White matter abnormalities in depression: a categorical and phenotypic diffusion MRI study.
Julie Coloigner, Jean-Marie Batail, Olivier Commowick, Isabelle Corouge, Gabriel Robert, Christian Barillot, Dominique Drapier

To cite this version:

HAL Id: inserm-01938407
https://www.hal.inserm.fr/inserm-01938407
Submitted on 28 Nov 2018

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L’archive ouverte pluridisciplinaire HAL, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d’enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.
White matter abnormalities in depression: A categorical and phenotypic diffusion MRI study

Julie Coloiner¹,⁎, Jean-Marie Batailla,b,c, Olivier Commovicka, Isabelle Corougea, Gabriel Roberta,b,c, Christian Barillota, Dominique Drapierb,c

¹ Univ Rennes, CNRS, Inria, Inserm, IRISA UMR 6074, Empenn U1228, F-35000 Rennes, France
² Centre Hospitalier Guillaume Régnier, Academic Psychiatry Department, 35703 Rennes, France
³ Univ of Rennes, “Behavior and Basal Ganglia” research unit (EA 4712), Rennes, France

⁎ Corresponding author at: Unité Empenn U1228, INSERM, INRIA, Université Rennes I, IRISA, UMR CNRS 6074 Campus de Beaulieu 35042 Rennes Cedex, France.
E-mail address: julie.coloiner@irisa.fr (J. Coloiner).

These authors contributed equally to this work.

ARTICLE INFO
Keywords:
Diffusion-weighted imaging
Voxel-based analysis
Fractional anisotropy value
Depression
Categorical and phenotypic approach

ABSTRACT
Mood depressive disorder is one of the most disabling chronic diseases with a high rate of everyday life disability that affects 350 million people around the world. Recent advances in neuroimaging have reported widespread structural abnormalities, suggesting a dysfunctional frontal-limbic circuit involved in the pathophysiological mechanisms of depression. However, a variety of different white matter regions has been implicated and is sought to suffer from lack of reproducibility of such categorical-based biomarkers. These inconsistent results might be attributed to various factors: actual categorical definition of depression as well as clinical phenotype variability. In this study, we 1/ examined WM changes in a large cohort (114 patients) compared to a healthy control group and 2/ sought to identify specific WM alterations in relation to specific depressive phenotypes such as anhedonia (i.e. lack of pleasure), anxiety and psychomotor retardation –three core symptoms involved in depression. Consistent with previous studies, reduced white matter was observed in the genu of the corpus callosum extending to the inferior fasciculus and posterior thalamic radiation, confirming a frontal-limbic circuit abnormality. Our analysis also reported other patterns of increased fractional anisotropy and axial diffusivity as well as decreased apparent diffusion coefficient and radial diffusivity in the splenium of the corpus callosum and posterior limb of the internal capsule. Moreover, a positive correlation between FA and anhedonia was found in the superior longitudinal fasciculus as well as a negative correlation in the cingulum. Then, the analysis of the anxiety and diffusion metric revealed that increased anxiety was associated with greater FA values in genu and splenium of corpus callosum, anterior corona radiata and posterior thalamic radiation. Finally, the motor retardation analysis showed a correlation between increased Widlöcher depressive retardation scale scores and reduced FA in the body and genu of the corpus callosum, fornix, and superior striatum. Through this twofold approach (categorical and phenotypic), this study has underlined the need to move forward to a symptom-based research area of biomarkers, which help to understand the pathophysiology of mood depressive disorders and to stratify precise phenotypes of depression with targeted therapeutic strategies.

1. Introduction
Mood Depressive Disorder (MDD) is one of the most disabling chronic diseases with a high rate of everyday life incapacity that affects 350 million people around the world (Smith, 2014). This pathology is considered undiagnosed, without adequate therapeutic resources, which emphasizes the need to be a public health priority (Ferrari et al., 2013). One of the most important causes of misdiagnosis is the poor intrarater reliability of actual classifications (Freedman et al., 2013). Mood Depressive Episode criterion of the Diagnostic and Statistical Manual of Mental Disorders (DSM–5) (Edition, 2013) indeed encompass a wide range of clinical phenotypes of depression “from gravely disabled melancholic patients to many individuals in the general population who do not seek treatment” (Freedman et al., 2013). This suggests that categorical approach provided by DSM-5 is far from the level of neurosciences (Maj, 2014) and therefore could limit reproducibility of its findings in helping in diagnosis and therapeutics. In this context, despite the extensive therapy options available for depression, up to 80% of patients will suffer from a relapse (Gotlib and Hamilton, 2008). On the neurobiological side, this disease is characterized by a profound...
and persistent dysregulation of affect and mood (Fitzgerald, 2013), which coexists with additional disturbance including cognitive dys-
function, insomnia, fatigue and appetite disturbance (Drevets, 2001). Consequently, understanding the neural correlates underlying depres-
sion, and its phenotype variability, will optimize the diagnosis and treatment of individual depressed patients.

