Research paper

Associations between anterior cingulate thickness, cingulum bundle microstructure, melancholia and depression severity in unipolar depression

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ABSTRACT

Background: Structural and functional alterations of the anterior cingulate cortex (ACC) have been related to emotional, cognitive and behavioral domains of major depressive disorder. In this study, we investigate cortical thickness of rostral and caudal ACC. In addition, we explore white matter microstructure of the cingulum bundle (CB), a white matter pathway connecting multiple segments of the ACC. We hypothesized reduced cortical thickness and reduced white matter microstructure of the CB in MDD, in particular in the melancholic subtype. In addition, we expect an association between depression severity and CB microstructure.
Methods: Fifty-four patients with a current depressive episode and 22 healthy controls matched for age, gender and handedness underwent structural and diffusion-weighted MRI-scans. Cortical thickness of rostral and caudal ACC were computed. The CB was reconstructed bilaterally using manual tractography. Cortical thickness and fractional anisotropy (FA) of bilateral CB were compared first between all patients and healthy controls and second between healthy controls, melancholic and non-melancholic patients. Correlations between FA and depression severity were calculated.
Results: We found no group differences in rostral and caudal ACC cortical thickness or in FA of the CB comparing all patients with healthy controls. Melancholic patients had reduced cortical thickness of bilateral caudal ACC compared to non-melancholic patients and compared to healthy controls. Across all patients, depression severity was associated with reduced FA in bilateral CB.
Limitations: Impact of medication
Conclusions: Cortical thickness of the caudal ACC is associated with the melancholic syndrome. CB microstructure may represent a marker of depression severity.

1. Introduction

Depression symptomatology is heterogeneous and does not reflect a homogeneous biological and clinical entity (Parker et al., 2010; Schrijvers et al., 2008; Shankman et al., 2020). Advances in neuroimaging offer new insights into functional and structural changes of the brain in depression and contribute to further identification of depression subtypes with differential patterns of treatment response or differences regarding disease trajectories (Drysdale et al., 2017; Musil et al., 2018). Thus, neuroimaging may help establishing a priori markers for treatment response. However, the clinical benefit and usability of these findings is still very limited and warrants further research elucidating the neurobiology of depression (Arnow et al., 2015; Dunlop and

Mayberg, 2017).

One approach to advance our understanding of depression pathophysiology is to link structural and functional alterations of anatomical networks to depression psychopathology. A minimum of four networks may underlie the depressive syndrome: a limbic affective network, a reward network, the default mode network and a cognitive control network (Coenen et al., 2020; Li et al., 2018). Different segments of the anterior cingulate cortex (ACC) represent important hubs of these networks. The rostral ACC forms part of the affective network that includes prefrontal (e.g. orbitofrontal) and limbic (e.g. amygdala) brain areas. In addition, the rostral ACC has connections with the fronto-striatal reward network (Haber and Knutson, 2010). Functionally, the rostral ACC contributes to the emergence of negative affectivity and anhedonia in

depression (Keedwell et al., 2005; Liu et al., 2021; Wacker et al., 2009). Furthermore, increased activity (as assessed with positron emission tomography (PET), electroencephalography (EEG), and functional magnetic resonance imaging (MRI)) of the rostral ACC may predict treatment response in depression (Godlewska et al., 2018; Mayberg et al., 1997; Pizzagalli, 2011; Pizzagalli et al., 2018; Tian et al., 2020). In addition, first evidence supports another ACC subregion to be associated with treatment outcome in depression, i.e. the caudal ACC (Baeken et al., 2021; Phillips et al., 2015). The caudal ACC forms part of the cognitive control network. Disturbed coupling of the caudal ACC and limbic brain regions may lead to deficits to regulate negative emotions in depression (Anand et al., 2005; Li et al., 2018). Furthermore, the caudal ACC has connections to premotor areas (e.g. supplementary motor area) and is implicated in initiating motivated behaviour (Rolls, 2019). This converges with analyses of resting-state functional connectivity demonstrating a temporal co-activation of the caudal ACC and premotor areas (Margulies et al., 2007; Walther et al., 2012). Therefore, the caudal ACC may contribute to the pathophysiology of motor symptoms in depression (e.g. psychomotor disturbances Shankman et al., 2020; Walther et al., 2019), which are particularly pronounced in the melancholic subtype (Parker and McCraw, 2017).

Structural MRI studies allow for the investigation of grey matter morphometry and may contribute to characterize depression subtypes (Abe et al., 2016; Cohen et al., 2013; Pizzagalli et al., 2009; Suh et al., 2019; Zhao et al., 2017). The MRI-derived cortical thickness is a measure that assesses the distance between the pial surface and the adjacent white matter (Fischl, 2012). Cortical thickness may be a more sensitive measure than grey matter volume for the identification of structural alterations in neuropsychiatric disorders such as depression (Suh et al., 2019). Furthermore, cortical thickness of the caudal ACC may predict treatment outcome in depression (Phillips et al., 2015) and cortical thickness of distinct brain regions may temporarily increase following electroconvulsive therapy (ECT) (Gbyl et al., 2019). A reduction of cortical thickness has been found in the ACC in the large Enhancing Neuro Imaging Genetics through Meta-Analysis (ENIGMA) study in adults with unipolar depression (Schmaal et al., 2017). However, this finding is not consistent with results of a more recent meta-analysis in unipolar depression based on different study samples (Suh et al., 2019), highlighting the need to further address this research question. This may be achieved by looking at distinct segments of the ACC (Rolls, 2019).

Segments of the ACC do not work in isolation but rather form a network with different relay stations. The cingulum bundle (CB) surrounds the corpus callosum and interconnects ipsilateral subcortical nuclei, the cingulate gyrus, and areas of the frontal, the temporal and the parietal lobe (Bubb et al., 2018). The CB can be reconstructed using diffusion weighted imaging based tractography (Jones et al., 2013a). White matter microstructure can be probed based on diffusion properties that rely on the directionality of diffusion of water molecules in the brain (e.g. fractional anisotropy, FA) (Jones et al., 2013b). Reductions of FA in the CB have been reported in women at familial risk for depression (Keedwell et al., 2012), in segments of the CB connecting to the amygdala (Bhatia et al., 2018), in the CB near the ACC (Dillon et al., 2018) and in treatment resistant depression (de Diego-Adelino et al., 2014). Nevertheless, findings remain inconsistent with a series of negative reports (Bracht et al., 2015c). Given that the CB mediates numerous brain functions that are impaired during depressive episodes such as attention, memory, executive functions and emotional processes it is possible that different clinical presentations contribute to inconsistent findings regarding CB microstructure (Bracht et al., 2015c). Due to the comprehensive and integrating role of the CB (Bubb et al., 2018) one may therefore assume that CB microstructure is associated with several symptoms of depression and therefore reflects overall depression severity, rather than clearly circumscribed symptoms.

Investigating homogeneous subgroups with clinical presentations that underlie circumscribed neuronal networks may advance our pathophysiological understanding of depression (Bracht et al., 2015c;

Pizzagalli et al., 2004; Shan et al., 2021). Melancholia is characterized by pervasive anhedonia and psychomotor retardation and represents a syndrome that can be regarded as a distinct depression entity (Parker et al., 2010). Neurobiological alterations are more pronounced in the melancholic subtype (Bracht et al., 2014; Denier et al., 2020; Pizzagalli et al., 2004) and patients with melancholic depression differ from non-melancholic depression regarding treatment outcome (Parker et al., 2010; van Diermen et al., 2019). As a consequence the melancholic subtype has been added as a specifier of major depressive disorder in the DSM-5 (APA, 2013). In the present study, we consider this and calculate additional analyses comparing melancholic with non-melancholic depressed patients (Bracht et al., 2014; Denier et al., 2020).

