are marked in red and green respectively.*

Prediction of sham effects

The data from patients from arm A (n = 21) were used to calculate the potential of baseline structural connectivity to predict the immediate response to sham stimulation (red blocks in Figure 7). No significant correlations were found between changes in HDRS scores, after sham stimulation with respect to baseline, and any of the structural connectivity metrics. Even though no significant correlations were found, clinical responses were found after sham aiTBS [(1)]. This might be caused by an active placebo effect. A recent meta-analysis showed a high sham response to rTMS [(2)] which is in accordance to sham responses to pharmacological treatments [(3)].

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Prediction of immediate effects of verum aiTBS

The data from patients from arm B (n=19) were used to calculate the potential of baseline structural connectivity to predict the immediate clinical response to verum aiTBS (green blocks in Figure 7). The baseline MD of the connection between the stimulation position and the left caudal and posterior part of the cingulate cortex and the left isthmus was significantly correlated with the change in depression severity. Higher baseline MD values here indicate better clinical response. Also, the FA of the connection to the right posterior part and the isthmus of the cingulate cortex predicted the immediate response to aiTBS (Figure 8, Table 4). However, these correlations have opposite sign.

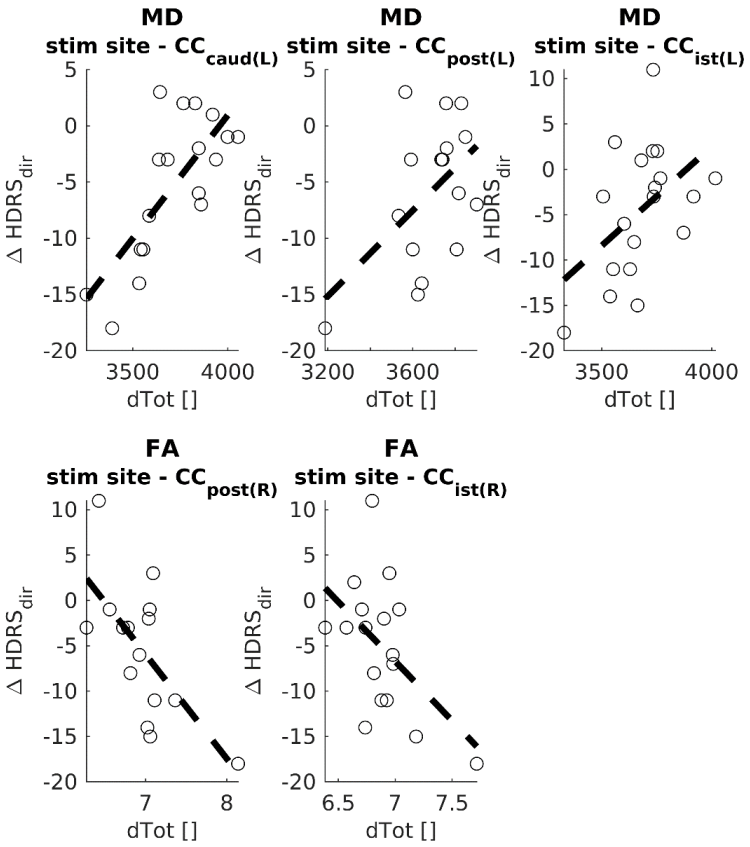

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Figure 8: *Overview of the correlations showing a significant predictive potential of the immediate clinical effects of aiTBS. Statistical details can be found in Table 4.*

Table 4: *Correlations, p-values, and slope of the significant results (belonging to Figure 8).*

	Correlation coefficient	***p* value**	**slope**
MD			
Caud (L)	0.73	< 0.01	0.02
Post (L)	0.51	0.04	0.01
Ist (L)	0.48	0.04	0.02
FA			
Post (R)	-0.66	<0.01	-11.49
Ist (R)	-0.51	0.03	-13.09

The structural connectivity between the patient-specific stimulation site and the left caudal and posterior part and the isthmus of the cingulate cortex, derived from the MD, was positively correlated with the immediate change in HDRS scores. The positive correlation indicates that lower dTot values (resulting from higher MD values) result in better clinical response. So, it might be speculated that higher MD values cause the effect of stimulation to propagate easier to deeper structures, in this case the left caudal and posterior parts and isthmus of the cingulate cortex, thereby inducing clinical effects.

