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Brain structural connectivity, anhedonia, and phenotypes of major depressive disorder: A structural equation model approach

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Abstract

Aberrant brain structural connectivity in major depressive disorder (MDD) has been repeatedly reported, yet many previous studies lack integration of different features of MDD with structural connectivity in multivariate modeling approaches. In $n = 595$ MDD patients, we used structural equation modeling (SEM) to test the intercorrelations between anhedonia, anxiety, neuroticism, and cognitive control in one comprehensive model. We then separately analyzed diffusion tensor imaging (DTI) connectivity measures in association with those clinical variables, and finally integrated brain connectivity associations, clinical/cognitive variables into a multivariate SEM. We first confirmed our clinical/cognitive SEM. DTI analyses (FWE-corrected) showed a positive correlation of anhedonia with fractional anisotropy (FA) in the right anterior thalamic radiation (ATR) and forceps minor/corpus callosum, while neuroticism was negatively correlated with axial diffusivity (AD) in the left uncinate fasciculus (UF) and inferior fronto-occipital fasciculus (IFOF). An extended SEM confirmed the associations of ATR FA with anhedonia and UF/IFOF AD with neuroticism impacting on cognitive control. Our findings provide evidence for a differential impact of state and trait variables of MDD on brain connectivity and cognition. The multivariate approach shows feasibility of explaining heterogeneity within MDD and tracks this to specific brain circuits, thus adding to better understanding of heterogeneity on the biological level.

KEYWORDS
anhedonia, connectivity, diffusion tensor imaging, major depressive disorder (MDD), neuroticism, structural equation modeling

1 | INTRODUCTION

Major depressive disorder (MDD) has one of the highest lifetime prevalence among psychiatric disorders (Kessler & Bromet, 2013) resulting in significant individual and social burden (Lépine & Briley, 2011). Symptom representations, course of illness, and treatment response are, however, highly heterogeneous, prompting the need for markers for group stratification or links to single facets to brain mechanisms (Goldstein & Klein, 2014).

Anhedonia is a core symptom of depression and predominantly manifests emotionally as a lack of feeling pleasure, as well as reduced motivation and drive on the behavioral level (Watson, Harvey, McCabe, & Reynolds, 2020). Indeed, the diagnostic criteria of depression in the Diagnostic and Statistical Manual of Mental Disorders (fifth ed.; American Psychiatric Association, 2013) consider anhedonia as one of the two main symptoms (besides depressed mood) necessary for a clinical MDD diagnosis. Previous studies have already shown the importance of anhedonia impacting on severity of illness course, shaping the disease course, as well as effectiveness of drug treatment and psychotherapy for MDD (Auerbach, Pagliaccio, & Pizzagalli, 2019; Craske, Treanor, Dour, Meuret, & Ritz, 2019; McMakin et al., 2012; Snaith, 1993; Trøstheim et al., 2020; Watson et al., 2020). Also, there is a strong relationship between expression of anhedonia and suicidal behavior, even independently of an MDD diagnosis (Auerbach et al., 2019; Auerbach, Millner, Stewart, & Esposito, 2015; Ducasse et al., 2018; Winer et al., 2014). Anhedonia is also associated with endophenotypes of depression, including psychosocial functioning and neuroticism (Gong et al., 2018; Langvik, Hjemdal, & Nordahl, 2016; Liao et al., 2019; Vinckier, Gourion, & Mouchabac, 2017). Genetic risk scores of depression phenotypes were found to be correlated with anhedonia-related phenotypes (Guffanti et al., 2019). In addition, cognitive impairments, such as attention, were related to anhedonia more strongly than depression per se (Grillo, 2016).

Recent brain imaging studies suggest associations of anhedonia with white matter microstructure of particular fiber tracts. In contrast to large case–control imaging showing wide-spread gray and white matter alterations in MDD (Schmaal et al., 2017; van Velzen et al., 2020), structural connectivity analyses focusing specifically on anhedonia found significant associations of fractional anisotropy (FA) in the left cingulum and forceps minor/anterior corpus callosum as well as radial diffusivity (RD) in the anterior thalamic radiation (ATR), corticospinal tract, superior longitudinal fasciculus (SLF), and uncinate fasciculus (UF; Yang et al., 2017). Similarly, a more recent study identified white matter abnormalities in patients with MDD related to anhedonia in the fronto-limbic circuits (Coloigner et al., 2019), which differed from associations with anxiety, which was associated with lower FA in the corpus callosum as well as anterior corona radiata and posterior thalamic radiation. Both, the cingulum bundle and the UF have also been found to be associated with neuroticism (Madsen et al., 2009; Mincic, 2015), a less specific risk factor for MDD, suggesting a structural overlap of brain structural correlates of anhedonia and neuroticism, although findings are not entirely consistent (Avinun, Israel, Knodt, & Hariri, 2020; Servaas et al., 2013). In addition, functional imaging studies focusing on anhedonia show a network of subcortical structures including the nucleus accumbens, ventral pallidum, and amygdala to underlie processing of pleasure (Berridge, Kringelbach, Arbor, & Hospital, 2016). In patients with MDD, these reward circuits are functionally impaired and functional hypoconnectivity of the fronto-striatal network contributes to the behavioral manifestations of anhedonia (Höflich, Michenthaler, Kasper, & Lanzenberger, 2018; Li et al., 2018).

Although there is now a better understanding of specific neural networks related to anhedonia in MDD, previous studies have often been limited to singular associations between a clinical symptom and brain markers, often in smaller samples. Larger multicenter studies, however, mostly lack analyses for specific symptom clusters or potential subgroups in depression (Schmaal et al., 2017; van Velzen et al., 2020).