The aim of this study is to investigate the role of cortical thickness of rostral and caudal ACC and of CB microstructure for melancholia and depression severity. First, we hypothesized reduced cortical thickness of rostral and caudal ACC (Schmaal et al., 2017) and reduced FA of the CB in currently depressed patients with unipolar depression (Bracht et al., 2015c). Second, we hypothesized more pronounced structural alterations in patients with the melancholic subtype than in non-melancholic patients (Bracht et al., 2014; Denier et al., 2020; Pizzagalli et al., 2004). Third, we hypothesized that reduced FA of the cingulum bundle is associated with overall depression severity.

2. Methods

2.1. Participants

Fifty-four patients with unipolar depression and a current depressive episode according to DSM-IV were recruited at the University Hospital of Psychiatry and Psychotherapy in Bern. Inclusion criterion was age between 18 and 65 years. Exclusion criteria were psychiatric comorbidities including substance abuse except from nicotine, personality disorders, neurological disorders and contraindications to perform an MRI. Twenty-two healthy controls without a history of a psychiatric disorder were recruited and matched for age and gender. Handedness was assessed using the Edinburgh Handedness Inventory (Oldfield, 1971). All participants were screened for psychiatric disorders using the Mini International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998). The presence of personality disorders was assessed using the Structured Clinical Interview for DSM-IV Axis II (SCID-II) (Wittchen et al., 1997). Depression severity was measured using the 21-item Hamilton rating scale for depression (HAMD) (Hamilton, 1967) and the 21-item self-report Beck Depression Inventory (BDI-II) (Beck et al., 1996). Psychomotor symptoms were assessed with the CORE (Parker and Hadzi-Pavlovic, 1996). Anhedonia was assessed using the Snaith–Hamilton Pleasure Scale (SHAPS) (Snaith et al., 1995). The SHAPS is a 14-item self-report questionnaire rating the capacity to derive pleasure hereby quantifying hedonic tone. Each item has four response categories. As suggested by Franken et al. (2007) we calculated a sum score based on the four response categories of the 14-items. Items were scaled on a range from 1 (strongly disagree) to 4 (strongly agree). Thus, higher sum scores indicate higher hedonic tone.

In line with previous publications (Bracht et al., 2014; Denier et al., 2020; Parker et al., 2013) the patient group was divided into a melancholic and a non-melancholic subgroup based on the HAMD subscale for endogenomorphic depression (HES) (Thase et al., 1983; Zimmerman et al., 1986). The HES score is a sum score of the HAMD items hopelessness, insomnia, work and activities, retardation, loss of weight and diurnal variation. Patients with HES scores $\geq$ 10 were classified as melancholic, whilst patients with HES-scores $<$ 10 were classified as non-melancholic. All patients provided informed written consent. The study was approved by the local cantonal ethics committee (KEK-BE: 2017–00731).

2.2. MRI data acquisition

Structural and functional MRI data were acquired using a 3 Tesla Magnetom Prisma scanner (Siemens, Erlangen, Germany) with a 64-channel head and neck coil at the University Hospital of Bern. High-contrast T1-weighted images were acquired using a bias-field corrected MP2RAGE sequence with two gradient echo images (INV1 and INV2) and a T1-weighted image (UNI). Parameters of the MP2RAGE sequence were: 256 Slices, FOV = 256 × 256, 256 × 256 matrix, 1 × 1 × 1 mm³ isotropic resolution, TR = 5000 ms, TE = 2.98 ms, TI = 700 ms and T2 = 2500 ms. Diffusion weighted images (DWI) were acquired with 64 non-collinear directions using a spin- echo-planar sequence. DWI parameters were: 64 × b = 1000s/mm², 1 × b = 0 s/mm2, 60 Slices, FOV = 269 × 269, 128 × 128 matrix, 2.2 × 2.2 × 2.2 mm3 isotropic resolution, TR = 6200 ms, TE = 69 ms.
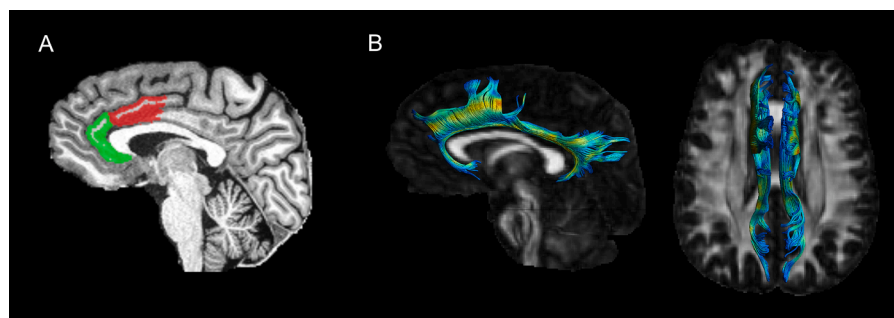
3. Data analyses

3.1. Cortical thickness

For segmentation of the MP2RAGE volumes we used *DL+DiReCT*, a novel deep learning-based neuroanatomy segmentation, followed by a diffeomorphic registration-based cortical thickness (DiReCT) estimation (Rebsamen et al., 2020). We applied HD-BET to the INV2 MP2RAGE volumes for brain extraction and applied the derived binary brain mask to the UNI volumes (Isensee et al., 2019). We computed cortical thickness of left and right rostral and caudal ACC. Masks were derived from FreeSurfer (Fischl, 2012). Finally, mean cortical thickness of the entire brain was calculated (see Fig. 1A).

3.2. Diffusion weighted imaging

FSL 6.0 (http://www.fmrib.ox.ac.uk/fsl/) and FSL-BET were used for robust brain extraction (-R option). Due to noisy background of MP2RAGE UNI images, we used INV2 images as input and applied a derived binary mask to the UNI image to get the extracted brain. Diffusion-weighted MRI-scans were processed using ExploreDTI 4.8.6 (Leemans et al., 2009) as described in previous publications e.g. (Bracht et al., 2021, 2018, 2019; Denier et al., 2020). We applied a motion distortion and an echo-planar imaging (EPI) correction warping the diffusion weighted images to the extracted MP2RAGE image (Leemans and Jones, 2009). Whole-brain deterministic tractography was conducting using a diffusion tensor model (Basser et al., 1994) with the termination criteria FA< 0.2 and angle threshold > 45°. We placed one ROI 5 slices anterior and one ROI 5 slices posterior of the rostro-caudal midpoint of the body of the corpus callosum to reconstruct bilateral CB (Bracht et al., 2015b; Jones et al., 2013a). FA was sampled and averaged separately over left and right CB (see Fig. 1B).