Over the last decades, recent advances in neuroimaging have greatly increased our knowledge of MDD, particularly its neural bases. Widespread structural abnormalities have been reported including re-
gional tissue loss in the hippocampus, amygdala, basal ganglia, pre-
frontal cortex and anterior cingulate cortex (Aronne et al., 2013; Zou
et al., 2010). These results suggested that a dysfunctional cortical-
subcortical neural circuit is involved in the pathophysiology and psy-
chopathology of depression (Chen et al., 2016; Korgaonkar et al., 2011;
Sacchet et al., 2014). More particularly, an abnormal frontal-limbic
network is considered as the locus of the dysfunction underlying mood-
regulation in MDD (Chen et al., 2016; Korgaonkar et al., 2011; Sacchet
et al., 2014). Structural connectivity analysis provides novel insights
into network dysfunctions. White matter (WM) investigations have
become a rapidly growing area of research in psychotic disorders in-
cluding schizophrenia (Buchbaum et al., 1998), bipolar disorder
(Benedetti et al., 2015; Magioncalda et al., 2016) and depression (Chen
et al., 2017). In this context, diffusion-weighted imaging (DWI), a
noninvasive magnetic resonance imaging (MRI) technique based on the
extent of water diffusion, enables the quantification of the fiber or-
ientation and abnormalities of WM pathways within neural networks
(Assaf and Pasternak, 2008; Taylor et al., 2004). The most common
DWI measure is the fractional anisotropy (FA), an invariant property
of DWI that reflects a nonspherical diffusion tensor with a preferential
orientation.

Several studies (Chen et al., 2017; Korgaonkar et al., 2011) have
revealed significant FA reductions in the body of the corpus callosum
(CC) (Han et al., 2014; Korgaonkar et al., 2011), bilateral anterior limb
of the internal capsule (ALIC) (Chen et al., 2016; Jia et al., 2016; Zou
et al., 2008) and superior longitudinal fasciculus (SLF) (Ota et al., 2015)
in MDD patients relative to healthy controls. However, existing
knowledge about WM changes is limited due to the variety of different
WM regions exhibited in these studies (Liao et al., 2013; Murphy and
Frodl, 2011; Sexton et al., 2009). These inconsistent results might be
attributed to various factors. The high heterogeneity of MDD indi-
viduals in terms of disease characteristics (i.e. symptoms and duration
of the disease), could be considered a main cause of this variability
(Chen et al., 2016). Previous studies have indeed demonstrated the
influence of episodes or illness duration (de Diego-Adelino et al., 2014),
ilness severity (Henderson et al., 2013) and antidepressant drugs (Dusi
et al., 2015; Taylor et al., 2014) on WM. The FA reduction was indeed
associated with depression severity and illness duration in MDD pa-
ients in the genu of corpus callosum, anterior thalamic radiation,
anterior cingulum, and sagittal striatum, which indicates that DWI may
be of clinical value in measuring and tracking disability in MDD (Chen
et al., 2016; Henderson et al., 2013). One additional source of hetero-
genecity could be the clinical phenotype (Fried, 2015), such as anhe-
donia (i.e. lack of pleasure), anxiety and psychomotor retardation
–three core symptoms involved in depression. As mentioned above,
DSM-5 diagnosis criteria include a wide panel of emotional, motiva-
tional and cognitive symptoms (Edition, 2013). Some of these dimen-
sions can be negatively correlated such as motivation and anhedonia
severity (Batali et al., 2017). Then, the high variability of diagnosis
criteria could lead to poor diagnosis interrater reliability (Freedman
et al., 2013). For the last two decades, neuroimaging studies in MDD
have identified many putative biomarkers, based on actual disease
classification, which remain inconsistent tools. Therefore, there is a
need to find new imaging biomarkers which could potentially improve
our understanding the pathophysiology of MDD (Young et al., 2016).

