The neurobiology of treatment-resistant depression: A systematic review of neuroimaging studies

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\section*{A R T I C L E  I N F O}

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\section*{A B S T R A C T}

Treatment-resistant depression (TRD) is a debilitating condition associated with higher medical costs, increased illness burden, and reduced quality of life compared to non-treatment-resistant major depressive disorder (MDD). The question arises whether TRD can be considered a distinct MDD sub-type based on neurobiological features. To answer this question we conducted a systematic review of neuroimaging studies investigating the neurobiological differences between TRD and non-TRD. Our main findings are that patients with TRD show 1) reduced functional connectivity (FC) within the default mode network (DMN), 2) reduced FC between components of the DMN and other brain areas, and 3) hyperactivity of DMN regions. In addition, aberrant activity and FC in the occipital lobe may play a role in TRD. The main limitations of most studies were related to inherent confounding issues like publication bias, failure to report negative results for pre-specified primary outcome measures, and patient selection, remission rates for antidepressant therapies may be inflated (Pigott et al., 2010). Consequently, it is probable that more MDD patients suffer from some degree of treatment resistance than is apparent from the current literature. This has major implications. Not only are medical costs of patients with TRD 40 \% higher compared to non-treatment-resistant MDD patients (Gibson et al., 2010), but also increasing levels of treatment resistance are associated with higher relapse rates, increased illness burden (Rush et al., 2006) and reduced quality of life (Johnston et al., 2019). Additionally, TRD is associated with impaired psychosocial functioning, including poor levels of involvement in recreational activities and global social adjustment (Petersen et al., 2004).

While the distinction between TRD and non-TRD patients is based on clinical features, the question arises whether it can also be considered a distinct MDD sub-type based on neurobiological features. One possibility to identify neurobiological differences related to treatment resistance is to study the brain before treatment and identify those patients who do not respond. Such studies have revealed that various regions involved in the pathophysiology of depression are involved in treatment resistance, including the prefrontal cortex (PFC), anterior cingulate cortex (ACC), hippocampus, amygdala, insula, salience network and default mode network (DMN) (Dunlop et al., 2019; Fonseka et al., 2018). Although these studies provide us with information on predictors of response to individual treatments for depression, they do not tell us which neurobiological abnormalities may be associated with the development of resistance to multiple consecutive treatments. Neither does it tell us which neurobiological features define MDD patients in a current state of...
treatment resistance. To investigate this, it is important to directly compare patients with TRD to MDD patients who are not treatment resistant (non-TRD) and preferably to patients for whom sensitivity to treatment is established (treatment sensitive depression; TSD). A previous systematic review on the relationship between resting-state fMRI and treatment response in MDD revealed that hyperconnectivity of the DMN and visual recognition circuits may be implicated in TRD compared to TSD (Dichter et al., 2015). To provide a more complete and up-to-date overview, we conducted a systematic review of all neuroimaging studies to investigate the neurobiological differences between TRD and non-TRD/TSD. The results may provide new insight into the neurobiological basis of TRD and may thereby enable us to develop more efficacious treatments specifically targeted at patients who do not respond to the currently available antidepressant treatment options.

2. Methods

Details of the protocol for this systematic review were registered on PROSPERO International Prospective Register of Systematic Reviews with registration number CRD42020204947. This systematic review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (Moher et al., 2009).

2.1. Search strategy

The online database PubMed was systematically searched for neuroimaging studies on treatment-resistant depression (see Supplementary Material, Part 1 for the entire search strategy). Search terms related to treatment resistance were combined with depression and further combined with terms related to neuroimaging (e.g., MRI, fMRI, PET, EEG, MEG, SPECT, CT). Terms related to treatment resistance included synonyms of treatment resistance as well as treatments that are typically only indicated for treatment-resistant depression (electroconvulsive therapy, deep brain stimulation and several atypical antipsychotics). Only studies published in English between 1980 and our final search date, the 23rd of September 2021, were assessed for eligibility. To enhance the search, the reference lists of the included studies were examined for additional eligible studies.

2.2. Eligibility criteria

In this review we included original human studies, published in English in an international peer-reviewed journal. Each study included a group of patients diagnosed with MDD, who were suffering from treatment resistance, defined as a failure to respond to at least two treatment attempts (Gaynes et al., 2018). Because there is no general consensus on the definition of an adequate antidepressant trial, confirmation of adequate dose and duration was not required. Patients were assessed with one or more in-vivo brain imaging modalities, and were compared to a group or groups of MDD patients who were not treatment resistant. Only studies with a sample size of at least 10 per group were included. Case studies and studies exclusively recruiting adolescents with depression or patients with late-life depression were excluded.

2.3. Study selection and data extraction

The references resulting from the electronic search were imported into Rayyan (Ouzzani et al., 2016) to facilitate study selection. First, two reviewers (NR and KJ) independently screened the titles and abstracts of all articles, and those who clearly did not fulfill the eligibility criteria were excluded. Subsequently, the full text of the remaining articles was reviewed to confirm eligibility. Any persisting disagreements on eligibility were resolved with the help of a third reviewer (GW).