4. Statistical analyses

4.1. Group comparisons of cortical thickness and white matter microstructure

We used the Statistical Package for Social Sciences SPSS 27.0 (SPSS, Inc., Chicago, Illinois) for data analyses. Demographics between healthy controls and all patients and between patient subgroups (melancholic, non-melancholic) were compared for continuous or dichotomous variables using two-sample t-tests or χ^2 tests as appropriate. First, a mixed-model MANCOVA controlling for age and gender was used to compare the between-subject factor group (all patients vs. healthy controls), the within subject factor hemisphere (left vs. right) and the dependent variables cortical thickness of rostral ACC, cortical thickness of caudal ACC and FA of the CB. Second, a mixed-model MANCOVA controlling for age and gender was used to compare the between-subject factor subgroups (melancholic patients, non-melancholic patients and healthy controls) the within subject factor hemisphere (left vs. right) and the dependent variables cortical thickness of rostral ACC, cortical thickness of caudal ACC and FA of the CB. In case of a significant main effect, post hoc tests were considered. In case of a significant group × hemisphere interaction, we tested each hemisphere separately; otherwise, we used a mean score of both hemispheres. Finally, to demonstrate anatomical specificity of putative alterations in cortical thickness of rostral ACC and caudal ACC, ANCOVAs controlling for age and gender were used to compare mean cortical thickness of the entire brain between first all patients and healthy controls and second between the patient subgroups (melancholic, and non-melancholic patients) and healthy controls.

4.2. Associations between depression severity and CB microstructure

Spearman correlations between HAMD total scores and FA of left and right CB were calculated. To consider the impact of chronicity we also calculated partial correlations between HAMD total scores and FA of left and right CB controlling for the impact of the duration of the episode and number of episodes. For all analyses, we applied a two-tailed level of significance of $p < 0.05$.

4.3. Exploratory correlations

To relate structural alterations identified in the melancholic subtype with the clinical core features of melancholia exploratory correlations were calculated with the CORE (total-score and sub-scores) and with the SHAPS total score. Correlations with the SHAPS were calculated across the entire sample. Correlations with the CORE were only calculated for the patient group because there was no variation in the healthy control group (for results see supplementary Table 1). In addition, we explored correlations between cortical thicknesses of rostral ACC, caudal ACC and FA of the CB (see supplementary Table 3).

Fig. 1. ACC and cingulum bundle.
Masks illustrating the rostral ACC (green) and the caudal ACC (red) are shown in Fig. 1A. Tractography results for bilateral cingulum bundle (1B) are displayed for a single subject in native space. FA values are superimposed on the tracts. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

5. Results

Patients and controls did not differ significantly regarding age, gender and handedness. Melancholic and non-melancholic patients differed significantly regarding overall depression severity and CORE total scores but not regarding SHAPS total scores, duration of episode, number of episodes or type of antidepressive medication. Comparison of demographics between all patients and healthy are shown in Table 1, comparisons between melancholic and non-melancholic patients in Supplementary Table 2.

Group comparisons of cortical thickness and white matter microstructure

For analyses of cortical thickness, one patient had to be excluded due to a storage problem of the MP2RAGE raw data. Comparing cortical thickness of rostral and caudal ACC and FA of the CB between all patients with depression and healthy controls there was no significant main effect of group (F (3, 69) =2.107, p = 0.107, η^2=0.084, see supplementary Fig. 1). Comparing melancholic patients, non-melancholic patients and healthy controls we detected a significant main effect of group with a large effect size (F (6, 138) =3.771, p = 0.002, η^2 = (0.143). Post hoc tests revealed a significant main effect for cortical thickness of the mean of left and right caudal ACC (F (2, 70) = 9.982, p <0.001, η^2=0.222). This result was driven by a reduction of cortical thickness of left and right caudal ACC in the melancholic subgroup as compared to both non-melancholic patients and to healthy controls (see Table 2 and Fig. 2). Post hoc tests failed to demonstrate a group difference of thickness in the rostral ACC (F (2, 70) =0.481, p = 0.620, η^2=0.014). There was a significant group x hemisphere interaction for FA of the CB (F (2, 70) =3.334, p = 0.041, η^2=0.087). Therefore, post hoc tests ANCOVAs comparing melancholic patients, non-melancholic patients and healthy controls controlling for age and gender were performed separately for each hemisphere. There were no significant main effects of group for left (F (2, 75) =1.803, p = 0.172, η^2=0.048) and right (F (2, 75) =0.187, p = 0.830, η^2=0.005) FA of the CB (see supplementary Fig. 2). Mean cortical thickness across the entire brain neither differed between all patients and healthy controls (F (1, 71) =0.160, p = 0.690, η^2=0.002), nor between subgroups (melancholic patients, non-melancholic patients, healthy controls, (F (2, 70) =0.928, p = 0.400,

Table 1
Demographics for all patients and healthy controls.

	Patients (n = 54)	Controls (n = 22)	P Value
Age (years)	43.9 ± 12	42.9 ± 13	P = 0.75
Gender (male)	54%	54%	P = 0.95
Handedness (right, left, ambidextrous)	(82%, 12%, 6%)	(90%, 5%, 5%)	P = 0.64
HAMD 21 item version	21.8 ± 5	0.6 ± 1	P < 0.001***
BDI-II	28.6 ± 9	1.5 ± 2	P < 0.001***
CORE total	11.8 ± 7	0.2 ± 1	P < 0.001***
CORE Retardation	6.1 ± 4	0.1 ± 0	P < 0.001***
CORE Agitation	1.9 ± 2	0.1 ± 0	P < 0.001***
CORE Non-interactiveness	3.7 ± 2	0.0 ± 0	P < 0.001***
SHAPS	35.8 ± 6	50.0 ± 4	P < 0.001***
Duration of episode (months)	12.2 ± 11	N/A	N/A
Number of episodes	3.5 ± 3	N/A	N/A
SSRI	18.5%	N/A	N/A
Dual antidepressants	37.1%	N/A	N/A
Tricyclic antidepressants	24.1%	N/A	N/A
Lithium	37.0%	N/A	N/A
No antidepressant	14.8%	N/A	N/A

Table 2
ANCOVAs controlling for age and gender comparing cortical thickness of caudal ACC between melancholic, non-melancholic patient subgroups and healthy controls.

	Melancholic	Non-Melancholic	Controls
Thickness caudal ACC (left) in mm	2.019 ± 0.2876	2.278 ± 0.2980	2.174 ± 0.2423
Thickness caudal ACC (right) in mm	2.123 ± 0.175	2.256 ± 0.2065	2.2690 ± 0.2162
Group comparisons			
Contrast	Mel vs. Non-Mel	Mel vs. HC	Non-Mel vs HC
Caudal ACC (left)	F (1, 52) =9.466 P = 0.003**	F (1, 56) =4.361 P = 0.042*	F (1, 39) =1.965 P = 0.170
Caudal ACC (right)	F (1, 52) =5.140 P = 0.028*	F (1, 56) =7.200 P = 0.010*	F (1, 39) =0.041 P = 0.841

η^2=0.026)).

### 5.1. Associations between depression severity and CB microstructure

Decreases of FA of both left and right CB were associated with increases in depression severity. There was a significant influence of duration of episode on the association between FA of the left CB and HAMD total scores (see Table 3 and Fig. 3).

6. Discussion

In this study, we combined measurements of cortical thickness of rostral and caudal ACC with manual tractography of the CB to investigate the role of these structures for melancholia and depression severity. We found reduced cortical thickness in bilateral caudal ACC in the melancholic subtype compared to non-melancholic patients and to healthy controls. CB microstructure did not differ between groups. However, there was a negative correlation between FA of both left and right CB and depression severity. This correlation remained significant controlling for number of episodes whilst there was an impact of duration of episode on the correlational strength for the right hemisphere.