In this context of research on biomarkers, the research domain
criteria (RDoC) program have been created. This initiative was
proposed by the American National Institute of Mental Health to de-
vlop “new ways of classifying mental disorder based on behavioral
dimensions and neurobiological measures” (NIMH, 2008). This
approach promises to increase our understanding of basic network-level
abnormalities and their relation to psychopathology (Insel et al., 2010).
Then, this new research framework based on dimension could help a
better understanding of phenotypic variability described in depres-
sion. This disease, as currently defined, spans two of the RDoC domains:
the loss construct within the negative valence systems domain and
various reward constructs within the positive valence systems domain.
Our study focuses specifically on these two dimensions, anxiety and
anhedonia by analyzing theirs relations with diffusion metrics
(Cuthbert and Insel, 2013; Insel et al., 2010). Then, although RDoC
program does not propose a behavioral domain, the relationship with
psychomotor retardation was investigated because of its central role in
depression and discriminatory potential for different phenotypes (mel-
ancholic subtype, bipolar/unipolar and consequences on treatment)
(Bennabi et al., 2013).

In this paper, we proposed a twofold approach (categorical and
phenotypical), in order to show that a phenotypic approach allows to
identify more reliable knowledge on pathophysiology underlying de-
pression than categorical one. Therefore, the first aim of this study was
to examine WM changes in a large cohort of MDD patients to address
more consistent and replicable WM microarchitecture abnormalities
than those found in previous studies. The second aim of our study was
to identify specific WM alterations in relation to specific dimensions of
depression such as anhedonia, anxiety and psychomotor retardation.

2. Materials and methods

2.1. Participants

One hundred and fourteen depressed patients were recruited from
routine care units in the psychiatric university hospital of Rennes be-
tween November 2014 and January 2017 and were enrolled in a nat-
uralistic prospective cohort study. The study was approved by an ethic
committee and is registered in www.clinicaltrial.gov (NCT02286024),
written informed consents were obtained from all subjects.

The study was proposed to patients suffering from a Mood
Depressive Episode (MDE) under DSM-5 criteria with or without
personal history of MDD (unipolar or bipolar subtype). Exclusion criteria
included other Axis-I disorders (except for obsessive-compulsive dis-
order and four anxious comorbidities such as posttraumatic stress dis-
order, social phobia, generalized anxiety disorder or panic disorder),
and psychotic symptoms, which were explored using the Mini-
International Neuropsychiatric Interview (Lecrubier et al., 1997). Pa-
ients with severe chronic physical illness were not included. Other
exclusion criteria were potential safety contraindications for MRI (pa-
cemakers, metal implants, pregnancy, and lactation), diagnosed neu-
rodegenerative disorders (e.g. Parkinson’s disease, Alzheimer’s disease,
Huntington’s disease), a history of significant head injury, or diagnosed
dementia (according to DSM-5 criteria).

Depressed patients underwent clinical interview and examination,
including routine neuropsychological testing and MRI. For each subject,
demographic data, comorbidities and medication, as well as clinical
variables were collected (see Table 1). A composite measure of medica-
tion load for each patient was assessed using a previously established
method (Sackeim, 2001), taking into account the number of medication
class prescribed to the patients as well as each dosage.

The control group was composed of 65 healthy volunteers, who
previously participated in neuroimaging studies. The two groups were
matched in terms of age (CTL: 48.6 ± 11.8, MDD: 48.3 ± 15.4;
Student t-test p-value = 0.5) and gender (CTL: 17M/48F, MDD: 43M/
71F; Chi-square p = 0.5).
2.2. Clinical assessment

Patients were assessed by a single structured clinical interview by a trained psychiatrist. Anxious comorbidities were retrieved using the Mini-International Neuropsychiatric Interview (Lecrubier et al., 1997). Depression severity was assessed using Montgomery and Åsberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979). Manic symptoms were retrieved using the Young Mania Rating Scale (YMRS) (Young et al., 1978). Additionally, the Widlócher Depressive Retardation Scale (WDRS) (Widlöcher, 1983) was used to estimate psychomotor retardation. State anxiety was measured using State Trait Anxiety Inventory A (STAI-YA) (Spielberger et al., 1970). Then, the anhedonia and apathy scores were assessed by Snaith Hamilton Pleasure Scale (SHAPS) (Snaith et al., 1995) and Apathy Evaluation Scale (AES) (Marin et al., 1991), respectively.