Also, clinical outcome was found to be significantly correlated with the structural connections to the right posterior part and right isthmus of the cingulate cortex, described by the dTot derived from the FA metric. This correlation is opposite to the MD findings and suggests that lower baseline FA values in the structural pathway result in better clinical response. FA is a measure of anisotropy. Low FA values might be associated with high MD values. Besides, previous studies have shown that decreased FA is a predictor of long-term motor outcome after stroke [(4)].

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Prediction of immediate versus delayed clinical response

Significant findings differ when predicting the immediate and the delayed effects. This might indicate that the propagation of the TMS effect via structural connections progress over time and suggests the involvement of the corpus callosum since also structural connectivity to right sided ROI areas in the cingulate cortex showed predictive potential [5]. The role of the corpus callosum in the pathophysiology of depression is still unclear and might also depend on the exact type of depression [6]. Indeed, previous work has shown that TMS alters structural brain connections [7,8]. Specifically in this cohort of patients, Caeyenberghs et al. [9] showed that active aiTBS induces decreases in modularity, a graph measure in this case derived from structural connections, after four days of stimulation treatment. Potentially, these progressive changes in structural connectivity cause changing structural pathways between the stimulated left DLPFC and the cingulate cortex over time, thereby also potentially changing the clinical effectiveness of aiTBS over time. This might, at least partly, explain the different findings of structural connections to predict the immediate versus delayed clinical effects.

Total overview of results: prediction of delayed clinical effects

A complete overview of the baseline structural connectivities between the patient-specific stimulation position in the left DLPFC and the ROIs in the cingulate cortices versus the clinical response to aiTBS can be found in Figures 9-13, for the different quantification measures. Correlations were shown in black and gray-blue, for all patients and for the subset of patients showing actual structural connectivity.

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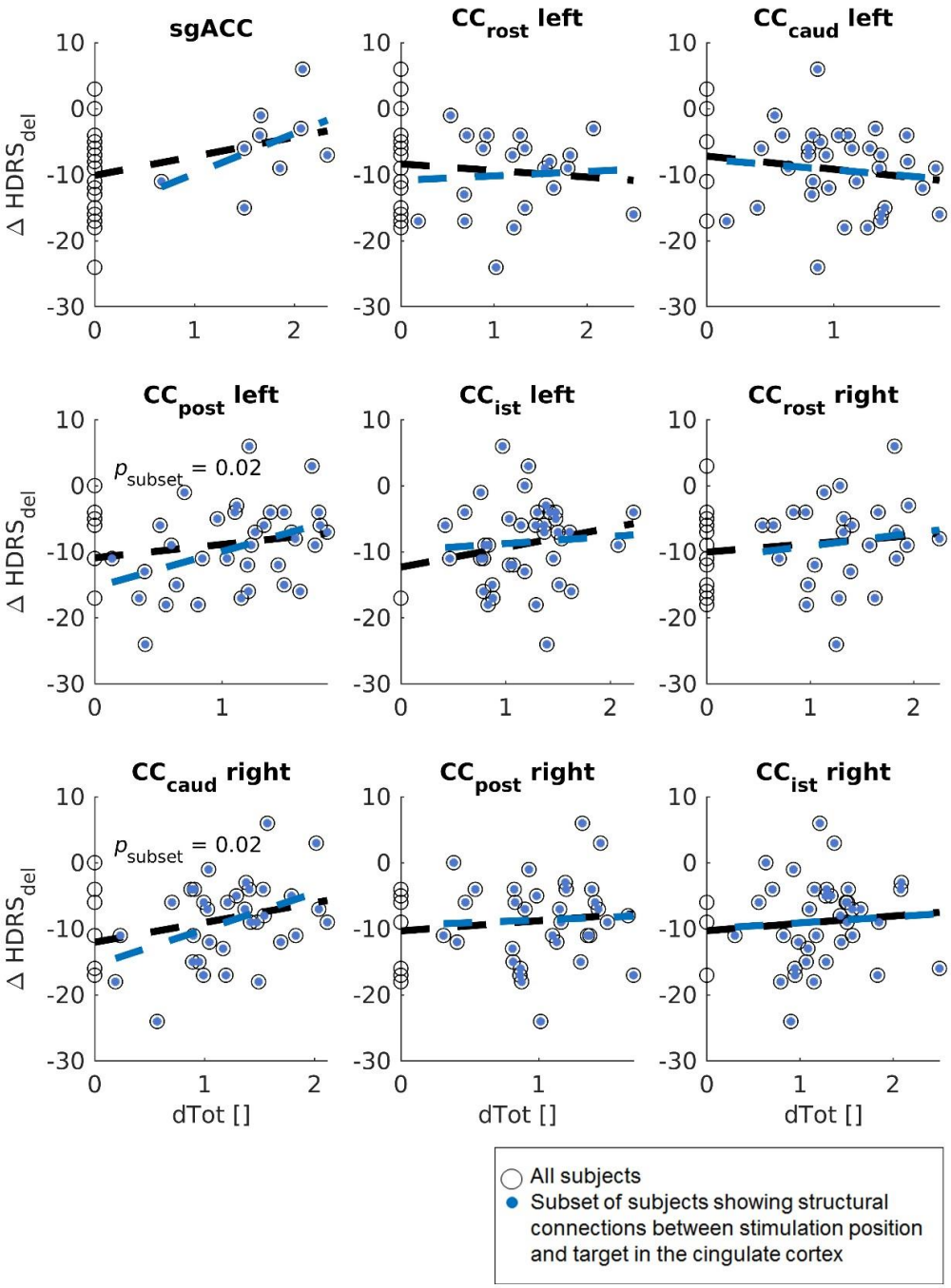