The identified reduction in cortical thickness of the caudal ACC in the melancholic subtype complements and extends previous studies investigating cortical thickness in depression. To date findings are rather inconsistent with meta-analyses including different study populations yielding both negative and positive results (Schmaal et al., 2017; Suh et al., 2019). We enhance specificity by looking at different compartments of the ACC and by investigating clinically homogeneous subgroups. Our results are in line with previous findings pointing to more pronounced neurobiological alterations in the melancholic subtype (Bracht et al., 2014; Denier et al., 2020; Hyett et al., 2015; Korgaonkar et al., 2011; Pizzagalli et al., 2004). Thus, stratifying patients into more homogeneous subgroups such as the melancholic subtype may yield structural and functional alterations of the brain and enhance our pathophysiological understanding linking those alterations to specific clinical syndromes. Increased thickness of the caudal ACC has been associated with better treatment outcome in depression (Phillips et al., 2015). Given that the melancholic subtype represents a clinical subgroup with specific patterns of response (e.g. low response rates of placebo, better response to tricyclic antidepressants and ECT) (Parker et al., 2017; van Diermen et al., 2019) our finding of reduced caudal ACC thickness in the melancholic subgroup may represent a biological marker of treatment response. While such conclusions would require longitudinal assessments, this explanation fits a plethora a findings suggesting a core role of the ACC for predicting treatment outcome (Godlewska et al., 2018; Mayberg et al., 1997; Pizzagalli, 2011; Pizzagalli et al., 2018; Tian et al., 2020).
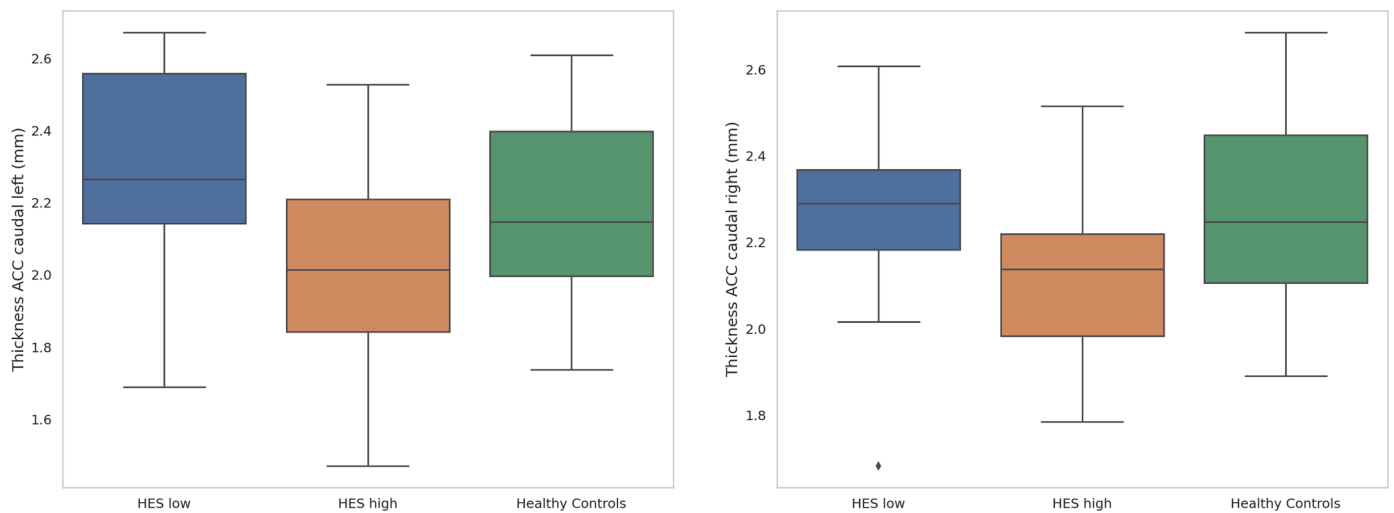
Fig. 2. Caudal ACC thickness.
Boxplots comparing cortical thickness of the left and right caudal ACC between melancholic (HES high), non-melancholic (HES low) and healthy controls. Cortical thickness is reduced in the HES high group in comparison to the HES low group and in comparison to healthy controls for both left and right caudal ACC.

Table 3
Correlations between depression severity and CB microstructure.

	HAMD		
Control variable	N/A	Duration of episode	Number of episodes
FA CB (left)	$R=-0.288, p = 0.035*$	$R=-0.323, p = 0.024*$	$R=-0.336, p = 0.034*$
FA CB (right)	$R = -0.323, p = 0.017*$	$R = -0.250, p = 0.083$	$R = -0.343, p = 0.030*$

Our exploratory correlations suggest that decreases of cortical thickness of the caudal ACC may be associated with the extent of non-interactiveness, a core feature of melancholic depression (see supplementary Table 1). Non-interactiveness (e.g. non-reactivity) represents a syndrome reflecting both the affective state and gestures (Pavlidou et al., 2021; Schrijvers et al., 2008). The caudal ACC may serve as a hub and links brain regions attributing emotional valence (e.g. subgenual ACC Keedwell et al., 2016) with premotor areas (e.g. supplementary motor area Bubb et al., 2018; Rolls, 2019). Therefore, impairments of cortical thickness of the caudal ACC as observed in our study may underlie emotional driven clinical features of motor behavior in depression (Pavlidou et al., 2021; Walther et al., 2019).

In addition, increased thickness of the caudal ACC was associated with increases in hedonic tone (see supplementary Table 1). Our result complement previous functional MRI studies pointing to a central role of the dorsal ACC regarding anticipatory and motivational aspects of reward (Borsini et al., 2020; Liu et al., 2021). It is likely that motivational aspects of reward (e.g. wanting Berridge et al., 2009) are influenced by (dopaminergic) projections from the ventral tegmental area to
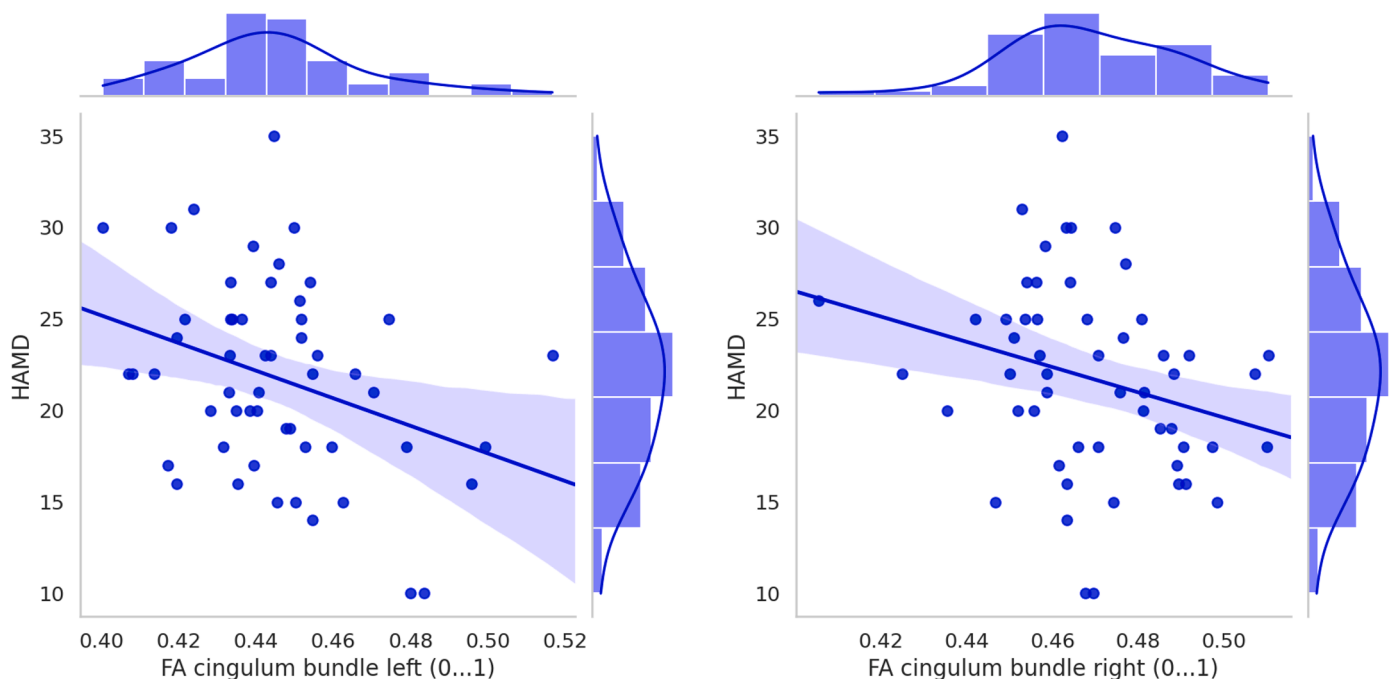
Fig. 3. Cingulum bundle and depression severity.
There is a negative correlation between total HAMD scores and FA for both left and right cingulum bundle.