2.3. MRI acquisition

Patients and healthy subjects were scanned on a 3 T whole body Siemens MR scanner (Magnetom Verio, Siemens Healthcare, Erlangen, Germany) with a 32-channel head coil. The 3D T1-weighted image was acquired covering the whole brain (176 sagittal slices) with TR = 1.9 s, TE = 2.26 ms, flip angle was 9°, in-plane resolution = 2 mm × 2 mm, FOV = 256 mm × 256 mm and thickness/gap = 1.0/0 mm. DWI data were gathered on 60 slices using an interleaved slice acquisition matrix of 128 × 128, the reconstruction matrix was 128 × 128, using 30 directions and a b-value of 1000 s/mm². TR /

\[ TE = 11.000/99 \text{ ms}, \text{ flip angle was 9°}, \text{ pixel bandwidth was 1698 Hz,} \text{ and the imaging frequency was 128 MHz.} \]

2.4. Image processing

Preprocessing of diffusion images was mainly performed using the open source medical image processing toolbox Anima (https://github.com/Inria-Visages/Anima-Public/wiki). Diffusion images were corrected for eddy current-induced image distortion using a block-matching distortion correction method ensuring an opposite symmetric transformation (Hedouin et al., 2017). Then, rigid realignment was then performed to compensate for subject motion and ensure voxel-to-voxel correspondence across gradients. Then, denoising step using blockwise non-local means filtering was applied (Coupé et al., 2008). Skull stripping was performed using an atlas-registration-based method. More precisely, the structural image of each patient was transformed to the atlas image, using the linear and non-linear block-matching algorithms (Commovick et al., 2012a; Ourselin et al., 2000). Then, the atlas intracranial brain mask was inversely transformed by applying the inverse of two calculated transformation matrix and multiplied with the original structural image of the patient. Diffusion tensor images were then estimated using a log-Euclidean estimation method proposed by Fillard et al. (Fillard et al., 2007), from which diffusion scalar maps were calculated.

For statistical comparisons, the diffusion metric maps were transformed into the Montreal Neurological Institute (MNI) template space, using a two-step co-registration method. First, the individual FA image was co-registered with the structural image with 1 mm isotropic resolution, using a rigid transformation following by a non-rigid registration, using the block-matching algorithm (Commovick et al., 2012b; Ourselin et al., 2000). Then the structural image was non-linearly transformed to the MNI template space, using the block-matching (Commovick et al., 2012b; Ourselin et al., 2000). Then, we applied those transformations to the other diffusion metric maps (ADC, AD and RD maps) to normalize them to the MNI space.

Next, a cross-subject mean FA image was computed to generate a WM tract skeleton, which was thresholded to FA > 0.3 to confine the statistical analysis within the major WM tracts (Du et al., 2017). Then, this map was used to mask the FA, apparent diffusion coefficient (ADC), axial diffusivity (AD) and radial diffusivity (RD) maps. The preprocessing pipeline is available online on github https://github.com/Inria-Visages/Anima-Scripts-Public (in diffusion/animaDiffusionImagePreprocessing.py).

2.5. Statistical analysis

For each diffusion metric map (FA, ADC, AD and RD), independent 2-sample t-tests were also performed on a voxel-by-voxel basis via AFNI’s 3dtttest+ + (p < 0.001) between MDD and CTI, with age, gender and duration of disease as nuisance covariates. To correct for multiple comparisons, Monte Carlo simulations via AFNI’s 3dClustSim command (Forman et al., 1995) were applied to obtain a corrected significance level of p < 0.05. This correction for multiple comparisons was achieved by setting a minimum cluster size of 214 voxels.

To investigate the relationship between diffusion metrics and clinical variables (WDRS, STAI-YA and SHAPS) in the MDD group, a voxelwise linear regression model was performed in MDD group. The normality of the clinical variable distribution was before verified using Shapiro-Wilk test. Minimum cluster size after correction for multiple comparisons at p < .05 was achieved by selecting a minimum cluster size of 234 voxels with a voxelwise alpha level of p < .001.

### Table 1

Demographic and clinical characteristics of the MDD group.