***Figure 9**: Overview of the baseline structural connectivity, quantified using the **number of tracts**, between the left DLPFC and the ROIs in the cingulate cortex versus the clinical response to aiTBS.*

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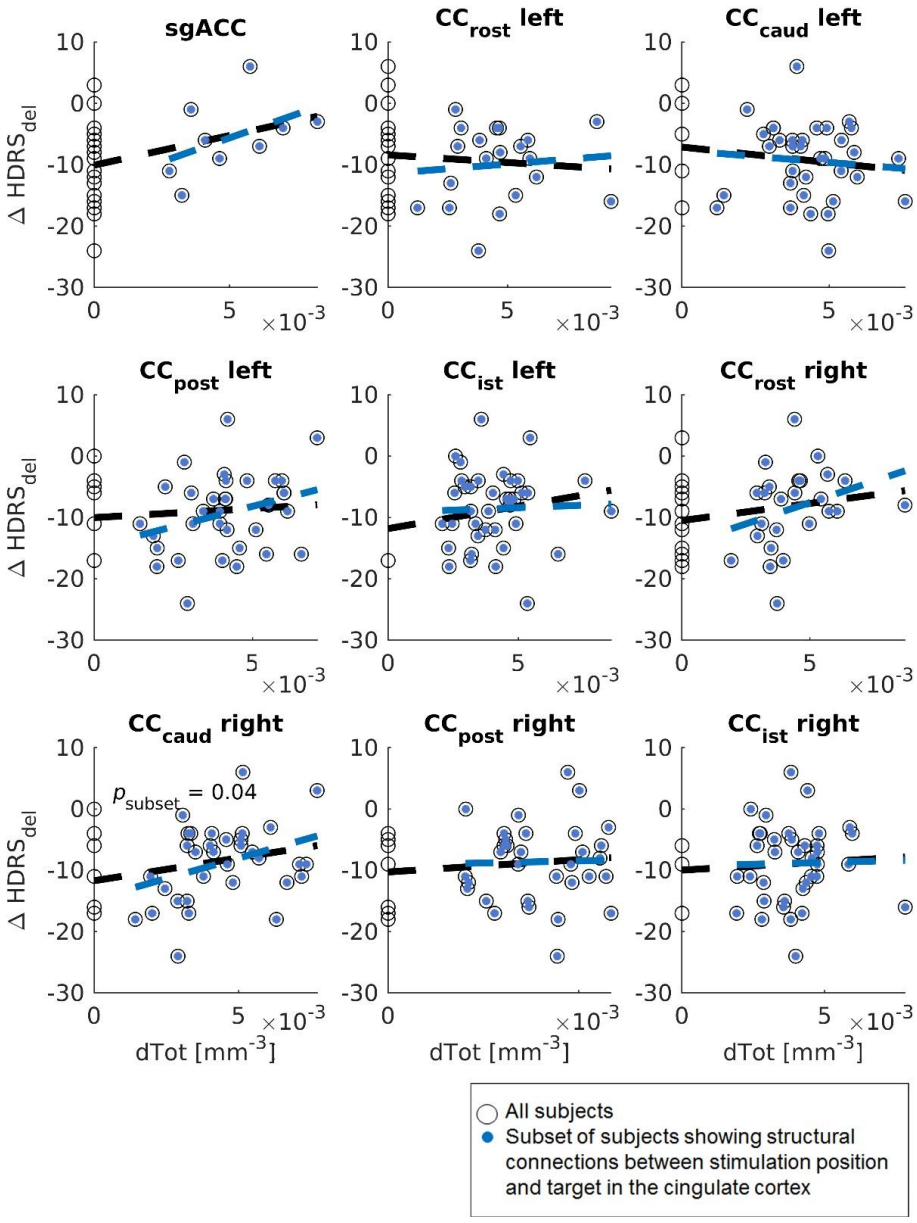