MDD, however, manifests as a combination of different symptom phenotypes, for example, anxiety, somatic symptoms, cognitive restraints. Respecting the dimensionality of those markers (e.g., neurophysiological, biochemical, neuroanatomical, cognitive data) rather than their categories, contributes to disentangle the full range of psychiatric disorders (Gottesman & McGue, 2014; Kozak & Cuthbert, 2016).

Despite some advances, there is a paucity of multivariate approaches integrating brain, cognitive, and clinical data, which so far have been mostly analyzed in separate studies. Multivariate modeling might improve our understanding of how these biological parameters interact with risk factors and clinical symptom dimensions like anhedonia—and might thus relate to the multidimensional nature of MDD. Multivariate models additionally offer the advantage to test both multiple direct and indirect effects within an overall model (Stein, Morris, Hall, & Nock, 2017).

Structural equation modeling (SEM) is a multivariate approach, which has already been used to integrate clinical and risk factors of MDD (Rezaei, Ghazanfari, & Rezaee, 2016; Tse, Rochelle, & Cheung, 2011). A recent clinical study described—on the phenotype/clinical level—a model of how anhedonia as well as anxiety interact with the depression-related phenotypes of neuroticism and cognitive control (Liao et al., 2019). With the proposed SEM, the authors acknowledge the impact of anhedonia and anxiety on MDD state and course, as well as their high intercorrelation. Besides symptom representations, risk factors like personality traits and cognitive aspects should be considered for a more integrated view on MDD or psychiatric disorders per se, respectively. Liao et al. (2019) considered a relationship between the mentioned symptoms and neuroticism as well as cognitive control, as they are established risk endophenotypes for MDD (Goldstein & Klein, 2014).

These models provide a basis for integrating structural connectivity mapping with differentiated SEM models to address and dissect multiple facets of MDD phenotypes. However, to this date, there is no such application drawing on large MDD samples in the field. This approach builds on the recent clinical/cognitive model by Liao et al. (2019) described above; we expand on this by integrating structural connectivity parameters, expected to differentially correlate to these clinical variables in a large sample of MDD patients.

We test the hypothesis that white matter tract integrity is associated with anhedonia, as well as anxiety, neuroticism, and cognitive control in different regional tracts. For this purpose, we first test a SEM integrating anhedonia, neuroticism, anxiety, and cognitive control, based on an extension of a previous study by Liao et al. (2019). We then analyzed white matter connectivity associations with clinical variables and finally integrated those into a testable multivariate model using SEM. More precisely, based on several studies on brain imaging and anhedonia described above, we expected anhedonia to be associated with brain structural aberrations mainly in tracts involved in emotion regulation, for example, ATR, UF (Coloigner et al., 2019; Yang et al., 2017). As previous studies on DTI and negative related emotions showed an involvement of the UF, we expected to find an association in this tract with neuroticism as well as with anxiety (Mincic, 2015).

We modeled cognitive control as executive function or inhibition ability, respectively, based on former studies finding those to not just be impaired in MDD but also to be related to particular risk factors for MDD (Crow, 2019; Pan et al., 2019).

2 | METHODS

2.1 | Study cohort

We analyzed $n = 595$ subjects with a lifetime diagnosis of MDD (365 female, 230 male; mean age 36.14 years, $SD = 13.09$) from the FOR 2107 consortium (Kircher et al., 2019), applying criteria of the DSM-IV based on face-to-face interviews using the German version of the SCID-I interview (Strukturiertes Klinisches Interview für DSM-IV Achse I Störungen; First & Gibbon, 2004; Wittchen, Wunderlich, Grushwitz, & Zaudig, 1997). We included patients within an age range of 18–65 years with at least one current or past MDD episode. We excluded patients with a history of traumatic brain injury or central nervous system neurological disorders, physical disorders that could have an impact on brain morphology (e.g., autoimmune diseases, cancer, and infections), substance dependence, as well as general contraindications to MRI scanning. Further exclusion criteria were intellectual impairment/learning disability, defined as verbal intelligence quotient lower than 80 (estimated with the German MWT-B test; Mehrfach-Wortschatz-Intelligenztest B; Lehrl, Triebig, & Fischer, 1995).

Participants were recruited within the Departments of Psychiatry at the University of Marburg and University of Münster, local psychiatric hospitals, outpatient departments and healthcare centers, as well as through local advertisements and flyers.

Clinical diagnostic assessment by trained interviewers as well as MRI scanning took place at the Departments of Psychiatry and Psychotherapy Marburg or Münster Universities, Germany, respectively. All subjects gave written informed consent before participation to a study protocol approved by the local Ethics Committee of the school of medicine, University of Marburg and University of Münster, according to the current version of the Declaration of Helsinki (World Medical Association, 2013). Subjects were financially compensated for participation. Following previous multivariate modeling studies, we focused on a clinical sample only, given that healthy control samples typically show little or no expressions of anhedonia, and a lack of significant associations between their low to moderate levels of neuroticism and brain structure (Avinun et al., 2020). The study cohort consisted of patients with one or more MDD episode(s) in an acute or (partially) remitted state (derived from SCID-I interviews and based on DSM-IV criteria), with or without psychiatric comorbidity as well as with a medicated/unmedicated state and/or receiving psychotherapy/no psychotherapy.

Clinical sample characteristics are presented in Table 1.