<table>
<thead>
<tr>
<th>Sociodemographic variables</th>
<th>Mean</th>
<th>SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (M/F)</td>
<td>43M</td>
<td>71F</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>48.2</td>
<td>15.3</td>
<td>18–77</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>43M/71F</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Education (years)</td>
<td>12.2</td>
<td>3.6</td>
<td>6–23</td>
</tr>
<tr>
<td>Duration of illness (years)</td>
<td>15.1</td>
<td>13.9</td>
<td>6–60</td>
</tr>
<tr>
<td>Number of episodes</td>
<td>4.4</td>
<td>4.5</td>
<td>0–30</td>
</tr>
<tr>
<td>Number of episode (weeks)</td>
<td>30.0</td>
<td>37.8</td>
<td>0–170</td>
</tr>
<tr>
<td>Number of suicidal attempts</td>
<td>1.1</td>
<td>2.0</td>
<td>0–10</td>
</tr>
<tr>
<td>Diagnosis (UP/BP)</td>
<td>68UP/32BP</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Anxious comorbidities</td>
<td>61.3%</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Medication</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Antidepressant</td>
<td>74.6%</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Mood stabilizer</td>
<td>35.1%</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Antipsychotic</td>
<td>14.0%</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Benzodiazepine</td>
<td>49.1%</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Clinical variables</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>WDRS</td>
<td>21.4</td>
<td>9.0</td>
<td>2–43</td>
</tr>
<tr>
<td>MADRS</td>
<td>27.1</td>
<td>5.9</td>
<td>15–43</td>
</tr>
<tr>
<td>STAI-YA</td>
<td>57</td>
<td>13.3</td>
<td>28–0</td>
</tr>
<tr>
<td>SHAPS</td>
<td>5.5</td>
<td>4.0</td>
<td>0–14</td>
</tr>
<tr>
<td>AES</td>
<td>40.3</td>
<td>8.9</td>
<td>24–69</td>
</tr>
<tr>
<td>YMRS</td>
<td>1.6</td>
<td>1.7</td>
<td>0–7</td>
</tr>
</tbody>
</table>

All results except gender and medications are given as mean, standard deviation (SD) and the range. The percentage of patients having used the prescribed medicines: antidepressant, mood stabilizer, antipsychotic and benzodiazepine as well as the medication load has been reported. The MDD group is divided into unipolar (UP) and bipolar (BP) subtypes. The percentage of patients with anxious comorbidities including posttraumatic stress disorder, social phobia, generalized anxiety disorder and panic disorder has been measured. WDRS: Widlócher Depressive Retardation Scale; MADRS: Montgomery-Åsberg Depression Rating Scale; STAI: State-Trait Anxiety Inventory A; SHAPS: Snaith Hamilton Pleasure Scale; AES: Apathy Evaluation Scale; YMRS: Young Mania Rating Scale.
3. Results

3.1. Demographics and clinical measures

Demographic and clinical variables of the MDD group is summarized in Table 1. Women, middle-aged predominantly represented the patient population. They have severe characteristics of disease with a long mean duration of illness (range: 25% < 3 years and 17% > 21 years) and episode (range: 50% ≥ 14 episodes). A large majority of patients suffered from recurrent depressive episodes (50% of the patients had more that 3 episodes). Actual depressive episode was moderately intense (MADRS total score = 27.4 ± 5.9). Patients did not show any significant manic symptomatology (YMRS total score = 1.6 ± 1.7). Moreover, 78% of this cohort suffered from high anxiety (36 ≤ STAI-YA ≤ 65) and 27% from very high anxiety higher than 65 as well as high rate of anxious comorbidities. All patients were under treatment (Table 1.). A significant correlation between medication load and disease duration was observed (r = 0.23 and p-value = 0.0072), in the cohort.

3.2. Whole brain structural alteration data: differences between groups

Comparing with CTL, the MDD group had lower FA in the cingulum, the inferior longitudinal fasciculus (ILF), posterior thalamic radiation (PTR), cingulum and the genu of CC (see Fig. 1). However, the MDD group had greater FA in the posterior limb of the internal capsule (PLIC) and splenium of CC. The maximum FA differences in genu of CC and splenium of CC were −33% and +11%, respectively. The identified WM regions and the maximum of the t-values for the clusters (corrected for age, gender and disease duration) are summarized in Table 2 (more detail information is reported in Table A.1 in Appendix A).

For these significant regions, the results of two-sample t-test were also reported in the Table 3 for the other diffusion metrics (ADC, AD and RD). Of the 6 clusters examined, all of them showed significant RD differences after FDR correction, whereas only 3 and 5 regions showed significant differences for ADC and AD, respectively.

3.3. Correlation of structural connectivity and clinical scores

Based on the previous results showing similar spatial distribution for all the diffusion metrics, the correlation analyses were restricted to FA values. Moreover, this metric is more likely to capture microstructure-induced diffusion abnormalities that than ADC, AD and RD (Westin et al., 2002).