***Figure 10**: Overview of the baseline structural connectivity, quantified using the **tract volume**, between the left DLPFC and the ROIs in the cingulate cortex versus the clinical response to aiTBS.*

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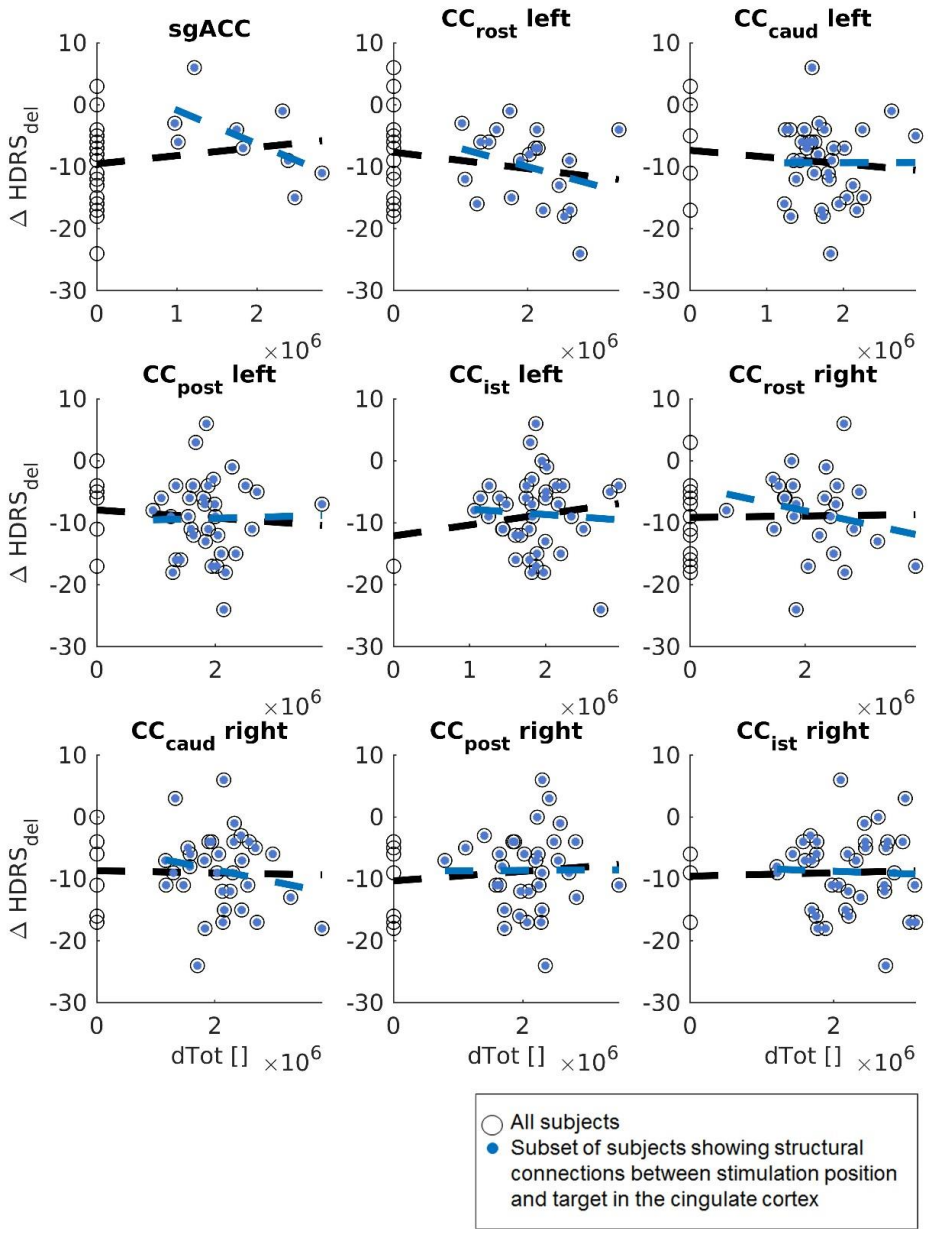