TABLE 1 Clinical characteristics of our $N = 595$ major depressive disorder (MDD) patients

	M (*SD*) or *n* (%)		
	Marburg $n = 283$	Münster $n = 312$	Total $N = 595$
Age of onset first depressive episode (in years)	26.25 (13.3)	25.02 (11.82)	25.60 (12.55)
Lifetime characterization depressive episodes			
Single episode	86 (30.4%)	129 (41.3%)	215 (36.1%)
Recurrent	197 (69.6%)	183 (57.7%)	380 (63.9%)
Remission status			
Current MDD episode	144 (50.9%)	111 (35.6%)	255 (42.9%)
Partially remitted	78 (27.6%)	75 (24%)	153 (25.7%)
Fully remitted	61 (21.6%)	126 (40.4%)	187 (31.4%)
Number of depressive episodes	5.09 (7.45)	2.89 (2.86)	3.88 (5.55)
Duration in depressive status (in months)	53.75 (81.17)	39.55 (63.54)	45.29 (71.46)
Number of psychiatric hospitalizations	1.59 (2.08)	1.33 (1.76)	1.46 (1.92)
Duration of lifetime psychiatric hospitalization (in weeks)	10.18 (13.83)	11.69 (19.43)	10.98 (17.03)

2.2 | Phenotyping

2.2.1 | Anhedonia

We assessed concurrent anhedonia using the German version of the Snaith–Hamilton Pleasure Scale (SHAPS-D; Franz et al., 1998; Snaith et al., 1995), a 14-item self-rating scale used in several previous studies (e.g., Franken, Rassin, & Muris, 2007; Trøstheim et al., 2020). SHAPS measures hedonic attributes or the amount of ability to experience pleasure, respectively, by subjects giving their accordance to statements like "I would enjoy being with family or close friends" in the last 14 days on a 4-point Likert scale ("Strongly Agree," "Agree," "Disagree," "Strongly Disagree"). Higher SHAPS total scores within a range of 0–14 indicate higher levels of anhedonia.

2.2.2 | Anxiety

We used the STAI-S of the State–Trait Anxiety Inventory (STAI; Laux, Glanzmann, Schaffner, & Spielberger, 1981; Spielberger, 1983) to assess state anxiety given the high correlation between depression and the construct of anxiety (Watson, 2009), but state anxiety is more likely to represent an emotional state or present feelings of tension (hence symptom representation), respectively (Spielberger & Reheiser, 2009), rather than anxiety as a trait. Statements are presented with a 4-point Likert scale in a manner of agreement ("not at all," "somewhat," "moderately," "very much so"). Total score range is 20–80 and higher scores indicate greater anxiety.

2.2.3 | Neuroticism

Trait neuroticism was measured using the German version of the Revised NEO Personality Inventory (NEO-FFI; Costa & McCrae, 1989). The neuroticism subscale contains 12 items on a 5-point Likert response format. Subjects indicate the degree to which they agree or disagree with each of the statements (0 = strongly disagree, 4 = strongly agree). Individual Neuroticism subscale scores were calculated as cumulative values of the 12 items, and can thus vary between 0 and 48 points.

2.3 | Neurocognitive assessment

Using a neuropsychological variable to reflect executive function/inhibition performance, we chose the Trail Making Test Version B (TMT-B; Allen & Haderlie, 2010; Army, 1944) which is part of the FOR2107 neuropsychological test battery (Kircher et al., 2019). It shares aspects of monitoring executive function and inhibition ability with the Flanker Task used in Liao et al. (2019). Besides, the TMT-B is well suited to model cognitive control as this concept is seen not just as the ability to show top-down processing by goal-directed but also flexible behavior (Badre & Nee, 2018; Miller & Cohen, 2001).

TABLE 2 Descriptive statistics and correlations for all measurements used in this study

Measurement	1	2	3	4	Mean	*SD*
1. SHAPS	–	.57*	.39*	.02	3.5	3.5
2. STAI-S	–	–	.66*	.09	50.5	12.99
3. NEOFFI-neuroticism	–	–	–	.11*	28.33	8.92
4. TMT-B	–	–	–	–	55.9	22.54

Abbreviations: NEOFFI-neuroticism, NEO-FFI-Neuroticism Scale; SHAPS, Snaith–Hamilton Pleasure Scale; STAI-S: State–Trait Anxiety Inventory-State Anxiety; TMT-B, Trail-Making Test-Version B (measured in RT).
*$p < .01$.

Descriptive statistics and correlations for all measurements used in this study are shown in Table 2.

2.4 | Diffusion tensor imaging acquisition and preprocessing

We obtained diffusion-weighted images on 3T MRI scanners (Münster: Prisma, Siemens, Erlangen, Germany; Marburg: Tim Trio, Siemens, Erlangen, Germany) using a 20 channel head matrix Rx-coil in Münster and a 12 channel head matrix Rx-coil in Marburg. At both sites, PAT mode was GRAPPA with an acceleration factor of 2 (TR 7300 ms, TE 90 ms, 56 slices with a 3 mm slice thickness, isotropic voxel resolution of $2.5 \times 2.5 \times 2.5$ mm^3). We acquired a total of 2x30 diffusion-weighted images with a *b*-value of 1000 s/mm^2 and four nondiffusion-weighted images ($b = 0$ s/mm^2).

Quality assurance methods included several aspects: First, we used an ongoing quality assurance protocol covering all MRI scans obtained in the FOR2107 study (Vogelbacher et al., 2018); Second, we visually inspected all scans for major artifacts and anatomical abnormalities ahead of preprocessing; Third, the TBSS approach in the FSL software (version 6.0; the Oxford Centre Functional Magnetic Imaging Software Library; Oxford, UK; Jenkinson, Beckmann, Behrens, Woolrich, & Smith, 2012; Smith et al., 2006) was used for DTI preprocessing and analysis. DTI data were corrected for Eddy-Current-artifacts as well as motion artifacts (Andersson & Sotiropoulos, 2016). We displayed each subject image and selected an optimal fractional intensity threshold (FIT) for brain masking to remove nonbrain structures.