Data was extracted by one reviewer (NR) and verified by a second reviewer (DY). We extracted the lead author, publication year, sample characteristics, assessment timing, definition of treatment (non)resistance, depression severity, illness duration, outcome measure(s), and the main findings. The authors of the studies were contacted if any of the extracted data was unclear or to confirm any overlap in samples.

2.4. Quality assessment

Two independent reviewers (NR and DY) assessed the quality of each included study with The Joanna Briggs Institute (JBI) Critical Appraisal checklist for Analytical Cross-Sectional studies (Moola et al., 2020). We excluded item 3 (“Was the exposure measured in a valid and reliable way?”) from the checklist, as our review did not include any exposures. Additionally, we applied item 5 and 6 (“Were confounding factors identified?” and “Were strategies to deal with confounding factors stated?”) only to the confounders age, sex/gender, illness duration and depression severity. Any persisting disagreements on the quality of the studies were resolved with the help of a third reviewer (GW).

2.5. Analysis

The heterogeneity of the outcome measures of the included studies prevented us from conducting a quantitative analysis. Instead, a qualitative summary of the results sorted by neuroimaging modality is provided here. The original terms used for the different patient groups were preserved in Tables 1 and 2. For more straightforward interpretation of the results, we will always refer to the treatment resistant group as TRD in our review below. Additionally, groups that consisted of treatment-responsive MDD patients or a mix of treatment-responsive MDD patients and spontaneously recovered MDD patients are referred to as TSD, and groups who included untreated MDD patients, first-episode MDD patients who only just started treatment, a mix of untreated and responsive MDD patients, or groups where it was not clear if the MDD patients were treatment-responsive, are referred to as non-TRD. Within modality sample overlap is indicated in the results section. The complete account of sample overlap is indicated in Table 1.

3. Results

3.1. Study inclusion and characteristics

Our search strategy identified 2297 potential articles, of which 26 were included in the current review. Three additional eligible studies were identified through reference list review, resulting in the final inclusion of 29 studies. The study selection process is visualized in an adapted PRISMA flow diagram (Fig. 1). Table 1 reports the sample characteristics of each study. The number of unique participants included in these 29 studies (all groups together) ranges from 1242 to 1481. The exact amount of unique participants could not be determined as many studies included partially overlapping samples with unknown amounts of overlap (indicated in Table 1). A complete overview of the main outcome measures and findings can be found in Table 2.

3.2. Quality assessment

The quality assessment of the included studies, according to The Joanna Briggs Institute (JBI) Critical Appraisal checklist for Analytical Cross-Sectional studies (Moola et al., 2020), is provided in Supplementary Material, Part 2.

3.3. Resting-state functional MRI

3.3.1. Default mode network

The DMN is a functional network which is active during resting wakefulness and is thought to be associated with spontaneous cognition or “mind-wandering” and self-referential processing (Andrews-Hanna et al., 2010). In this review, brain areas as defined by the comprehensive
model of Alves et al. (2019) will be considered part of the DMN. These regions include (but are not limited to) the ventro- and antero-medial prefrontal cortex (VMPFC/AMPFC), dorsal prefrontal cortex (DPFC), ventral lateral prefrontal cortex (VLPFC; orbital part of the inferior frontal gyrus (IFG/BA47), the posterior cingulate cortex (PCC), posterior parietal cortex (PPC) around the angular gyrus, precuneus, middle temporal gyrus (MTG), parahippocampal cortex, and subcortical components including the hippocampus, thalamus, amygdala, caudate, and basal forebrain.

3.3.1.1. Functional connectivity. Resting-state fMRI (rs-fMRI) is a useful measure to study FC between or within functional networks at rest. Four rs-fMRI studies have found decreased FC within the DMN in TRD compared to TSD (de Kwaasteniet et al., 2015; Guo et al., 2013b; He et al., 2016; Ma et al., 2012). He et al. (2016) found a significant network of reduced FC in TRD patients, centered on the parahippocampal gyrus, comprised of reduced connections with several posterior components of the DMN: the left precuneus, left posterior cingulate gyrus, and the left inferior parietal lobe (IPL), which in turn had a reduced connection with the right caudate. Furthermore, a seed-based analysis by de Kwaasteniet et al. (2015) revealed decreased FC between the anterior DMN and the posterior DMN (PCC and precuneus), and between the DMN and other brain regions (Lui et al., 2011; Ma et al., 2012). They additionally found significantly decreased FC between the motor control network (DLPFC) and the posterior DMN (left and right precuneus) (Ma et al., 2012). They further found that there was significantly decreased FC between the motor cortex and other brain regions, including the PCC. This suggests that reduced resting-state connectivity is widespread and not just between specific neurocognitive networks. No altered FC was found in TRD patients between the salience network (anterior insula) and the DMN. In the same seed-based analysis as described above, Ma et al. (2012) found significantly decreased connectivity between the right MTG and the right superior temporal gyrus (STG). Lastly, in a partially overlapping sample, Guo et al. (2013a) placed several seeds in different parts of the cerebellum associated with different cognitive networks. Although they did not find any significant differences in FC between the cerebellar DMN seed and the rest of the brain in TRD patients compared to TSD patients, they did find significantly decreased FC between the cerebellar executive and affective limbic network seeds and the posterior DMN (left and right precuneus, right angular gyrus and the left IPL). Furthermore, when they repeated the analysis without global signal regression, TRD patients exhibited reduced FC between one of the cerebellar executive network seeds and the MFG (note: the indication that this cluster belongs to the DMN based on Alves et al. (2019) is not conclusive).