the orbitofrontal cortex (as shown for the supero-lateral medial forebrain bundle (slMFB) (Bracht et al., 2015a; Coenen et al., 2011, 2020; Denier et al., 2020). Those prefrontal brain areas (e.g. the orbitofrontal cortex) form a network with the rostral and the caudal ACC and link information regarding emotional valence with motivational information (Kringelbach, 2005). Disturbances of this network, as exemplified by our result of cortical thinning of the caudal ACC in melancholic depression may therefore be associated with core features of melancholia related to liking, wanting and to motivated behaviour (Bracht et al., 2014; Cantisani et al., 2016).

In contrast to our finding of reduced thickness of the caudal ACC in melancholic depression, there were no differences of CB microstructure between patients and controls, or between depression subtypes. This adds to rather conflicting results of previous DWI-studies investigating the CB (Bracht et al., 2015c). CB microstructure in depression is likely influenced by series of factors such as familial risk (Keedwell et al., 2012), genetic variability (Murphy et al., 2012), age (Cetin-Karayumak et al., 2020) or the extent of treatment resistance (de Diego-Adelino et al., 2014), which all adds to heterogeneity of findings. In addition, structural alterations may be specific for sub-compartments (Bhatia et al., 2018; Dillon et al., 2018; Keedwell et al., 2016). The CB integrates a series of functions relevant to the depressive syndrome (e.g. affective, cognitive, and reward-related motivational disturbances) (Bubb et al., 2018; Dillon et al., 2018). Furthermore, the CB may play a role for rumination because it connects anterior and posterior regions of the default mode network that have been related to rumination-processes in depression (Zhu et al., 2012). Given these diverse functions of the CB, the clinical correlates of CB microstructural alterations may be broader than it is the case for pathways with more circumscribed functions (e.g. the slMFB Bracht et al., 2015c; Denier et al., 2020). This assumption fits our finding of a negative association between overall depression severity (covering diverse symptoms of depression) and FA of bilateral CB.

Correlations remained significant controlling for number of episodes, whilst there was a modest impact of duration of episode. This implies a rather weak impact of chronicity on CB microstructure. Previous research suggests that the process of remission is associated with FA increases of the right cingulum bundle (Bracht et al., 2015b). One may speculate whether increased activity of the ACC, an early marker of treatment response (Godlewska et al., 2018; Mayberg et al., 1997; Pizzagalli, 2011; Pizzagalli et al., 2018; Tian et al., 2020), induces such neuroplastic processes. Assuming such an association CB microstructure may represent a state marker of depression severity. However, longitudinal studies including comparison groups would be required to draw conclusions on this research question.

Finally, this study has some limitations. First, the study consists of patients with a rather long duration of the current episode. Therefore, results cannot be generalized to acutely depressed patient subgroups. Second, patients were mainly medicated. However, there were no significant differences between melancholic and non-melancholic depressed patients regarding medication status. Third, the applied pleasure scale (SHAPS) does not assess motivational aspects of reward. Fourth, due to the lack of neurobiological specificity of MRI-derived measures we can only speculate on the nature of the identified cortical thinning in the melancholic subgroup (e.g. reductions in glial density, amount and volume of neurons (Suh et al., 2019). The same applies for the lack of specificity of FA (which is influenced by axonal diameter, myelination and fibre architecture (Jones et al., 2013b). Fifth, we discuss our results referring to uncorrected exploratory correlations (see supplementary Table 1) that require further replication in independent study samples.

In sum, our results suggest cortical thinning of the caudal ACC in melancholic depression, corroborating research pointing to more pronounced neurobiological alterations in melancholia (Bracht et al., 2014; Denier et al., 2020; Hyett et al., 2015; Korgaonkar et al., 2011; Pizzagalli et al., 2004). This cortical thinning may be a structural correlate of psychomotor disturbances and anhedonia. In contrast, there are no

specific alterations of CB microstructure in the melancholic subtype. However, CB microstructure relates to depression severity, and may reflect broader and more diverse symptoms of depression. Future longitudinal studies should include measures of cortical thickness and CB microstructure to investigate if those alterations are state or trait markers and to investigate their putative role as biomarkers for treatment response in depression (Bracht et al., 2015b; Phillips et al., 2015; Pizzagalli et al., 2018; Tian et al., 2020).

CRediT authorship contribution statement

Nicolas Mertse: Resources, Data curation, Formal analysis, Writing – original draft. **Niklaus Denier:** Resources, Data curation, Formal analysis. **Sebastian Walther:** Conceptualization, Formal analysis. **Sigrid Breit:** Resources, Data curation, Formal analysis. **Elmar Grosskurth:** Resources, Data curation, Formal analysis. **Andrea Federspiel:** Methodology, Supervision, Data curation. **Roland Wiest:** Methodology, Supervision, Data curation. **Tobias Bracht:** Conceptualization, Resources, Data curation, Formal analysis, Writing – original draft.

Declaration of Competing Interest

The authors declare that they have no conflict of interest

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jad.2022.01.035.

References

Abe, C., Ekman, C.J., Sellgren, C., Petrovic, P., Ingvar, M., Landen, M., 2016. Cortical thickness, volume and surface area in patients with bipolar disorder Types I and II. J. Psychiatry Neurosci. 41, 240–250.

Anand, A., Li, Y., Wang, Y., Wu, J., Gao, S., Bukhari, L., Mathews, V.P., Kalnin, A., Lowe, M.J., 2005. Activity and connectivity of brain mood regulating circuit in depression: a functional magnetic resonance study. Biol. Psychiatry 57, 1079–1088.

APA, 2013. Diagnostic and statistical manual of mental disorders (DSM-5). Arlington, United States.

Arnow, B.A., Blasey, C., Williams, L.M., Palmer, D.M., Rekshan, W., Schatzberg, A.F., Etkin, A., Kulkarni, J., Luther, J.F., Rush, A.J., 2015. Depression subtypes in predicting antidepressant response: a report from the iSPOT-D trial. Am. J. Psychiatry 172, 743–750.

Baeken, C., van Beek, V., Vanderhasselt, M.A., Duprat, R., Klooster, D., 2021. Cortical Thickness in the Right Anterior Cingulate Cortex Relates to Clinical Response to Left Prefrontal Accelerated Intermittent Theta Burst Stimulation: An Exploratory Study. Neuromodulation.