***Figure 11**: Overview of the baseline structural connectivity, quantified using the **tract density**, between the left DLPFC and the ROIs in the cingulate cortex versus the clinical response to aiTBS.*

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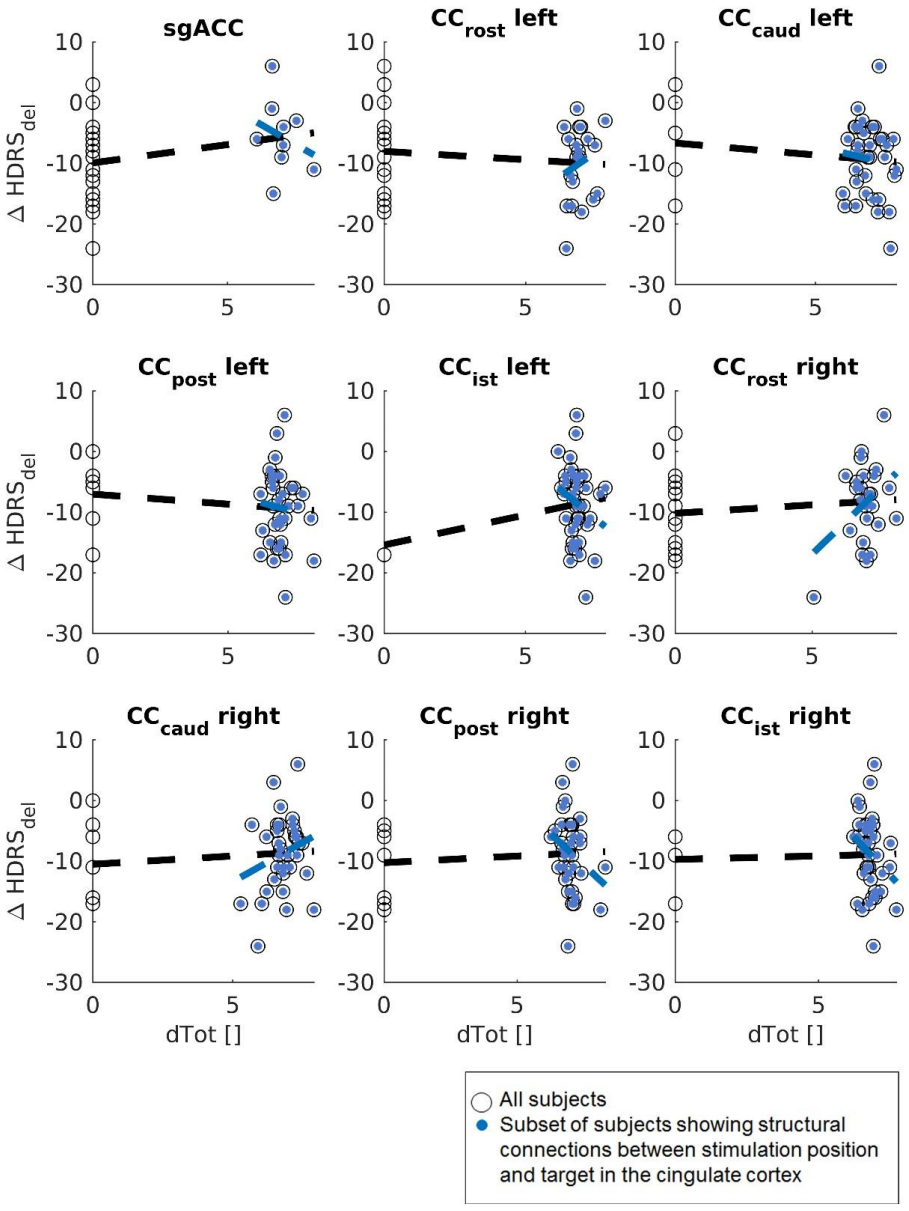