In addition to these findings of decreased FC, two studies also reported some increases in FC in TRD compared to TSD within the DMN and between the DMN and other brain regions (Lui et al., 2011; Ma et al., 2012). TRD patients were found to have significantly increased connectivity between the right MTG and the anterior DMN (right medial frontal gyrus and bilateral superior frontal gyrus (SFG; note: the indication that this SFG cluster belongs to the DMN based on Alves et al. (2019) is not conclusive)) and posterior DMN (right angular gyrus and right precuneus) (Ma et al., 2012). They additionally found significantly increased connectivity between the right MTG and the right rectus, and between the right caudate and the right IFG and the left corpus callosum in TRD. A seed-based analysis by Lui et al. (2011) revealed significantly increased connectivity between the right insula (part of the salience network) and the posterior DMN (PCC and precuneus), and between the left amygdala and the ACC in TRD. Other seeds in components of the subcortical DMN (hippocampus and thalamus) did not show significantly altered FC in TRD.
Table 1
Sample characteristics.

| Lead author and year | Sample characteristics (male/female ratio and age per group) | Timing of the assessment (pre-treatment/post-treatment) | Terminology and definition of TRD | Definition of non-TRD (per group) | Depression severity | Illness duration (lifetime, unless specified as current episode) per group (months) |
|----------------------|-------------------------------------------------------------|----------------------------------------------------------|----------------------------------|----------------------------------|-------------------|------------------------------------------------------------------|
| Zhang et al. (2019)  | 15 TRD, 6/9 M/F, 36.87 ± 8.98 years                         | Pre-treatment                                            | "Treatment-resistant" - Non-    | MDD patients who were in remittance at a 2-year follow-up. | HAMD-17           | TRD: 14.53 ± 19.32; non-TRD: 20.17 ± 3.59 |
|                      | 18 non-TRD, 7/11 M/F, 36.06 ± 9.48 years                  |                                                          | responsiveness to at least two adequate trials of different classes of antidepressants for at least 4–6 weeks. | MDD patients showing response after 6-week antidepressant treatment (SSRI/SNRI/TCA). | HAMD-17           | TRD: 37.41 ± 50.73; TSD: 2.59 ± 1.32 |
| He et al. (2016)     | 17 TRD, 10/7 M/F, 26.88 ± 7.66 years                      | TRD: post-treatment; TSD: pre-treatment                 | "Treatment-resistant" - Non-    | Untreated MDD patients or patients treated with a single antidepressant at an insufficient dose and duration. | HAMD-17           | Current: TRD: 58.5 ± 10.8; non-TRD: 3.0 ± 0.6 |
|                      | 17 TSD, 10/7 M/F, 26.72 ± 7.72 years                      |                                                          | responsiveness to at least two adequate trials of different classes of antidepressants for at least 6 weeks. |                                              | HAMD-17           |                                             |
| Yamamura et al. (2016) | 16 TRD, 10/6 M/F, 44.6 ± 9.7 years                        | Post-treatment                                           | "Treatment-resistant" - At stage II* according to the Thase and Rush (1997) staging-model of resistance. |                                              | Current: TRD: 83.3 ± 44.6; non-TRD: 11.9 ± 8.9 |
|                      | 16 non-TRD, 7/9 M/F, 45.7 ± 11.7 years                   |                                                          |                                                |                                              |                                              |                                                                 |
| de Kwaasteniet et al. (2015) | 17 TRD, 8/9 M/F, 52.5 ± 9.3 years                               | Post-treatment                                           | "Treatment-resistant" - Non-    | Medication-free MDD patients with a history of at least two major depressive episodes with remission in between (either spontaneously or with treatment). Patients were excluded when they did not achieve remission during a follow-up period of 2.5 years after assessment. | HAMD-D            |                                             |
|                      | 18 non-TRD, 6/12 M/F, 48.9 ± 7.3 years                   |                                                          | responsiveness to at least two adequate trials with different classes of antidepressants, a tricyclic antidepressant, an irreversible MAO inhibitor, and at least six sessions of bilateral ECT. |                                              |                                              |                                                                 |
| Guo et al. (2013b)   | 23 TRD, 11/2 M/F, 27.35 ± 7.26 years                      | TRD: post-treatment; TSD: pre-treatment                 | "Treatment-resistant" - Non-    | MDD patients showing response after 6-week treatment (after assessment) with an antidepressant (SSRI/SNRI/TCA). | HAMD-17           | Lifetime: TRD: 27.43 ± 35.89; TSD: 2.95 ± 1.73 |
|                      | 22 TSD, 12/10 M/F, 28.09 ± 9.91 years                    |                                                          | responsiveness to at least two adequate treatments with different classes of antidepressants for at least 6 weeks. | MDD patients showing response after 6-week treatment (after assessment) with an antidepressant (SSRI/SNRI/TCA). | HAMD-17           | TRD: 24.52 ± 14.7; TSD: 25.89 ± 6.26 |