Maps of the four DTI parameters (FA, RD, axial diffusivity AD, and mean diffusivity MD) were generated for whole brain analyses and nine major association tracts (derived from previous DTI studies of major depression): inferior fronto-occipital fasciculus (IFOF), inferior longitudinal fasciculus (ILF), cingulum bundle, cingulum hippocampus, SLF, SLF temporal part, forceps minor and major (i.e., anterior and posterior parts of the corpus callosum), and UF, as well as for two projection tracts: the corticospinal tract (CST) and the ATR (Warrington et al., 2020). Following to the automated nonlinear registration tool FNIRT implemented in FSL (Andersson, Jenkinson, & Smith, 2007;

Andersson, Jenkinson, & Smith, 2010) all subjects data were aligned to a standard space. A mean FA skeleton was created and used for projection of FA, RD, AD, and MD data with a threshold <0.2 to counteract for alignment errors.

2.5 | Statistical analyses

First, SEM analysis was run in R using the R package *lavaan* (Rosseel, 2012) to replicate and extend the clinical-cognitive model by Liao et al. (2019). Error-adjusted latent variables were created by the standard measurement sum scores of the variables of interest and applying the factor loading to 1.0 for each observed variable. We adopted the reported relationships of the final model by Liao et al. (2019) to our sample: SHAPS and STAI-S as endogenous variables, NEOFFI-neuroticism and TMT-B as exogenous variables, leading to the proposed relationships as shown in Figure 1a.

SEM was estimated by maximum likelihood estimation and goodness of fit was assessed by the model fit indices χ^2, χ^2/df, Comparative Fit Index (CFI), Tucker-Lewis Index (TLI), Root mean square error of approximation (RMSEA; Ullman & Bentler, 2003), based on recommendations of a study evaluating SEM fit indices regarding their robustness when analyzing large sample sizes and multivariate normality (Cangur & Ercan, 2015). Both direction and power of effects are specified by path coefficients.

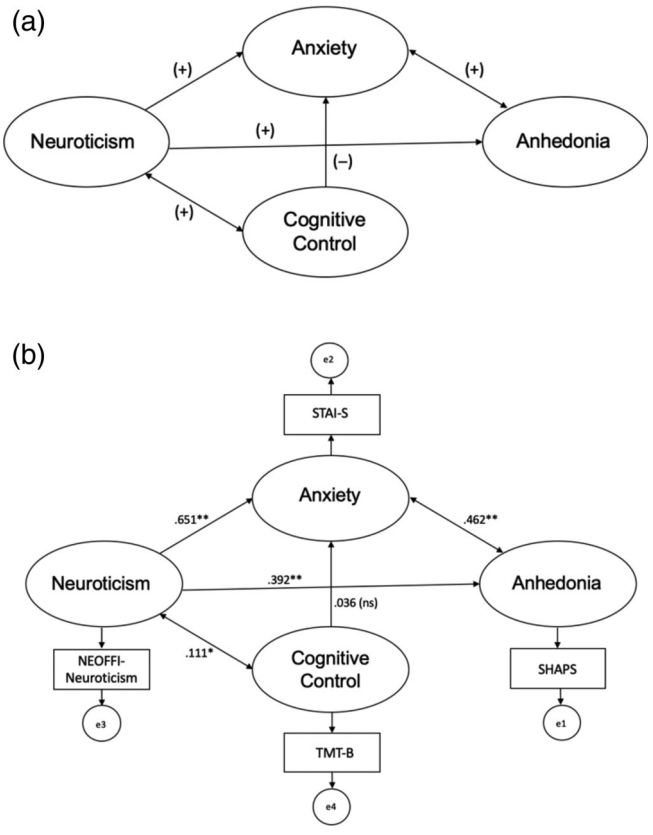

FIGURE 1 (a) Proposed relationships of the clinical-cognitive model. Rectangles represent the observed variables, ovals represent the error-adjusted latent variables. (+) and (−) indicate the hypothesized direction of the relationships to reach significance at $p < .05$. One-headed arrows stand for regressions, double-headed arrows stand for correlations. (b) Estimated clinical-cognitive model. Numbers show the standardized path coefficients with ** = $p < .001$ and *$p < .05$. (ns) indicates a nonsignificant relationship

Correlation analyses shown in Table 2 indicate the absence of multicollinearity.

Second, we computed multiple regression analyses applying the GLM approach implemented in FSL. We set up separate models for each variable of interest described above (SHAPS, STAI-S, NEOFFI-neuroticism, and TMT-B), including age, sex, site and TIV as nuisance variables. Exchange of the body-coil in Marburg during scanning period was accounted for by including it as an additional nuisance variable (pre body-coil change: yes/no; post body-coil change: yes/no). We used threshold-free-cluster-enhancement (TFCE) running voxel-wise analyses using the FSL program *randomise*. Contrasts were generated with 5,000 permutations (Winkler, Ridgway, Webster, Smith, & Nichols, 2014) and tested with FA, RD, AD, and MD. We applied the JHU DTI 81 white-matter labels atlas (Mori, Van Zijl, & Tamminga, 2007) for anatomical labeling. Clusters were considered significant at a statistical threshold $p < .05$ after correcting for family-wise error (FWE).

Third, we established a multivariate model based on those two proceeding analyses to include the clinical and brain structural data.

3 | RESULTS

3.1 | Clinical-cognitive model/ SEM

Our first SEM analysis of clinical-cognitive data based on Liao et al. (2019) showed good fit ($\chi^2 = 0.36$, $p = .55$, $\chi^2/df = 0.36$, CFI = 1.000, TLI = 1.007, RMSEA < 0.001) and we, therefore, replicated all proposed significant relationships except for the negative association of cognitive control and anxiety (unstandardized coefficient = 0.021, standardized coefficient = 0.036, $p = .13$; see Figure 1b). Path coefficients show that greater neuroticism is associated with increased anhedonia (unstandardized coefficient = 0.154, standardized coefficient = 0.392, $p < .001$), as well as increased anxiety (unstandardized coefficient = 0.948, standardized coefficient = 0.651, $p < .001$). There was a positive correlation between neuroticism and cognitive control ($r = .11$, $p < .001$), as well as a positive correlation of anhedonia and anxiety ($r = .46$, $p < .001$).