Basser, P.J., Mattiello, J., LeBihan, D., 1994. Estimation of the effective self-diffusion tensor from the NMR spin echo. J. Magn. Reson. B 103, 247–254.

Beck, A.T., Steer, R.A., Brown, G., 1996. Beck Depression Inventory -II. APA PsyTests.

Berridge, K.C., Robinson, T.E., Aldridge, J.W., 2009. Dissecting components of reward: 'liking', 'wanting', and learning. Curr. Opin. Pharmacol. 9, 65–73.

Bhatia, K.D., Henderson, L.A., Hsu, E., Yim, M., 2018. Reduced integrity of the uncinate fasciculus and cingulum in depression: a stem-by-stem analysis. J. Affect. Disord. 235, 220–228.

Borsini, A., Wallis, A.S.J., Zunszain, P., Pariante, C.M., Kempton, M.J., 2020. Characterizing anhedonia: a systematic review of neuroimaging across the subtypes of reward processing deficits in depression. Cogn. Affect. Behav. Neurosci. 20, 816–841.

Bracht, T., Doidge, A.N., Keedwell, P.A., Jones, D.K., 2015a. Hedonic tone is associated with left supero-lateral medial forebrain bundle microstructure. Psychol. Med. 45, 865–874.

Bracht, T., Horn, H., Strik, W., Federspiel, A., Schnell, S., Hofle, O., Stegmayer, K., Wiest, R., Dierks, T., Muller, T.J., Walther, S., 2014. White matter microstructure alterations of the medial forebrain bundle in melancholic depression. J. Affect. Disord. 155, 186–193.

Bracht, T., Jones, D.K., Muller, T.J., Wiest, R., Walther, S., 2015b. Limbic white matter microstructure plasticity reflects recovery from depression. J. Affect. Disord. 170, 143–149.

Bracht, T., Linden, D., Keedwell, P., 2015c. A review of white matter microstructure alterations of pathways of the reward circuit in depression. J. Affect. Disord. 187, 45–53.

Bracht, T., Soravia, L., Moggi, F., Stein, M., Grieder, M., Federspiel, A., Tschumperlin, R., Batschelet, H.M., Wiest, R., Denier, N., 2021. The role of the orbitofrontal cortex and the nucleus accumbens for craving in alcohol use disorder. Transl. Psychiatry 11, 267.

Bracht, T., Steinau, S., Federspiel, A., Schneider, C., Wiest, R., Walther, S., 2018. Physical activity is associated with left corticospinal tract microstructure in bipolar depression. Neuroimage Clin. 20, 939–945.

Bracht, T., Viher, P.V., Stegmayer, K., Strik, W., Federspiel, A., Wiest, R., Walther, S., 2019. Increased structural connectivity of the medial forebrain bundle in schizophrenia spectrum disorders is associated with delusions of paranoid threat and grandiosity. Neuroimage Clin. 24, 102044.

Bubb, E.J., Metzler-Baddeley, C., Aggleton, J.P., 2018. The cingulum bundle: anatomy, function, and dysfunction. Neurosci. Biobehav. Rev. 92, 104–127.

Cantisani, A., Stegmayer, K., Bracht, T., Federspiel, A., Wiest, R., Horn, H., Muller, T.J., Schneider, C., Hofle, O., Strik, W., Walther, S., 2016. Distinct resting-state perfusion patterns underlie psychomotor retardation in unipolar vs. bipolar depression. Acta Psychiatr. Scand. 134, 329–338.

Cetin-Karayumak, S., Di Biase, M.A., Chunga, N., Reid, B., Somes, N., Lyall, A.E., Kelly, S., Solgun, B., Pasternak, O., Vangel, M., Pearlson, G., Tamminga, C., Sweeney, J.A., Clementz, B., Schretlen, D., Viher, P.V., Stegmayer, K., Walther, S., Lee, J., Crow, T., James, A., Voineskos, A., Buchanan, R.W., Szeszko, P.R., Malhotra, A.K., Hegde, R., McCarley, R., Keshavan, M., Shenton, M., Rathi, Y., Kubicki, M., 2020. White matter abnormalities across the lifespan of schizophrenia: a harmonized multi-site diffusion MRI study. Mol. Psychiatry 25, 3208–3219.

Coenen, V.A., Schlaepfer, T.E., Maedler, B., Panksepp, J., 2011. Cross-species affective functions of the medial forebrain bundle-implications for the treatment of affective pain and depression in humans. Neurosci. Biobehav. Rev. 35, 1971–1981.

Coenen, V.A., Schlaepfer, T.E., Sajonz, B., Dobrossy, M., Kaller, C.P., Urbach, H., Reisert, M., 2020. Tractographic description of major subcortical projection pathways passing the anterior limb of the internal capsule. Corticopetal organization of networks relevant for psychiatric disorders. Neuroimage Clin. 25, 102165.

Cohen, J.D., Nichols, T., Keller, J., Gomez, R.G., Schatzberg, A.F., Reiss, A.L., 2013. Insular cortex abnormalities in psychotic major depression: relationship to gender and psychotic symptoms. Neurosci. Res. 75, 331–339.

de Diego-Adelino, J., Pires, P., Gomez-Anson, B., Serra-Blasco, M., Vives-Gilabert, Y., Puigdemont, D., Martin-Blanco, A., Alvarez, E., Perez, V., Portella, M.J., 2014. Microstructural white-matter abnormalities associated with treatment resistance, severity and duration of illness in major depression. Psychol. Med. 44, 1171–1182.

Denier, N., Walther, S., Schneider, C., Federspiel, A., Wiest, R., Bracht, T., 2020. Reduced tract length of the medial forebrain bundle and the anterior thalamic radiation in bipolar disorder with melancholic depression. J. Affect. Disord. 274, 8–14.

Dillon, D.G., Gonenc, A., Belleau, E., Pizzagalli, D.A., 2018. Depression is associated with dimensional and categorical effects on white matter pathways. Depress. Anxiety 35, 440–447.

Drysdale, A.T., Grosenick, L., Downar, J., Dunlop, K., Mansouri, F., Meng, Y., Fetcho, R. N., Zebley, B., Oathes, D.J., Etkin, A., Schatzberg, A.F., Sudheimer, K., Keller, J., Mayberg, H.S., Gunning, F.M., Alexopoulos, G.S., Fox, M.D., Pascual-Leone, A., Voss, H.U., Casey, B.J., Dubin, M.J., Liston, C., 2017. Resting-state connectivity biomarkers define neurophysiological subtypes of depression. Nat. Med. 23, 28–38.

Dunlop, B.W., Mayberg, H.S., 2017. Neuroimaging advances for depression. Cerebrum 2017.

Fischl, B., 2012. FreeSurfer. Neuroimage 62, 774–781.

Franken, I.H., Rassin, E., Muris, P., 2007. The assessment of anhedonia in clinical and non-clinical populations: further validation of the Snaith-Hamilton Pleasure Scale (SHAPS). J. Affect. Disord. 99, 83–89.

Gbyl, K., Rostrup, E., Raghava, J.M., Carlsen, J.F., Schmidt, L.S., Lindberg, U., Ashraf, A., Jorgensen, M.B., Larsson, H.B.W., Rosenberg, R., Videbech, P., 2019. Cortical thickness following electroconvulsive therapy in patients with depression: a longitudinal MRI study. Acta Psychiatr. Scand. 140, 205–216.