| Guo et al. (2013a)   | 23 TRD, 11/2 M/F, 27.35 ± 7.26 years                      | TRD: post-treatment; TSD: pre-treatment                 | "Treatment-resistant" - Non-    | MDD patients showing response after 6-week treatment (after assessment) with an antidepressant (SSRI/SNRI/TCA). | HAMD-17           | TRD: 24.52 ± 14.7; TSD: 25.89 ± 6.26 |
|                      | 22 TSD, 12/10 M/F, 28.09 ± 9.91 years                    |                                                          | responsiveness to at least two adequate trials with different classes of antidepressants for at least 6 weeks. | MDD patients showing response after 6-week treatment (after assessment) with an antidepressant (SSRI/SNRI/TCA). | HAMD-17           | TRD: 24.52 ± 14.7; TSD: 25.89 ± 6.26 |
| Guo et al. (2012a)   | 23 TRD, 11/2 M/F, 27.35 ± 7.26 years                      | TRD: post-treatment; TSD: pre-treatment                 | "Treatment-resistant" - Non-    | MDD patients showing response after 6-week treatment (after assessment) with an antidepressant (SSRI/SNRI/TCA). | HAMD-17           | TRD: 24.52 ± 14.7; TSD: 25.89 ± 6.26 |
|                      | 22 TSD, 12/10 M/F, 28.09 ± 9.91 years                    |                                                          | responsiveness to at least two adequate trials with different classes of antidepressants for at least 6 weeks. | MDD patients showing response after 6-week treatment (after assessment) with an antidepressant (SSRI/SNRI/TCA). | HAMD-17           | TRD: 24.52 ± 14.7; TSD: 25.89 ± 6.26 |
| Guo et al. (2012b)   | 18 TRD, 11/7 M/F, 27.39 ± 7.74 years                      | TRD: post-treatment; TSD: pre-treatment                 | "Treatment-resistant" - Non-    | MDD patients showing response after 6-week treatment (after assessment) with an antidepressant (SSRI/SNRI/TCA). | HAMD-17           | TRD: 24.52 ± 14.7; TSD: 25.89 ± 6.26 |
|                      | 17 TSD, 10/7 M/F, 26.71 ± 7.73 years                      |                                                          | responsiveness to at least two adequate trials with different classes of antidepressants for at least 6 weeks. | MDD patients showing response after 6-week treatment (after assessment) with an antidepressant (SSRI/SNRI/TCA). | HAMD-17           | TRD: 24.52 ± 14.7; TSD: 25.89 ± 6.26 |
| Ma et al. (2012)***  | 18 TRD, 11/7 M/F, 27.39 ± 7.74 years                      | TRD: post-treatment; TSD: pre-treatment                 | "Treatment-resistant" - Non-    | MDD patients with a current illness duration < 6 months, showing response after 6-week treatment (after assessment) with an antidepressant (SSRI/SNRI/TCA). | HAMD-17           | TRD: 23.89 ± 3.69; TSD: 25.58 ± 6.32 |
|                      | 17 TSD, 10/7 M/F, 26.71 ± 7.73 years                      |                                                          | responsiveness to at least two adequate trials with different classes of antidepressants for at least 6 weeks. | MDD patients with a current illness duration < 6 months, showing response after 6-week treatment (after assessment) with an antidepressant (SSRI/SNRI/TCA). | HAMD-17           | TRD: 23.89 ± 3.69; TSD: 25.58 ± 6.32 |
| Lui et al. (2011)††  | 28 Patients With Refractory Depression, 18/10 M/F, 33 ± 11 years | Pre-treatment                                           | "Refractory" - A poor response after at least two adequate trials with different classes of antidepressants for at least 6 weeks. | MDD patients who were not treatment refractory, i.e., showing response after treatment (after assessment) with an antidepressant (SSRI/SNRI/TCA). | HAMD-17           | Refractory: 193 ± 120 |
|                      | 32 Patients With Nonrefractory Depression, 21/11 M/F, 32 ± 10 years |                                                        |                                                | Nonrefractory: 22 ± 18 |  |
| Wu et al. (2011)     | 22 TRD, 15/7 M/F, 35 ± 13 years                           | Pre-treatment (unclear if patients were treatment-naive) | "Refractory" - Non-responsiveness to at least two adequate trials with different classes of antidepressants for at least 6 weeks. | MDD patients who were not treatment refractory, i.e., they did not meet the treatment-refractory criteria after treatment (after assessment) with an antidepressant (SSRI/SNRI/TCA). | HAMD-17           | TRD: 22.0 ± 2.5; NDD: 32 ± 64 |
|                      | 22 NDD, 10/12 M/F, 35 ± 13 years                          |                                                          |                                                | MDD patients who were not treatment refractory, i.e., they did not meet the treatment-refractory criteria after treatment (after assessment) with an antidepressant (SSRI/SNRI/TCA). | HAMD-17           | TRD: 22.0 ± 2.5; NDD: 32 ± 64 |
| Abdallah et al. (2015)† † | 14 TRD, 10/4 M/F, 43.9 ± 3.3 years (mean ± SEM)            | Post-treatment                                           | "Treatment-resistant" - Patients with three failed adequate antidepressant trials in | MDD patients who were not treatment refractory, i.e., they were treatment-naive or | HAMD-17           |                                                                 |
|                      |                                                            |                                                          |                                                | MDD patients who were not treatment resistant, i.e., they were treatment-naive or | HAMD-17           |                                                                 |