Analyses revealed eight clusters, as shown in Table 4 and Fig. 2. As the psychomotor retardation increased (i.e. WRDS values increased), the FA value decreased in the body and the genu of the CC, the superior corona radiata, the superior striatum (see Fig. 2.A.). Additionally, as displayed in Fig. 2.B., a positive correlation was found between the FA values and anxiety, measured by STAI-YA, in the genu and splenium of the CC, anterior corona radiata and posterior thalamic radiation. However, anxiety was negatively correlated with FA values in the body of CC. Similarly, a negatively correlation was found between the FA values and anhedonia with cingulum, genu of CC and posterior thalamic radiation. However, reductions of FA in this region were reported in treatment-resistant MDD (de Diego-Adelino et al., 2014). The structural brain

Fig. 1. Axial, coronal and sagittal brain slices showing significant differences of the FA values between MDD and CTL groups. Voxels with negative t-values (MDD < Control) are shown in blue and positive values (MDD > Control) with red. The acronym gCC indicates the genu of corpus callosum (CC); sCC, splenium of CC; AGR, anterior of the corona radiata; PTR, posterior thalamic radiation; ILF, inferior longitudinal fasciculus; PLIC, posterior Limb of the internal capsule; CCG, cingulum. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)
Table 2
Brain areas with significant FA differences between the MDD and CTL groups.

<table>
<thead>
<tr>
<th>Cerebral regions</th>
<th>Tracts</th>
<th>Right or Left</th>
<th>MNI coordinates</th>
<th>t-value</th>
<th>cluster size</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior cingulate</td>
<td>gCC</td>
<td>R/L</td>
<td>[± 11,35,5]</td>
<td>−7.41</td>
<td>6959</td>
<td>&lt; 10^{-6}</td>
</tr>
<tr>
<td>Cingulum gyrus</td>
<td>CCG</td>
<td>R/L</td>
<td>[± 11,25,33]</td>
<td>−9.36</td>
<td>36,859</td>
<td>&lt; 10^{-6}</td>
</tr>
<tr>
<td>Insula</td>
<td>ILF</td>
<td>R/L</td>
<td>[± 6,16,31]</td>
<td>−3.39</td>
<td>4338</td>
<td>&lt; 10^{-4}</td>
</tr>
<tr>
<td>Thalamus</td>
<td>PTR</td>
<td>R/L</td>
<td>[± 27, −28,7]</td>
<td>−10.15</td>
<td>4109</td>
<td>&lt; 10^{-6}</td>
</tr>
<tr>
<td>Parahippocampal gyrus</td>
<td>PLIC</td>
<td>R/L</td>
<td>[± 15,18,16]</td>
<td>7.01</td>
<td>451</td>
<td>&lt; 10^{-4}</td>
</tr>
<tr>
<td>Posterior cingulate</td>
<td>SCC</td>
<td>R/L</td>
<td>[−8,38,7]</td>
<td>3.91</td>
<td>398</td>
<td>0.0004</td>
</tr>
</tbody>
</table>

The t-value and the p-value are the maximum statistics of the cluster and the corresponding p-value. Their coordinates are reported in the Montreal Neurological Institute (MNI) template. The cluster size is given in mm³. The acronym gCC and sCC indicates the genu and splenium of the corpus callosum; ILF, Inferior Longitudinal Fasciculus; PTR, Posterior Thalamic Radiation; PLIC, Posterior Limb of the Internal Capsule; CCG, cingulum.

Table 3
Statistic results of diffusion metric (FA, ADC, AD and RD) in MDD group compared to healthy control group obtained with two-sample t-test (p < 0.05). Only the arrows in bold show the significant difference. gCC and sCC, genu and splenium of the Corpus Callosum; ILF, Inferior Longitudinal Fasciculus; PTR, Posterior Thalamic Radiation; PLIC, Posterior Limb of the Internal Capsule.

<table>
<thead>
<tr>
<th>Cerebral regions</th>
<th>Tracts</th>
<th>FA</th>
<th>ADC</th>
<th>AD</th>
<th>RD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior cingulate</td>
<td>gCC</td>
<td>R</td>
<td>L</td>
<td>L</td>
<td>L</td>
</tr>
<tr>
<td>Cingulum gyrus</td>
<td>Cingulum</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insula</td>
<td>ILF</td>
<td>L</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thalamus</td>
<td>PTR</td>
<td>R/L</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parahippocampal</td>
<td>PLIC</td>
<td>L</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Posterior cingulate</td>
<td>SCC</td>
<td>L</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 4
Voxel-wise correlations between FA and clinical variables.