3.2 | DTI-phenotype association analyses

We identified the following main correlations between white matter structure and phenotype variables (all *p*-values FWE corrected; *k* denotes number of voxels):

SHAPS correlated positively with FA and RD in the right ATR and the forceps minor ($p = .03$, $k = 49$; $p = .04$, $k = 18$; see Figure 2a). Furthermore, analyses showed a positive correlation with MD in the

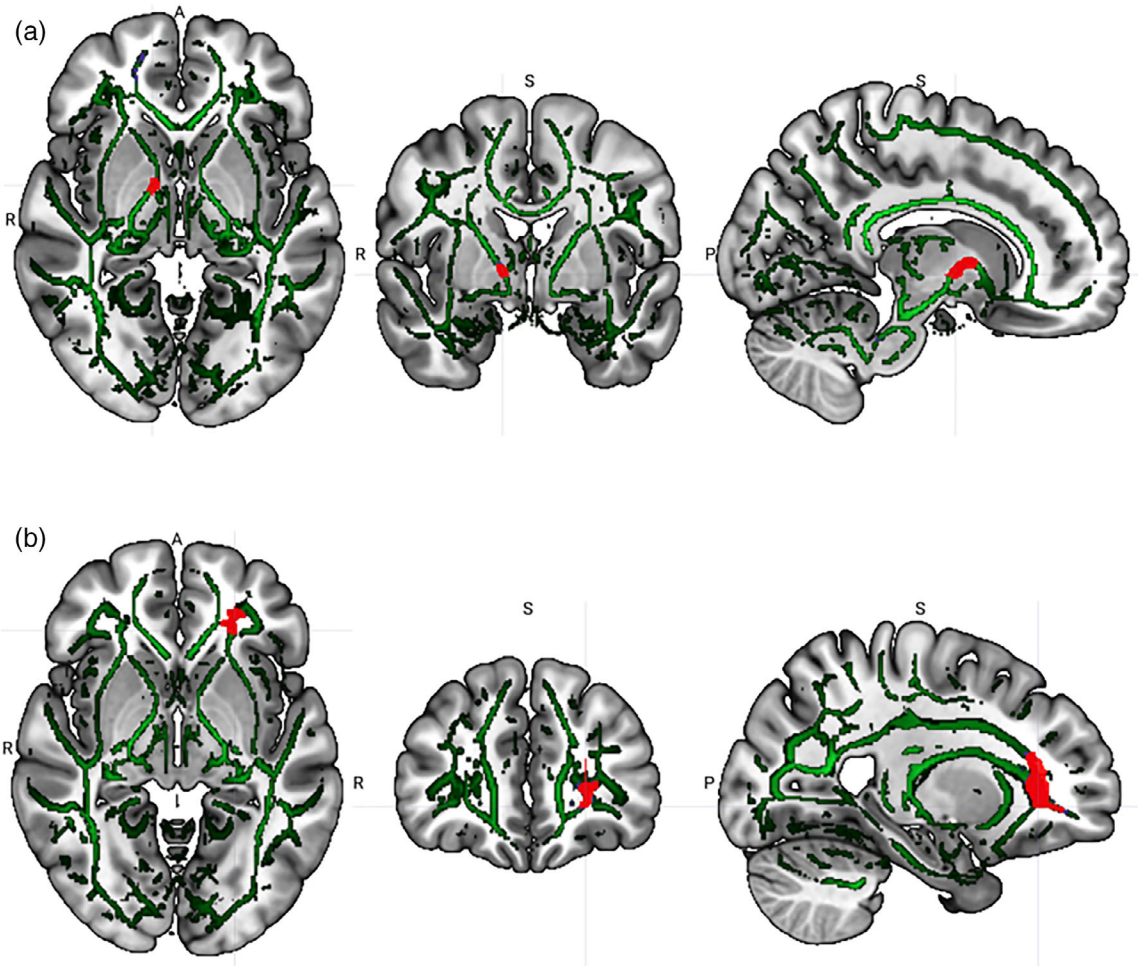

FIGURE 2 (a) Significant ($p < .05$ after FWE-correction) association of SHAPS with FA in the right ATR and forceps minor (coordinates maximum intensity voxel = 69/172/87). (b) Significant ($p < .05$ after FWE-correction) association of NEOFFI-neuroticism with AD in the left IFOF/UF (coordinates maximum intensity voxel = 114/162/74). Maximum intensity voxels coordinates were used for cutting plane placement. Illustrations were prepared using MRIcroGL (version v2.1.52-0; https://www.nitrc.org; © Copyright 2007, NITRC). ATR, anterior thalamic radiation; AD, axial diffusivity; FA, fractional anisotropy; FWE, family-wise error; IFOF, inferior fronto-occipital fasciculus; UF, uncinate fasciculus

left UF ($p = .04$, $k = 18$), as well as a negative correlation in the left cingulum hippocampus ($p = .02$, $k = 11$) and the CST ($p = .04$, $k = 22$).

NEOFFI-neuroticism was negatively correlated with AD in the left UF, left ATR and left IFOF ($p = .03$, $k = 74$; see Figure 2b). Negative correlation with AD also showed one significant cluster mainly located in the left ATR ($p = .02$, $k = 192$) and two clusters in right ATR and right IFOF ($p = .04$, $k = 49$ and $p = .04$, $k = 28$). There were no significant clusters associated with NEOFFI-neuroticism with either FA, MD, or RD.