Godlewska, B.R., Browning, M., Norbury, R., Igoumenou, A., Cowen, P.J., Harmer, C.J., 2018. Predicting treatment response in depression: the role of anterior cingulate cortex. Int. J. Neuropsychopharmacol. 21, 988–996.

Haber, S.N., Knutson, B., 2010. The reward circuit: linking primate anatomy and human imaging. Neuropsychopharmacology 35, 4–26.

Hamilton, M., 1967. Development of a rating scale for primary depressive illness. Br. J. Soc. Clin. Psychol. 6, 278–296.

Hyett, M.P., Breakspear, M.J., Friston, K.J., Guo, C.C., Parker, G.B., 2015. Disrupted effective connectivity of cortical systems supporting attention and interoception in melancholia. JAMA Psychiatry 72, 350–358.

Isensee, F., Schell, M., Pflueger, I., Brugnara, G., Bonekamp, D., Neuberger, U., Wick, A., Schlemmer, H.-.P., Heiland, S., Wick, W., Bendszus, M., Maier-Hein, K.H., Kickingereder, P., 2019. Automated brain extraction of multisequence MRI using artificial neural networks. Hum. Brain Mapp. 40, 4952–4964.

Jones, D.K., Christiansen, K.F., Chapman, R.J., Aggleton, J.P., 2013a. Distinct subdivisions of the cingulum bundle revealed by diffusion MRI fibre tracking: implications for neuropsychological investigations. Neuropsychologia 51, 67–78.

Jones, D.K., Knosche, T.R., Turner, R., 2013b. White matter integrity, fiber count, and other fallacies: the do's and don'ts of diffusion MRI. Neuroimage 73, 239–254.

Keedwell, P.A., Andrew, C., Williams, S.C., Brammer, M.J., Phillips, M.L., 2005. The neural correlates of anhedonia in major depressive disorder. Biol. Psychiatry 58, 843–853.

Keedwell, P.A., Chapman, R., Christiansen, K., Richardson, H., Evans, J., Jones, D.K., 2012. Cingulum white matter in young women at risk of depression: the effect of family history and anhedonia. Biol. Psychiatry 72, 296–302.

Keedwell, P.A., Doidge, A.N., Meyer, M., Lawrence, N., Lawrence, A.D., Jones, D.K., 2016. Subgenual cingulum microstructure supports control of emotional conflict. Cereb. Cortex 26, 2850–2862.

Korgaonkar, M.S., Grieve, S.M., Koslow, S.H., Gabrieli, J.D., Gordon, E., Williams, L.M., 2011. Loss of white matter integrity in major depressive disorder: evidence using tract-based spatial statistical analysis of diffusion tensor imaging. Hum. Brain Mapp. 32, 2161–2171.

Kringelbach, M.L., 2005. The human orbitofrontal cortex: linking reward to hedonic experience. Nat. Rev. Neurosci. 6, 691–702.

Leemans, A., Jeurissen, B., Sijbers, J., Jones, D.K., 2009. ExporeDTI: a graphical toolbox for processing, analyzing and visualizing diffusion MR data. In: Proceedings of the International Society for Magnetic Resonance in Medicine 17th Annual Meeting April 18-24. Honolulu Hawaii, p. 3536.

Leemans, A., Jones, D.K., 2009. The B-matrix must be rotated when correcting for subject motion in DTI data. Magn. Reson. Med. 61, 1336–1349.

Li, B.J., Friston, K., Mody, M., Wang, H.N., Lu, H.B., Hu, D.W., 2018. A brain network model for depression: from symptom understanding to disease intervention. CNS Neurosci. Ther. 24, 1004–1019.

Liu, X., Li, L., Li, M., Ren, Z., Ma, P., 2021. Characterizing the subtype of anhedonia in major depressive disorder: a symptom-specific multimodal MRI study. Psychiatry Res. Neuroimaging 308, 111239.

Margulies, D.S., Kelly, A.M., Uddin, L.Q., Biswal, B.B., Castellanos, F.X., Milham, M.P., 2007. Mapping the functional connectivity of anterior cingulate cortex. Neuroimage 37, 579–588.

Mayberg, H.S., Brannan, S.K., Mahurin, R.K., Jerabek, P.A., Brickman, J.S., Tekell, J.L., Silva, J.A., McGinnis, S., Glass, T.G., Martin, C.C., Fox, P.T., 1997. Cingulate function in depression: a potential predictor of treatment response. Neuroreport 8, 1057–1061.

Murphy, M.L., Carballedo, A., Fagan, A.J., Morris, D., Fahey, C., Meaney, J., Frodl, T., 2012. Neurotrophic tyrosine kinase polymorphism impacts white matter connections in patients with major depressive disorder. Biol. Psychiatry 72, 663–670.

Musil, R., Seemuller, F., Meyer, S., Spellmann, I., Adli, M., Bauer, M., Kronmuller, K.T., Brieger, P., Laux, G., Bender, W., Heuser, I., Fisher, R., Gaebel, W., Schennach, R., Moller, H.J., Riedel, M., 2018. Subtypes of depression and their overlap in a naturalistic inpatient sample of major depressive disorder. Int. J. Methods Psychiatr. Res. 27.

Oldfield, R.C., 1971. The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia 9, 97–113.

Parker, G., Bassett, D., Outhred, T., Morris, G., Hamilton, A., Das, P., Baune, B.T., Berk, M., Boyce, P., Lyndon, B., Mulder, R., Singh, A.B., Malhi, G.S., 2017. Defining melancholia: a core mood disorder. Bipolar Disord. 19, 235–237.

Parker, G., Blanch, B., Paterson, A., Hadzi-Pavlovic, D., Sheppard, E., Manicavasagar, V., Synnott, H., Graham, R.K., Friend, P., Gilfillan, D., Perich, T., 2013. The superiority of antidepressant medication to cognitive behavior therapy in melancholic depressed patients: a 12-week single-blind randomized study. Acta Psychiatr. Scand. 128, 271–281.

Parker, G., Fink, M., Shorter, E., Taylor, M.A., Akiskal, H., Berrios, G., Bolwig, T., Brown, W.A., Carroll, B., Healy, D., Klein, D.F., Koukopoulos, A., Michels, R., Paris, J., Rubin, R.T., Spitzer, R., Swartz, C., 2010. Issues for DSM-5: whither melancholia? The case for its classification as a distinct mood disorder. Am. J. Psychiatry 167, 745–747.

Parker, G., Hadzi-Pavlovic, D., 1996. Melancholia: A Disorder of Movement and Mood - A Phenomenological and Neurobiological Review. Cambridge University Press, Cambridge.

Parker, G., McCraw, S., 2017. The properties and utility of the CORE measure of melancholia. J. Affect. Disord. 207, 128–135.

Pavlidou, A., Viher, P.V., Bachofner, H., Weiss, F., Stegmayer, K., Shankman, S.A., Mittal, V.A., Walther, S., 2021. Hand gesture performance is impaired in major depressive disorder: a matter of working memory performance? J. Affect. Disord. 292, 81–88.

Phillips, J.L., Batten, L.A., Tremblay, P., Aldosary, F., Blier, P., 2015. A prospective, longitudinal study of the effect of remission on cortical thickness and hippocampal volume in patients with treatment-resistant depression. Int. J. Neuropsychopharmacol. 18.

Pizzagalli, D.A., 2011. Frontocingulate dysfunction in depression: toward biomarkers of treatment response. Neuropsychopharmacology 36, 183–206.