(continued on next page)
| Lead author and year | Sample characteristics (male/female ratio and age per group) | Timing of the assessment (pretreatment/post-treatment) | Terminology and definition of TRD | Definition of non-TRD (per group) | Depression severity | Illness duration (lifetime, unless specified as current episode) per group (months) |
|----------------------|---------------------------------------------------------------|------------------------------------------------------|----------------------------------|----------------------------------|-------------------|---------------------------------|
| de Diego-Adelino et al. (2013)† | 20 Treatment-resistant/chronic depression, 80% female, 49.6 ± 7.6 years | Post-treatment | "Treatment-resistant/chronic" - No response to several antidepressants. | First-episode depression: first-episode MDD patients; Remitted-recurrent depression: MDD patients with greater past illness burden (≥ 3 previous episodes of MDD) who were euthymic (score < 8 on the HAM-D) in at least the 6 months preceding the study. | First-episode: first-episode MDD patients; Remitted-recurrent: MDD patients with three or more previous episodes of depression but were asymptomatic (score < 8 on the HAM-D-17) for at least 6 months before the study. | Chronic MDD: 266.1 ± 133.5; Remitted-recurrent MDD: 206.8 ± 124.0; First episode MDD: 5.5 ± 4.3 |
| Serra-Blasco et al. (2013)† | 22 Treatment-resistant/chronic, 4/18 M/F, 49 ± 8 years | Post-treatment | "Treatment-resistant/chronic" - No response to several antidepressant strategies and at least stage III* according to the Thase and Rush (1997) staging model of resistance. | First-episode: first-episode MDD patients; Remitted-recurrent: MDD patients with three or more previous episodes of depression but were asymptomatic (score < 8 on the HAM-D-17) for at least the 6 months preceding the study. | First-episode: first-episode MDD patients; Remitted-recurrent: MDD patients with three or more previous episodes of depression but were asymptomatic (score < 8 on the HAM-D-17) for at least the 6 months preceding the study. | Treatment-resistant/chronic: 271.5 ± 145; Remitted-recurrent: 214.3 ± 129; First episode: 5.6 ± 4.2 |
| Liu et al. (2012)*** | 18 TRD, 11/7 M/F, 27.39 ± 7.74 years | TRD: post-treatment; TSD: pre-treatment | "Treatment resistant" - A poor response to at least two adequate trials with different classes of antidepressants for at least 6 weeks. | MDD patients showing response after 6-week treatment (after assessment) with an antidepressant (SSRI/SNRI/TCA). | HAM-D Treatment-resistant/chronic: 21.4 ± 4.6 | Current TRD: 16.87 ± 19.37; MDD: 11.1 ± 15.07 |
| Zhou et al. (2011) | 20 TRD, 12/8 M/F, 32.7 ± 1.3 years | Pre-treatment | "Treatment resistant" - Non-responsiveness to at least two adequate trials with different classes of antidepressants for at least 8 weeks. | Recovered MDD patients who previously fulfilled DSM-IV criteria for a major depressive disorder and had had severe illness episodes. Recovery was defined as scoring 5 or less on the HAM-D for at least 3 months prior to the study. | HAM-D Treatment: 21.87 ± 3.03 MDD: 23.6 ± 4.56 | TRD: 263 ± 133 weeks; recovered: 76 ± 58 weeks |
| Shah et al. (2002)‡ | 20 TRD, 13/7 M/F, 48.9 ± 9.8 years | Post-treatment | "Treatment-resistant" - Non-responsiveness to at least two courses of treatments from different pharmacological groups (or ECT) for at least 4 weeks. | Recovered MDD patients who previously fulfilled DSM-IV criteria for a major depressive disorder. Recovery was defined as scoring 5 or less on the HAM-D for at least 3 months prior to the study. | HAM-D Treatment: 20.6 ± 5.3 recovered: 2.6 ± 1.7 | TRD: 263 ± 133 weeks; recovered: 76 ± 58 weeks |
| Shah et al. (1998)‡ | 20 TRD, 13/7 M/F, 48.9 ± 9.8 years | Post-treatment | "Treatment-resistant" - Non-responsiveness to at least two courses of treatments from different pharmacological groups (or ECT) for at least 4 weeks. | Recovered MDD patients who previously fulfilled DSM-IV criteria for a major depressive disorder. Recovery was defined as scoring 5 or less on the HAM-D for at least 3 months prior to the study. | HAM-D Treatment: 20.6 ± 5.3 range: 10–30; recovered: | TRD: 263 ± 133 weeks; recovered: 76 ± 58 weeks |
| Portella et al. (2011)‡ | 19 Chronic patients, 79% female, 50.95 ± 7.3 years | Post-treatment | "Chronic" - No response to antidepressant strategies. | First-episode: first-episode MDD patients; Remitted-recurrent patients: Individuals who had experienced three or more previous episodes of MDD and were currently euthymic for at least six months. | HAM-D Chronic patients: 21.39 ± 4.5 | Chronic patients: 22.8 ± 10.1 years; Remitted-recurrent patients: 21.1 ± 9.8 years; First Episode: 1.2 ± 1.8 years |