***Figure 12**: Overview of the baseline structural connectivity, quantified using the **FA**, between the left DLPFC and the ROIs in the cingulate cortex versus the clinical response to aiTBS.*

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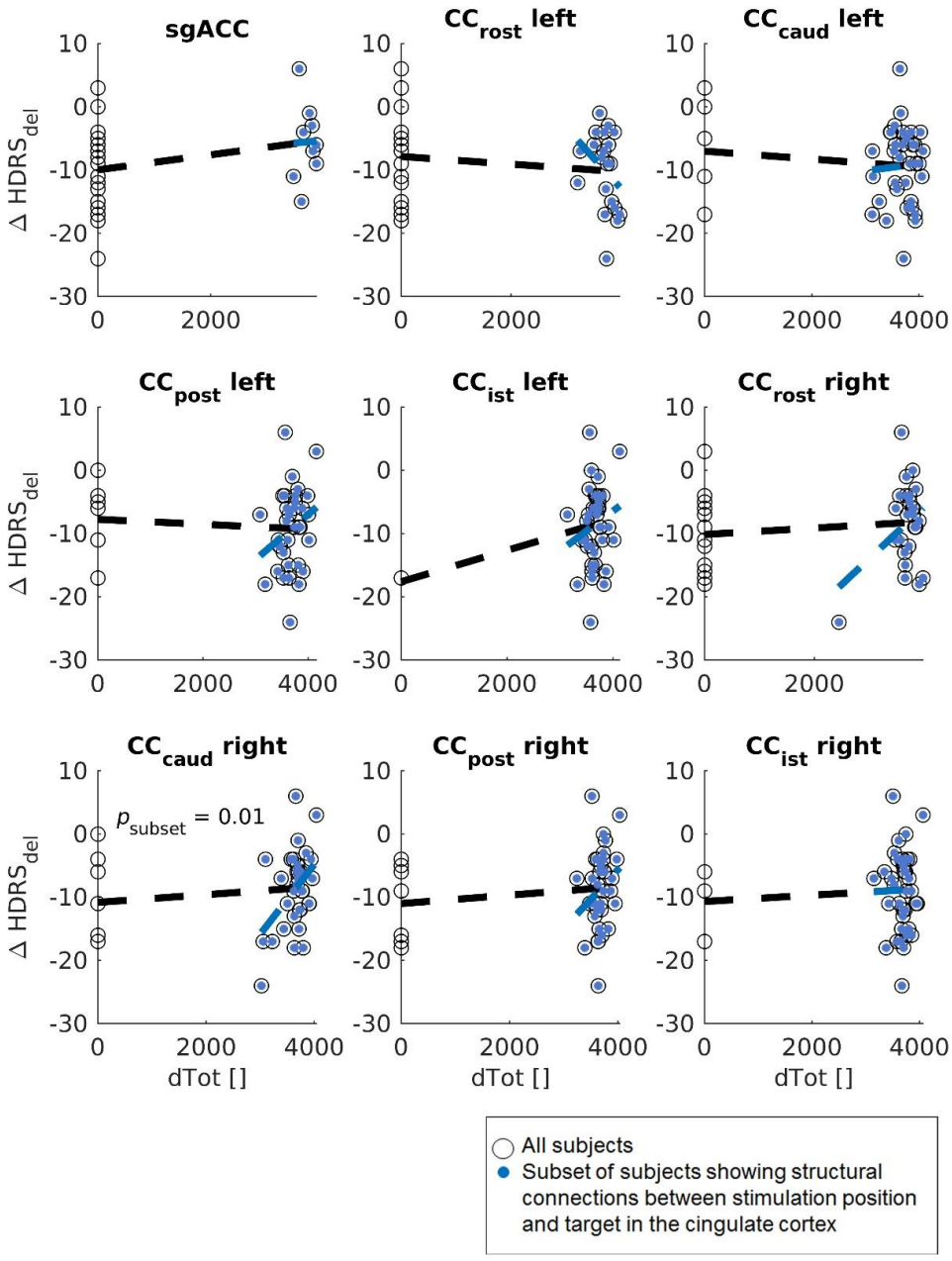