For the STAI-S, only one positive association with AD in the left UF reached significance ($p = .03$, $k = 149$), with no further associations to FA, MD, or RD. Analyses of the TMT-B also yielded significant correlations with AD only. There was one positive cluster in the left CST ($p = .02$, $k = 351$) and two negative clusters in the right cingulum hippocampus ($p = .009$, $k = 71$) and in the right IFOF ($p = .04$, $k = 88$), respectively.

3.3 | Multivariate SEM models

Based on the above findings, we tested an integrated multivariate SEM including the variables from the replicated basic clinical-cognitive SEM and ATR-FA (which was correlated with anhedonia) and IFOF/UF-AD correlated with neuroticism. In defining this model, we considered to only include the most robust brain associations to avoid inflated fit estimates while providing a parsimonious model (Kline, 2015).

Based on previous brain structural findings (Cologner et al., 2019; Madsen et al., 2009; Mincic, 2015; Yang et al., 2017), we focused on the positive correlation of SHAPS with FA in the right ATR/forceps minor, and the negative correlation of NEOFFI-neuroticism with AD in the left IFOF/UF and the left ATR.

Hypothesized relationships between brain structural correlates and clinical-cognitive variables are shown in Figure 3. We considered a putative relationship between the ATR-FA cluster associated with

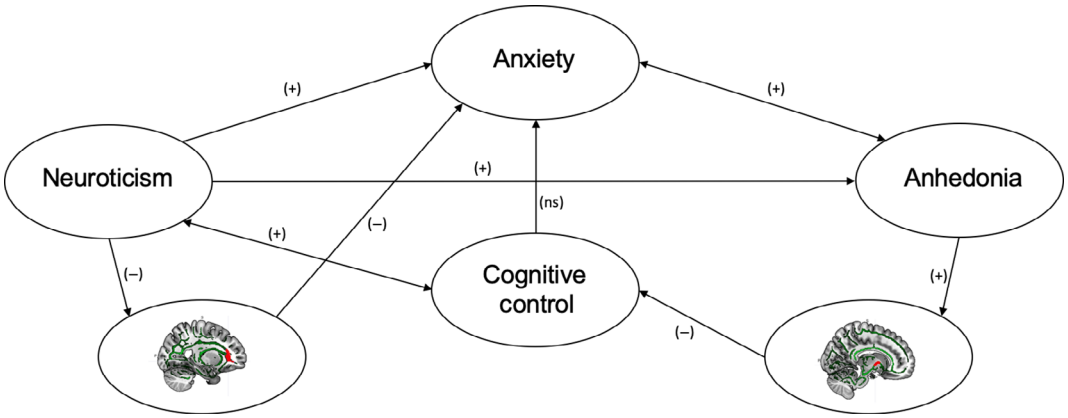

FIGURE 3 Proposed relationships of the multivariate model. Rectangles represent the observed variables, ovals represent the error-adjusted latent variables. (+) and (−) indicate the hypothesized direction of the relationships to reach significance at $p < .05$. One-headed arrows stand for regressions, double-headed arrows stand for correlations. Proposed relationships to brain imaging data: Neuroticism—IFOF/UF-AD cluster—anxiety; Anhedonia—ATR-FA cluster—cognitive control. ATR, anterior thalamic radiation; AD, axial diffusivity; FA, fractional anisotropy; FWE, family-wise error; IFOF, inferior fronto-occipital fasciculus; UF, uncinate fasciculus

anhedonia and cognitive control, as well as a relationship between the IFOF/UF-AD cluster associated with neuroticism and anxiety, based on previous literature showing those associations on a behavioral level (Grahek, Shenhav, Musslick, Krebs, & Koster, 2019; McIntyre et al., 2016; Servaas et al., 2015). Although the path between cognitive control and anxiety did not reach significance, we modeled this path in our multivariate SEM again, as nonsignificant paths also can explain meaningful variance in the overall model (Steinmetz, 2015).

We extracted eigenvalues of the significant brain structural clusters of interest and further z-transformed them. Clusters were integrated in the clinical-cognitive SEM as described above with a factor loading of 1.0. Analyses were re-run in in R using the R package *lavaan* (Rosseel, 2012).

Results showed a moderate fit of the model ($\chi^2 = 13.39$, $p = .02$, $\chi^2/df = 2.68$, CFI = 0.985, TLI = 0.955, RMSEA = 0.055).

Path coefficients indicated a decrease of cognitive control with the ATR-FA cluster associated with anhedonia (unstandardized coefficient = −2.064, standardized coefficient = −0.092, $p = .029$). The proposed relationship between anxiety and the IFOF/UF-AD cluster associated with neuroticism did not reach significance (unstandardized coefficient = 0.242, standardized coefficient = 0.019, $p = .53$) and in line with the clinical-cognitive SEM, there was no significant relationship between anxiety and cognitive control (unstandardized coefficient = 0.020, standardized coefficient = 0.035, $p = .15$). We, therefore, excluded those two paths from re-estimation of our model. Modification indices indicated a significant improvement of model fit by considering a path between the cluster associated with neuroticism and cognitive control (mi = 10.34), wherefore we included this path in the re-estimation of the model.

The modified model showed a good fit ($\chi^2 = 4.05$, $p = .40$, $\chi^2/df = 1.01$, CFI = 1.000, TLI = 1.000, RMSEA = 0.005). The path between cognitive control and the IFOF/UF-AD cluster associated with neuroticism reached significance (unstandardized coefficient = −2.929, standardized coefficient = −0.130, $p = .004$). The estimated final model is shown in Figure 4.