Table 1 (continued)
| Lead author and year | Sample characteristics (male/ female ratio and age per group) | Timing of the assessment (pre-treatment/post-treatment) | Terminology and definition of TRD | Definition of non-TRD (per group) | Depression severity | Illness duration (lifetime, unless specified as current episode) per group (months) |
|----------------------|---------------------------------------------------------------|--------------------------------------------------------|----------------------------------|---------------------------------|-------------------|-------------------------------------------------|
| Price et al. (2009)[†] | 15 TRD, 8/7 M/F, 46.80 ± 11.9 years; range: 28–68 years | Post-treatment | "Treatment resistant" - Three failed adequate antidepressant trials in the current episode (determined by the ATHF (Sackheim, 2001)). | Treatment-naive MDD patients (50%) and MDD patients with less than three failed adequate antidepressant trials in the current episode (50%). | HAMD-17 | TRD: 26.93 ± 10.8 years; nTRD MDD: 21.80 ± 16.4 years |
| de Diego-Adelino et al. (2014)[†] | 18 Treatment-resistant/chronic MDD, 3/15 M/F, 48.5 ± 7.5 years | Post-treatment | "Treatment-resistant/chronic" - At least stage III** according to the Thase and Rush (1997) staging-model of resistance. | First-episode MDD: first-episode MDD patients; Remitted-recurrent MDD: Patients who had experienced three or more major depressive episodes and were currently euthemic (score < 8 in the HAM-D) for at least 6 months before the enrolment. | HAM-D Treatment-resistant/chronic MDD: 272.7 ± 125.8; Remitted-recurrent MDD: 238.1 ± 133.2; First-episode MDD: 4.9 ± 2.88 |
| Lui et al. (2009)[†] | 24 RDD, 16/8 M/F, 35 ± 12 years; range 18–60 years | Pre-treatment | "Refractory" - A poor response to at least two adequate trials with different classes of antidepressants for at least 6 weeks. | MDD patients who were not treatment refractory, i.e., who did not meet the criteria for the RRD group after treatment. | HAMD-17 | RDD: 192 ± 118; NDD: 24 ± 21 |
| Jia et al. (2017) | 30 TRD, 20/10 M/F, 36.7 ± 12.7 years | Post-treatment | "Treatment-resistant" - A poor response to at least two adequate trials with different classes of antidepressants for at least 6 weeks. | MDD patients who had previously responded to antidepressant treatment. | HAMD-17 | TRD: 119 ± 108; non-TRD: 40 ± 60 |
| Li et al. (2015) | 22 MRD, 50% female, 41.5 ± 13.0 years | MRD: post-treatment; non-MRD: pre-treatment (but patients were not necessarily treatment-naive) | "Medication-resistant" - Non-responsiveness to at least two different classes of adequate antidepressant trials (including one SSRI) in the present episode or in the past. | MDD patients with no history of medication resistance and responded well to antidepressants as confirmed by a prospective 6-week adequate trial with an SSRI (sertraline, citalopram, or escitalopram). | HAMD-17 | Lifetime: MRD: 12.3 ± 4.0 years; non-MRD: 13.3 ± 2.6 years Current: MRD: 5.6 ± 3.7; non-MRD: 9.5 ± 9.6 |
| Baeken et al. (2012) | 15 TRD, 6/9 M/F, 38.55 ± 9.53 years | Post-treatment | "Treatment-resistant" - At least stage III** according to the Thase and Rush (1997) staging-model of resistance. | First-episode antidepressant-naive MDD patients | HAMD-17 | Current: TRD: 4.47 ± 3.25 years; range: 1–12 years; ADN: |
| Cavanagh et al. (2006) | 13 Nonresponders, 10/3 M/F, 42.3 ± 10.9 years | Post-treatment | "Treatment resistance" - Non-responsiveness to at least two adequate trials with different classes of antidepressants for at least 6 weeks. | MDD patients who responded to an adequate dose of a standard antidepressant. | HAMD-17 | TRD: 26.53 ± 3.29 range: 21–32 ADN: 22.4 ± 6.8 |
| Qiao et al. (2017) | 107 TRD, 44/63 M/F, 33.8 ± 12.5 years | Post-treatment | "Treatment resistant" - A poor response to appropriate courses of at least two antidepressants for at least 6 weeks. | MDD patients who were not treatment resistant, i.e., who did not meet the criteria for the TRD group. | TRD: 45.3 ± 15.7 years NTRD: 29.3 ± 8.2 |
| Wang et al. (2009) | 50 TRD, 32/18 M/F, 45 ± 14 years | TRD: post-treatment; NTRD: pre-treatment (but patients were not necessarily treatment-naive) | "Treatment-resistant" - Little improvement after at least two adequate trials with different classes of antidepressants for at least 6 weeks. | First episode MDD patients who responded to a 6-week treatment of a single antidepressant such as fluoxetine, paroxetine, or sertraline (after assessment), without any manic or hypomanic episode. | HAMD-17 | TRD: 23.42 ± 4.29 NTRD: 22.80 ± 4.35 |

**Abbreviations:** DSM, Diagnostic and Statistical Manual of Mental Disorders; TRD, treatment-resistant depression; TSD, treatment-sensitive depression; MDD, major depressive disorder; NDD, nonrefractory MDD; HAMD, Hamilton Depression Rating Scale; ECT, electroconvulsive therapy; nTRD, nonrefractory-resistant MDD; RDD, refractory depressive disorder; MRD, medication-resistant depression; ADN, antidepressant-naive; NTRD, non-treatment-resistant depression; SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin-norepinephrine reuptake inhibitor; MAO, monoamine oxidase inhibitor; DBS, deep brain stimulation; ATHF, Antidepressant Treatment History Form; TCA, tricyclic antidepressant.