***Figure 13**: Overview of the baseline structural connectivity, quantified using the **MD**, between the left DLPFC and the ROIs in the cingulate cortex versus the clinical response to aiTBS.*

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Specificity to frontocingulate structural connectivity

The results of correlation between overall baseline structural connectivity measures, derived from whole brain data, and clinical outcome can be found in Figure 14. The whole brain FA and MD measures were calculated by averaging these values in every tract, and subsequently these values were summed over the whole brain. No significant correlations were found.

Neither significant correlations were found between baseline nodal structural connectivity measures, derived from the stimulation node, and clinical response to aiTBS (Figure 15).

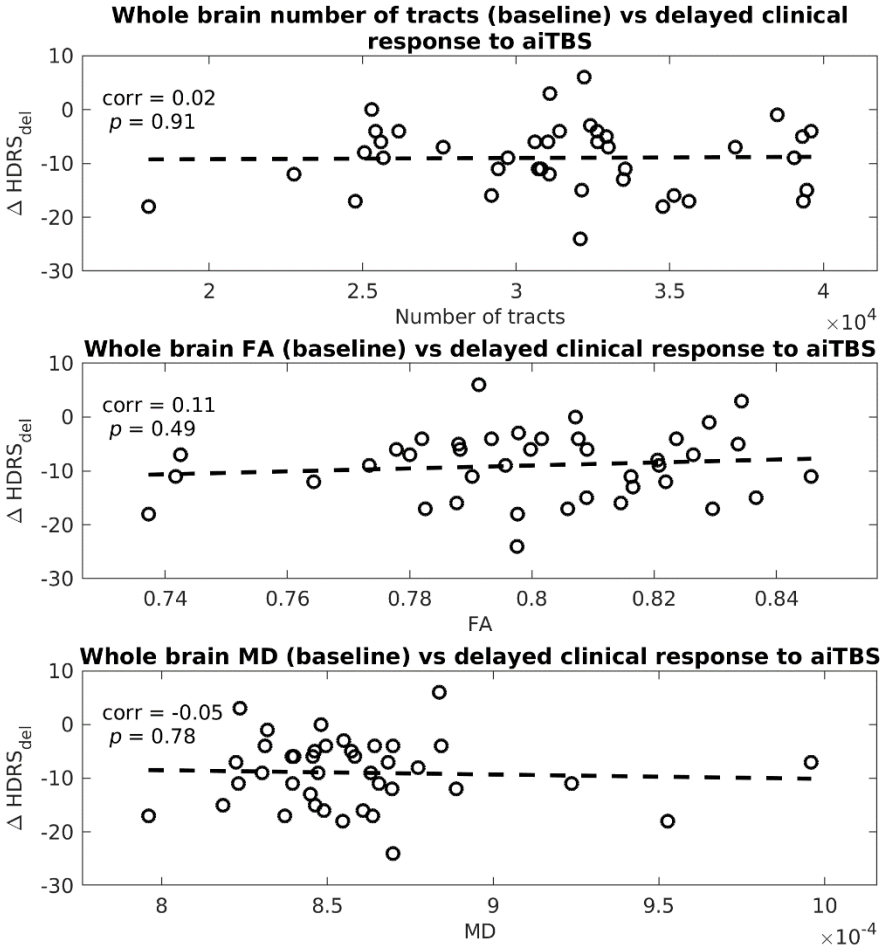

Figure 14*: Correlation between baseline whole brain structural connectivity measures, number of tracts, FA, and MD, and clinical response to aiTBS.*