<table>
<thead>
<tr>
<th>Cerebral regions</th>
<th>Tracts</th>
<th>Right or Left</th>
<th>MNI coordinates</th>
<th>r-coef</th>
<th>Cluster size</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Correlation with WDRS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior cingulate</td>
<td>gCC/bCC</td>
<td>R</td>
<td>[14,2,27]</td>
<td>−0.40</td>
<td>676</td>
<td>0.0001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>L</td>
<td>[−4,10,29]</td>
<td>−0.29</td>
<td>476</td>
<td>0.0002</td>
</tr>
<tr>
<td>Correlation with STAI-YA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior cingulate</td>
<td>gCC</td>
<td>R/L</td>
<td>[1,27,5]</td>
<td>0.35</td>
<td>863</td>
<td>0.0001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>L</td>
<td>[−24,29,10]</td>
<td>0.30</td>
<td>554</td>
<td>0.002</td>
</tr>
<tr>
<td>Prefrontal</td>
<td>PTR</td>
<td>L</td>
<td>[−26,69,19]</td>
<td>0.35</td>
<td>534</td>
<td>0.0001</td>
</tr>
<tr>
<td>Correlation with SHAPS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cingulum gyrus</td>
<td>SCR/CC</td>
<td>R</td>
<td>[23,−31,44]</td>
<td>−3.36</td>
<td>233</td>
<td>0.0001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>L</td>
<td>[−4,1,32]</td>
<td>−3.36</td>
<td>240</td>
<td>0.0001</td>
</tr>
<tr>
<td>Posterior cingulate</td>
<td>PTR</td>
<td>L</td>
<td>[−22,69,10]</td>
<td>−3.49</td>
<td>342</td>
<td>0.0005</td>
</tr>
</tbody>
</table>

The t-value corresponds to the maximum correlation of the cluster and their coordinates are reported in the MNI template. The cluster size is given in mm³. WDRS: Widlócher Depressive Retardation Scale; MADRS: Montgomery-Åsberg Depression Rating Scale; STAI-YA: State-Trait Anxiety Inventory; SHAPS: Snaith Hamilton Pleasure Scale, gCC, bCC and sCC: genu, body and splenium of the Corpus Callosum, ACR and SCR: anterior and superior corona radiata, SS: sagittal stratum, PLIC: posterior limb of the internal capsule, PTR: posterior thalamic radiation, SLF: superior longitudinal fasciculus, PTR: posterior thalamic radiation.
samples in order to better link behavior and biological measures. This issue has been drawn as a good way to take into account clinical variability in depressive disorder (Olvet et al., 2016).

4.2.1. Anhedonia

Consistent with previous studies, we found decreased FA as anhedonia increased in the cingulum. Indeed, Bracht et al. suggested that this tract could be a biomarker of vulnerability to depression (Bracht et al., 2015). Thus, the FA value in the cingulum bundle was also described negatively correlated with trait anhedonia (Keedwell et al., 2012). In addition, the same abnormality was described in women with a family history of depression (Keedwell et al., 2012), or in first depressed un-medicated patients (Zhang et al., 2012). Altogether, these results suggested that cingulum WM alteration is involved in the pathophysiological mechanism of depression and is probably linked with reward sensitivity dimension.

Increased FA related to increased anhedonia was also found in SLF. Some studies reported the role of this tract in linking aspects of default mode network and cognitive control and its consequence on executive functioning (Jenkins et al., 2016). Moreover, patients suffering from depression could exhibit a deficit in executive functioning and related with a deficit in programing actions relative to hedonic valence. However, based on these arguments, the opposite correlation between FA and SHAPS was found in SLF. This result may represent a compensatory neuroplasticity or selective neurodegeneration mechanism (Jenkins et al., 2016; Mole et al., 2016).

Other significant decreased FA were found associated with decreased anhedonia in PTR. This result echoes the literature that pointed out the involvement of thalamic cortical projections in MDD (Hermesdorf et al., 2017; Korgaonkar et al., 2011). Previous studies have found that such WM alterations were particularly significant in melancholic MDD (Korgaonkar et al., 2011). Our study is the first that links anhedonia and PTR. Moreover, decreased FA was related with increased anhedonia in gCC. The WM abnormalities in this region were linked with the severity of depression (Chen et al., 2016). This tract is involved in decision making, reward processing (i.e. anhedonia) and emotional regulation (Chen et al., 2016). The structural alteration in this area leads to disturbances in cognitive functioning such as memory, executive functions and emotions (Chen et al., 2016). Taken together, our result can lead to the hypothesis that WM alteration in gCC and PTR participates to the severity of depression through one specific phenotype involved in emotion regulation, executive functioning, reward, and decision-making such as anhedonia.

4.2.2. Anxiety

To our knowledge, no study has correlated patient anxiety with white matter diffusion metrics in depressed patients. Most of the studies have chosen a categorical approach in comparing MDD with or without anxious comorbidity (Canu et al., 2015; Delaparte et al., 2017). Despite a large sample, no significant connectivity abnormality has been linked with anxiety (Delaparte et al., 2017).