*Stage II Resistance: failure of at least two adequate trials of antidepressants in distinctly different classes (Thase and Rush, 1997).

**Stage III Resistance: failure of at least two adequate trials of antidepressants in distinctly different classes plus failure of an adequate trial of a TCA (Thase and Rush, 1997).
3.3.1.2. Regional resting-state activity. In contrast to the predominant reductions in DMN FC, studies that analyzed regional spontaneous neuronal activity mainly reported increased activity in DMN components in TRD patients compared to non-TRD/TSD patients. Three studies that measured the (fractional) amplitude of low-frequency fluctuations ((f)ALFF) (Guo et al., 2012b; Yamamura et al., 2016; Zhang et al., 2019) reported increased local activity, as did one study that used regional homogeneity (ReHo) analysis (Wu et al., 2011) which measures local synchronization of rs-fMRI signals. All studies conducted a whole-brain analysis. Increased ALFF values were found in TRD patients in the ACC/medial frontal gyrus (anterior DMN) (Guo et al., 2012b) (same sample as Ma et al. (2012)), and in a region of the DLPFC that is part of the DMN (Zhang et al., 2019). In contrast, Yamamura et al. (2016) did not find any increases in ALFF in TRD patients. However, this study was the only rs-fMRI study that included a non-TRD control group instead of a TSD control group. As this group may include some patients who at a later time could be categorized as TRD, this could explain why no increases in ALFF were found. That said, Yamamura et al. (2016) also reported fractional ALFF (fALFF), a more specific measure of low-frequency oscillatory phenomena, as it is the normalized index of ALFF (Zuo et al., 2010). They found a cluster of significantly increased fALFF values in TRD patients in the right thalamus and the supramarginal gyrus, at the edge of the angular gyrus (close to the center of gravity coordinates of the PPC ROI of the DMN in Alves et al. (2019), but the indication that this cluster is part of the DMN is not conclusive). Lastly, Wu et al. (2011) found significantly increased ReHo in two DMN components in TRD patients: the right middle temporal gyrus (BA22/21) and the middle cingulate (BA24)/PCC (BA31).

In addition to the increased spontaneous neuronal activity in the DMN, there is also limited evidence for reduced regional spontaneous neuronal activity in components of the DMN in TRD. Wu et al. (2011) found significantly decreased ReHo in the posterior DMN (left precuneus, BA7) in TRD patients. However, their seed-based analysis did not reveal any differences in ReHo in any of their ROI’s, including several subcortical components of the DMN (amygdala, hippocampus, thalamus and caudate).

To summarize, TRD seems to be associated with reduced FC within the DMN and between components of the DMN and other cognitive networks/brain regions. This appears to be accompanied by increased spontaneous neuronal activity in several DMN components. However, it should be noted that this limited number of studies produced findings across a wide variety of components within the DMN with little overlap. Especially the studies that reported altered regional spontaneous activity in TRD, did so in entirely different components of the DMN.

3.3.2. Occipital lobe

The results of the included studies also point to impaired spontaneous neuronal activity and FC in or with occipital regions in TRD compared to TSD/non-TRD. However, the directions of these effects are less consistent. As described above, de Kwaasteniet et al. (2015) found decreased FC between the anterior DMN and the cuneus in TRD. In addition, in one of the significant networks of reduced FC in TRD found by He et al. (2016), the olfactory cortex had reduced connections with the left and right inferior occipital gyrus and the left fusiform gyrus. Moreover, Guo et al. (2013b) revealed decreased interhemispheric FC in TRD in the occipital part of the fusiform gyrus and the calcarine cortex. Subsequently, they placed seeds within the bilateral calcarine cortex, which showed substantial decreased FC with other regions in the occipital lobe (see Table 2), and with the right inferior temporal gyrus and right insula in TRD patients. They also showed significantly increased FC between the right calcarine cortex and vermis 6. In the same sample (Guo et al., 2012a) and a partially overlapping sample (Guo et al., 2012b), TRD patients showed significantly increased coherence-based ReHo in the occipital part of the left fusiform gyrus and significantly decreased ALFF values in the lingual gyrus/cuneus, respectively. Similarly, Yamamura et al. (2016) found decreased ALFF
Table 2: Main outcome measures and findings.