Pizzagalli, D.A., Holmes, A.J., Dillon, D.G., Goetz, E.L., Birk, J.L., Bogdan, R., Dougherty, D.D., Iosifescu, D.V., Rauch, S.L., Fava, M., 2009. Reduced caudate and nucleus accumbens response to rewards in unmedicated individuals with major depressive disorder. Am. J. Psychiatry 166, 702–710.

Pizzagalli, D.A., Oakes, T.R., Fox, A.S., Chung, M.K., Larson, C.L., Abercrombie, H.C., Schaefer, S.M., Benca, R.M., Davidson, R.J., 2004. Functional but not structural subgenual prefrontal cortex abnormalities in melancholia. Mol. Psychiatry 9 (325), 393–405.

Pizzagalli, D.A., Webb, C.A., Dillon, D.G., Tenke, C.E., Kayser, J., Goer, F., Fava, M., McGrath, P., Weissman, M., Parsey, R., Adams, P., Trombello, J., Cooper, C., Deldin, P., Oquendo, M.A., McInnis, M.G., Carmody, T., Bruder, G., Trivedi, M.H., 2018. Pretreatment rostral anterior cingulate cortex theta activity in relation to symptom improvement in depression: a randomized clinical trial. JAMA Psychiatry 75, 547–554.

Rebsamen, M., Rummel, C., Reyes, M., Wiest, R., McKinley, R., 2020. Direct cortical thickness estimation using deep learning-based anatomy segmentation and cortex parcellation. Hum. Brain Mapp. 41, 4804–4814.

Rolls, E.T., 2019. The cingulate cortex and limbic systems for emotion, action, and memory. Brain Struct. Funct. 224, 3001–3018.

Schmaal, L., Hibar, D.P., Samann, P.G., Hall, G.B., Baune, B.T., Jahanshad, N., Cheung, J. W., van Erp, T.G.M., Bos, D., Ikram, M.A., Vernooij, M.W., Niessen, W.J., Tiemeier, H., Hofman, A., Wittfeld, K., Grabe, H.J., Janowitz, D., Bulow, R., Selonke, M., Volzke, H., Grotegerd, D., Dannlowski, U., Arolt, V., Opel, N., Heindel, W., Kugel, H., Hoehn, D., Czisch, M., Couvy-Duchesne, B., Renteria, M.E., Strike, L.T., Wright, M.J., Mills, N.T., de Zubicaray, G.I., McMahon, K.L., Medland, S. E., Martin, N.G., Gillespie, N.A., Goya-Maldonado, R., Gruber, O., Kramer, B., Hatton, S.N., Lagopoulos, J., Hickie, I.B., Frodl, T., Carballedo, A., Frey, E.M., van Velzen, L.S., Penninx, B., van Tol, M.J., van der Wee, N.J., Davey, C.G., Harrison, B. J., Mwangi, B., Cao, B., Soares, J.C., Veer, I.M., Walter, H., Schoepf, D., Zurowski, B., Konrad, C., Schramm, E., Normann, C., Schnell, K., Sacchet, M.D., Gotlib, I.H., MacQueen, G.M., Godlewska, B.R., Nickson, T., McIntosh, A.M., Papmeyer, M., Whalley, H.C., Hall, J., Sussmann, J.E., Li, M., Walter, M., Aftanas, L., Brack, I., Bokhan, N.A., Thompson, P.M., Veltman, D.J., 2017. Cortical abnormalities in adults and adolescents with major depression based on brain scans from 20 cohorts worldwide in the ENIGMA major depressive disorder working group. Mol. Psychiatry 22, 900–909.

Schrijvers, D., Hulstijn, W., Sabbe, B.G., 2008. Psychomotor symptoms in depression: a diagnostic, pathophysiological and therapeutic tool. J. Affect. Disord. 109, 1–20.

Shan, X., Cui, X., Liu, F., Li, H., Huang, R., Tang, Y., Chen, J., Zhao, J., Guo, W., Xie, G., 2021. Shared and distinct homotopic connectivity changes in melancholic and non-melancholic depression. J. Affect. Disord. 287, 268–275.

Shankman, S.A., Mittal, V.A., Walther, S., 2020. An examination of psychomotor disturbance in current and remitted MDD: an RDoC study. J. Psychiatr. Brain Sci. 5.

Sheehan, D.V., Lecrubier, Y., Sheehan, K.H., Amorim, P., Janavs, J., Weiller, E., Hergueta, T., Baker, R., Dunbar, G.C., 1998. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J. Clin. Psychiatry 59 (Suppl 20), 22–33 quiz 34-57.

Snaith, R.P., Hamilton, M., Morley, S., Humayan, A., Hargreaves, D., Trigwell, P., 1995. A scale for the assessment of hedonic tone the Snaith-Hamilton pleasure scale. Br. J. Psychiatry 167, 99–103.

Suh, J.S., Schneider, M.A., Minuzzi, L., MacQueen, G.M., Strother, S.C., Kennedy, S.H., Frey, B.N., 2019. Cortical thickness in major depressive disorder: a systematic review and meta-analysis. Prog. Neuropsychopharmacol. Biol. Psychiatry 88, 287–302.

Thase, M.E., Hersen, M., Bellack, A.S., Himmelhoch, J.M., Kupfer, D.J., 1983. Validation of a Hamilton subscale for endogenomorphic depression. J. Affect. Disord. 5, 267–278.

Tian, S., Sun, Y., Shao, J., Zhang, S., Mo, Z., Liu, X., Wang, Q., Wang, L., Zhao, P., Chattun, M.R., Yao, Z., Si, T., Lu, Q., 2020. Predicting escitalopram monotherapy response in depression: the role of anterior cingulate cortex. Hum. Brain Mapp. 41, 1249–1260.

van Diermen, L., Vanmarcke, S., Walther, S., Moens, H., Veltman, E., Fransen, E., Sabbe, B., van der Mast, R., Birkenhager, T., Schrijvers, D., 2019. Can psychomotor disturbance predict ect outcome in depression? J. Psychiatr. Res. 117, 122–128.

Wacker, J., Dillon, D.G., Pizzagalli, D.A., 2009. The role of the nucleus accumbens and rostral anterior cingulate cortex in anhedonia: integration of resting EEG, fMRI, and volumetric techniques. Neuroimage 46, 327–337.

Walther, S., Bernard, J.A., Mittal, V.A., Shankman, S.A., 2019. The utility of an RDoC motor domain to understand psychomotor symptoms in depression. Psychol. Med. 49, 212–216.

Walther, S., Hofle, O., Federspiel, A., Horn, H., Hugli, S., Wiest, R., Strik, W., Muller, T.J., 2012. Neural correlates of disbalanced motor control in major depression. J. Affect. Disord. 136, 124–133.

Wittchen, H.U., Zaudig, M., Fydrich, T., 1997. Strukturiertes Klinisches Interview für DSM-IV. Hogrefe, Göttingen.

Zhao, K., Liu, H., Yan, R., Hua, L., Chen, Y., Shi, J., Lu, Q., Yao, Z., 2017. Cortical thickness and subcortical structure volume abnormalities in patients with major depression with and without anxious symptoms. Brain Behav. 7, e00754.

Zhu, X., Wang, X., Xiao, J., Liao, J., Zhong, M., Wang, W., Yao, S., 2012. Evidence of a dissociation pattern in resting-state default mode network connectivity in first-episode, treatment-naive major depression patients. Biol. Psychiatry 71, 611–617.

Zimmerman, M., Coryell, W., Pfohl, B., Stangl, D., 1986. Validity of the Hamilton endogenous subscale: an independent replication. Psychiatry Res. 18, 209–215.