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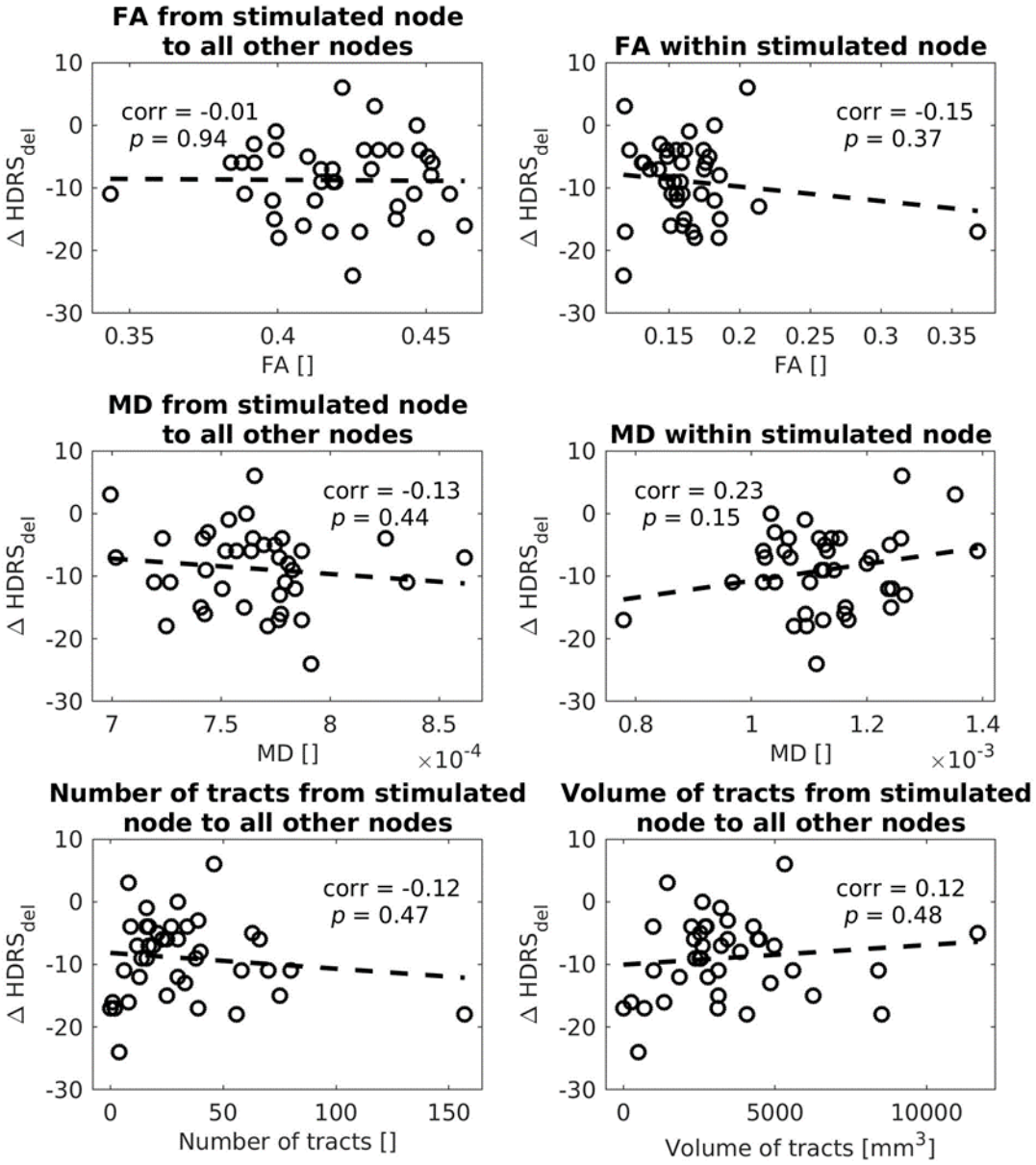

Figure 15*: Correlation between baseline nodal structural connectivity measures, FA and MD in and from the stimulation node, and the number and volume of tracts, and clinical response to aiTBS.*

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