In this study, the phenotypic analysis of anxiety revealed a
4.2.3. Psychomotor retardation

Our phenotypic analysis with motor retardation revealed a correlation between increased WRDS scores and reduced FA in body and genu of CC, superior corona radiata and superior striatum. To date, only two studies had explored the relationship between diffusion metrics and motor retardation in depression, using a behavioral metric called actiometry. First, a positive association was found between activity level and structural alterations of cortico-cortical white matter in motor pathways, such as the connection between the rostral anterior cingulate cortex and pre-Supplementary Motor Area (SMA) and between the dorsolateral prefrontal cortex and pre-SMA in MDD (Bracht et al., 2012). The authors attributed this result to a relation between these circuits and movement initiation. Then, the second study has pointed out a negative link between FA and left parahippocampal gyrus (Walther et al., 2012), suggesting a plausible link between cerebral alteration in this region and impaired motor planning. Consistent with these results, we exhibited the implication of parahippocampal gyrus and the cingulate. Furthermore, we found that striatal pathway could also play a role in psychomotor retardation. This circuit was also reported in (Bennabi et al., 2013), showing a link between this behavior impairment and dopamine as well as noradrenergic transmission in basal ganglia such as striatum and caudate nucleus.

To sum up, this phenotypic approach pointed out abnormal structural connectivity that have never been demonstrated in depression. One critical finding concerns anxiety which has been linked with higher connectivity in areas such as corpus callosum, anterior corona radiata and posterior thalamic radiation whereas categorical approach for depression have shown strictly the opposite findings for posterior thalamic radiation and genu of corpus callosum. These results support the stratification of patients suffering from depression according to these core dimensions. The phenotypic approach appeared to be a useful way to complete the categorical approach in a better definition of the variability of different clinical profiles. This study is in line with dimensional approach suggested by Olvet et al. (2016) as it allowed a better understanding of critical mechanism involved in pathophysiology of depression and could help to develop more reliable imaging biomarkers.

5. Limitations

The depression cohort is heterogeneous with regard to demographic and clinical parameters such as age and gender of subjects, age of onset of depression, bipolar disorder, potentially increasing variability. However, the patient heterogeneity is also a strength of this study because it disrupts coincidental associations.

Another investigation will be needed to determine whether diffusion changes are associated with poorer neurocognitive performance. Further studies should include neurocognitive tests in order to refine clinical phenotype such as executive functioning, memory, attention, information treatment speed, and emotional patterns, and therefore permit a better accuracy of biomarkers.

The clinical variables, SHAPS, WRDS and STAI-YA, were not reported for the CTL group. Further studies could evaluate their effects on WM organization using a cohort including control subject and patients.

All patients were under psychotropic medication. There is some evidence that psychotropic treatment could lead to decreased FA in schizophrenic patients after medication (Wang et al., 2013). Moreover, in the context of depression, several studies reported that brain changes of white matter are associated with the disease process rather than being effects of medication (Bracht et al., 2015).

6. Conclusions

Our study aimed to conduct both categorical and dimensional approach in the study of anatomical connectivity biomarkers in MDD. First, our results highlight the well-known WM abnormalities in a large cohort of currently depressed patients and compared to controls. The frontolimbic disconnection hypothesis has been replicated as well as large decreased connectivity in widespread brain areas (corpus callosum extending to the inferior fasciculus and posterior thalamic radiation). In addition to previous studies with smaller samples, our results reveal other patterns of increased FA in posterior limb of internal capsule and splenium of corpus callosum.

On the other side, the phenotypic approach has identified some specific patterns related to anxiety, anhedonia and psychomotor retardation – three core symptoms of depression. This latter approach highlighted that within a depressive population, there is a wide variability of anatomic connectivity depending on the severity of each core dimension. This study pointed out that such an approach probably allows more specific and accurate biomarkers than categorical ones, which emphasized widespread abnormalities. Ours brings some evidence for the development of more symptom-based approach within depressed samples.

In the future, a dimensional approach, in addition to the categorical one, could help stratifying different depressive phenotypes, better understanding the pathophysiology characterizing core dimensions, and consequently propose a robust framework for developing targeted therapeutic strategies.

Acknowledgments

MRI data acquisition was supported by the Neurinfo MRI research facility from the University of Rennes I. Neurinfo is granted by the European Union (FEDER), the French State, the Britanny Council, Rennes Metropole, Inria, Inserm and the University Hospital of Rennes. This work has been funded by Institut des Neurosciences Cliniques de Rennes (INCR). The authors thank Mr. Stéphane Brousse and Mr. Jacques Soulabaile for their involvement in the conduct of the study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2019.101710.

References