4 | DISCUSSION

This study integrates, in a multivariate model, brain structural connectivity variability with clinical, risk phenotype variables, and cognition in MDD. Focusing on anhedonia as a core symptom, we demonstrate new insights into brain structural connectivity networks in a large sample of MDD patients. This study reveals two important aspects: (a) Bivariate association analyses demonstrates correlation between anhedonia and FA in the right ATR as well as a correlation between AD and neuroticism in the left IFOF/UF in MDD. (b) Our multivariate model collaborates and expands a previous model conceptualizing the relation between clinical/cognitive and brain connectivity measures by acknowledging the fact of interactions of multiple variables and measures in MDD.

DTI results showed among others an association of SHAPS and FA in the right ATR and forceps minor and an association of NEOFFI neuroticism and AD in the left IFOF/UF. In our multivariate SEM, findings revealed an impact of differential associations between the ATR-FA cluster as well as the IFOF/UF-AD cluster on cognitive control. Results bring several implications:

DTI results of anhedonia and neuroticism yielded associations with different DTI parameters (i.e., anhedonia-FA, neuroticism-AD). FA measures the overall expanse of the directionality of water diffusion along the fibers, AD displays the amount of water diffusion parallel to white matter tracts (Winklewski et al., 2018). Although interpretation of DTI parameters is still inconclusive, FA is interpreted as a combined measure of axon density and myelin content (Friedrich et al., 2020), while AD tends to indicate mostly the axonal conditions and/or orientation of axons (De Erausquin & Alba-Ferrara, 2013). The differential effects on FA versus AD might in part reflect effects on

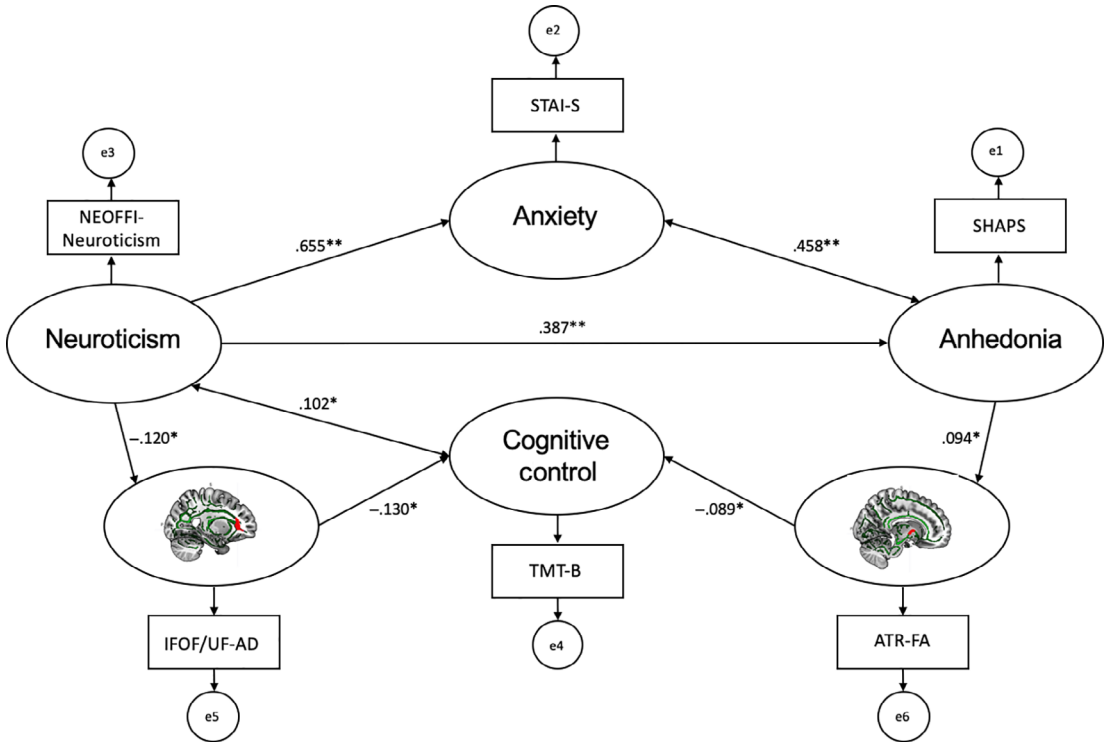

FIGURE 4 Estimated final model after modification. Numbers show the standardized path coefficients with ** = $p < .001$ and *$p < .05$

fiber orientation versus myelination as influenced by both anatomical variation and dynamic expressions of myelination across the lifespan. In particular, given the rather low scores of anhedonia in our sample, the positive correlation of FA and anhedonia in the ATR might reflect early stages (e.g., compensation mechanisms) of alterations impacting the brains pleasure system. The negative correlation of AD and neuroticism in the left IFOF/UF, however, can be interpreted as a result of stress reactivity to constant experience of negative emotions.

Anhedonia and neuroticism indeed can be linked to distinct white matter tracts and different DTI parameters while concurrently either showing an impact on cognitive functioning, hence giving new insights on intercorrelations on a biomarker level. DTI results in our large MDD sample clarify frontal-limbic circuit abnormalities found in previous smaller structural/functional neuroimaging studies of anhedonia (Coloigner et al., 2019; Gong et al., 2018; He et al., 2020; Henderson et al., 2013; Mincic, 2015; Rizvi, Lambert, & Kennedy, 2018; Yang et al., 2017). Findings elucidate a brain structural overlap between anhedonia and cognitive control, expanding previous studies stating a relationship between brain structures like the PFC (including ACC) and cognitive control in MDD (Joormann, Yoon, & Zetsche, 2007). With a substantial multivariate approach, our model thus underpins previous hypotheses about a neural overlap between anhedonia and cognitive mechanisms (Barrett, Mesquita, Ochsner, & Gross, 2007; Berridge et al., 2016; Phelps, 2006).

Moreover, our model suggests a more comprehensive involvement of the ATR in cognitive control mechanisms in addition to the already demonstrated role of ATR in memory-guided attention (Leszczyński & Staudigl, 2016). This link between FA in the ATR and cognitive control is also consistent with the finding, that decreased FA in frontal and temporal lobes is linked to poorer executive function (Grieve, Williams, Paul, Clark, & Gordon, 2007).

Although the ATR connects the (dorsolateral) prefrontal cortex with thalamic nuclei, it may also play a crucial role in the salience network. Regarding the Research Domain Criteria, anhedonia is yet associated with the negative valence domain whereas cognitive control represents (among others) the cognitive systems domain (Kozak & Cuthbert, 2016). Our finding of a brain structural overlap of anhedonia and cognitive control taken together with the already proposed major cortical nodes of the salience network (i.e., dorsolateral anterior cingulate cortex, anterior insula, mediodorsal thalamus; Peters, Dunlop, & Downar, 2016) puts a stronger focus on emotional regulation within the salience network and might help brain stimulation improvement.

In this large MDD sample, we replicated and extended a recent clinical-cognitive model of anhedonia (Liao et al., 2019) and demonstrate a relation of anhedonia to neuroticism and anxiety as well as cognitive functioning/cognitive control.

Refining the role of anhedonia in MDD, the indirect effect of anhedonia on cognitive control mediated by connectivity alterations illustrates an important impact of anhedonic features on a biomarker level beyond the overall effect of MDD. Anhedonia is an important treatment target in affective disorders (Höflich et al., 2018) and there is clearly a strong connection between anhedonia and cognitive control in individuals with MDD on a behavioral (Grahek et al., 2019; McIntyre et al., 2016) and brain structural level. Future studies might further examine the underlying common neural correlates of

anhedonia and cognitive control to use it in cognitive-behavioral therapy for affective disorders.

This multivariate approach also includes an established risk phenotype, that is, neuroticism, serving as a trait component to be compared with clinical variables. Findings elucidate the white matter tracts involved in a proposed shared network of neuroticism and cognitive control (Servaas et al., 2015) as well as a specific direction of the effect. Furthermore, our results indicate a stronger relation of neuroticism to cognitive control than supposed so far (Servaas et al., 2015), which points toward the need to consider both emotional and cognitive subnetworks when investigating the impacts of high neuroticism. Our model can thus be used to test these intercorrelations in cohorts of high-risk individuals, leading to findings important for early intervention. Moreover, a multivariate model of these two MDD phenotypes together with genetic and environmental factors of neuroticism could result in a differentiated "risk model."

SEM makes it possible to illustrate specific directions of relationships which allow to better describe the actual impacts of the variables on one another. Our results show, that distinct phenotypes of MDD are represented by overlapping brain structural correlates and also demonstrate the feasibility to use DTI in deconstructing the more complex MDD phenotype into single facets and associations with symptoms or symptom clusters. These points toward the potential of multivariate models when unraveling illness heterogeneity of MDD.

Moreover, for future transdiagnostic research, the approach of multivariate modeling is of particular importance. Multivariate models like ours can help to further unravel the dimensionality of psychiatric disorders and eventually to better predict individual disease course. Therefore, future research on psychiatric disorders should focus more on multivariate stratification.

We are aware that our approach has some limitations. Effects of the brain imaging data are not large considering the fact that path coefficients should ideally show an effect of ≥0.2/−0.2 to indicate a meaningful relationship, as considered by some standards (Chin, 1998); however, these recommendations mostly arose from psychometric research in social science (MacCallum & Austin, 2000) and therefore do not completely serve interpretation of multivariate models integrating brain imaging data. Furthermore, although the final model showed a good fit to our data, the method of SEM implicates the existence of equivalent models (Kline, 2015). In case of an extremely heterogeneous illness like MDD, it is obvious that our model cannot capture every possible effect or relationship, also especially due to the limitations of the SEM method (Kline, 2015). Our SEM approach also has some limitations in fitting nonlinear relations, which might, for example, lead to different directions of correlations depending on the range of phenotype expression (see for example, Besteher, Gaser, & Nenadić, 2020). We also did not examine effects of remission state, duration of hospitalization or medication effects due to our novel model approach. Constructive future studies using this kind of approach can take those variables into account to unravel possible unknown interaction effects. In our study, we focused on DTI data and some clinical-cognitive variables. To further examine the potential of SEM as a method to model intercorrelations of psychometric and brain imaging data, more studies of this kind with varying variables of interest (e.g., environmental factors, functional brain imaging data and so forth) are needed.

5 | CONCLUSION

Our findings advance the current understanding of white matter microstructure of MDD by specifying shared connectivity networks of phenotype variables of MDD. Brain structural correlates found in our DTI analyses showed two autonomous connectivity paths, one representing the impact of a personality trait on brain structure and one representing the impact of a main symptom representation on brain structure in an MDD sample. Both, however, had an effect on cognitive control independently of each other. This indicates a more reliant "disconnection syndrome" in MDD than initially proposed by previous studies investigating brain connectivity networks in MDD (Li et al., 2018). Our study thus adds meaningful insights into interrelations of features of MDD on a brain structural level compared to previous brain connectivity studies of MDD (Jiang et al., 2019; Nugent et al., 2019; Repple et al., 2017, 2020). Also, findings provide a connectome approach to disentangling symptom clusters neural underpinnings, which can ultimately serve personalized treatment planning, as demonstrated in recent neurostimulation studies (Siddiqi et al., 2020).

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DATA AVAILABILITY STATEMENT

Research data are not shared due to privacy and ethical restrictions.

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