| Lead author and year | Main outcome measure(s) | Main findings |
|----------------------|-------------------------|--------------|
| Zhang et al. (2019)  | Whole-brain (264 partitions) ALFF | Significantly higher ALFF in the right sensory/somatomotor (hand) RSN, right auditory RSN (temporal lobe), and left DMM (DLFPC) in TRD compared to non-TRD. |
| He et al. (2016)     | FC of whole-brain (90 ROI’s) functional networks at different frequency bands (0.01 – 0.027 Hz and 0.027 – 0.073 Hz). | One subnetwork with reduced FC at the 0.01 – 0.027 Hz frequency band in TRD compared to TSD: reduced FC between the left parahippocampal gyrus and the left IPL, left prefrontal cortex, and reduced FC between the left IPL and the left caudate. Two subnetworks with reduced FC at the 0.027 – 0.073 Hz frequency band in TRD compared to TSD: Subnetwork 1: reduced FC between the left Heschl’s gyrus and the left parahippocampal gyrus and left rectus gyrus, and reduced FC between the left parahippocampal gyrus and the right Heschl’s gyrus. Subnetwork 2: reduced FC between the right olfactory cortex and the bilateral inferior occipital gyrus, left fusiform gyrus, right SFG, lateral prefrontal cortex (left MFG, right IFG (triangular)) and the right OFC (inferior), and reduced FC between the right inferior occipital gyrus and the left olfactory cortex. |
| de Kwaasteniet et al. (2015) | Seed-based FC with four seeds in: anterior insula (SN), DLPFC (CCN) and PCC and MPFC (posterior and anterior DMN). Reference seed: primary motor cortex. | Significantly decreased FC between the right DLPFC (CCN) and the left and right angular gyrus (DMN) in TRD compared to non-TRD. Significantly decreased FC between the MPFC (anterior DMN) and the cuneus/prefrontal cortex, and the left SFG (posterior DMN) in TRD compared to non-TRD. No significant differences in SN connectivity. Reference seed: Significantly decreased FC between the right motor cortex and the right STG and PCC in TRD compared to non-TRD. Significantly decreased FC between the left motor cortex and the right STG, left IFG and PCC in TRD compared to non-TRD. |
| Guo et al. (2013b)   | Whole-brain VMHC and seed-based FC with the left and right calcarine cortex as seeds. | Significantly decreased VMHC in the calcarine cortex, fusiform gyrus, precentral gyrus, hippocampus, STG and middle cingulum in TRD compared to TSD. No significant increases in VMHC were found. Significantly increased FC between the right calcarine cortex and vermis 6 in TRD compared to TSD. Significantly decreased FC between left calcarine cortex and the right ITG, right calcarine cortex, left MOG, left cuneus and right insula in TRD compared to TSD. Significantly decreased FC between the right calcarine cortex and the left and right lingual gyrus, left and right calcarine cortex and left MOG in TRD compared to TSD. With global signal regression: Significantly decreased FC between left and right Crus Ia and right precentral gyrus, between right Crus II and left precentral gyrus, and between the left Lobule VIb and left precentral gyrus, right angular gyrus and left IPL in TRD compared to TSD. No significant increases in FC were found. No significant differences in FC between the right Cruss Ib/lobule VIa/lobule V and the rest of the brain were found. Without global signal regression: Significantly decreased FC between right Crus Ia and left MFG in TRD compared to TSD. Significantly lower CoHe-ReHo in the bilateral cerebellum and significantly higher CoHe-ReHo in the left fusiform gyrus in TRD compared to TSD. |
| Guo et al. (2013a)   | Seed-based FC with various cerebellar seeds of the executive network (Crus Ia, Crus II and Lobule VIa), DMN (Crus Ib), affective limbic network (Lobule VIb and vermis) and motor network (Lobule V). | Significantly increased ALFF values in the right lingual gyrus/cuneus/precuneus, and the left parahippocampal gyrus and the left SFG, bilateral SFG and right rectus. right caudate seed TRD vs. TSD: Significantly decreased connectivity with the right MFG and right SFG, and significantly increased connectivity with the right IFG and the left corpus callosum. Significantly increased connectivity between the left amygdala and the ACC (BA24), between the right insula and the PCC (BA31), and between the right insula and the precuneus (BA7), in patients with refractory depression compared to patients with nonrefractory depression. No significant differences in FC between any of the other seeds and the rest of the brain. |
| Guo et al. (2012a)   | Whole-brain CoHe-ReHo. | Significantly increased ALFF values in the posterior lobes of the cerebellum and the ACC/midfrontal gyrus (DMN) in TRD compared to TSD. Significantly decreased ALFF values in the lingual gyrus/cuneus visual recognition circuit) in TRD compared to TSD. right MTG seed TRD vs. TSD: Significantly decreased connectivity with the right STG, and significantly increased connectivity with the right medial frontal gyrus, right angular gyrus, right precentral gyrus, bilateral SFG and left rectus. right caudate seed TRD vs. TSD: Significantly decreased connectivity with the right MFG and right SFG, and significantly increased connectivity with the right IFG and the left corpus callosum. Significantly increased connectivity between the left amygdala and the ACC (BA24), between the right insula and the PCC (BA31), and between the right insula and the precuneus (BA7), in patients with refractory depression compared to patients with nonrefractory depression. No significant differences in FC between any of the other seeds and the rest of the brain. |
| Guo et al. (2012b)   | Whole-brain ALFF. | Significantly increased ALFF values in the right sensory/somatomotor (hand) RSN, right auditory RSN (temporal lobe), and left DMM (DLFPC) in TRD compared to non-TRD. |
| Ma et al. (2012)     | Seed-based FC with seed regions in gray matter abnormal regions: right MTG and right caudate. | |
| Lui et al. (2011)    | Seed-based FC, with 13 seeds in: the left and right hippocampus, insula, dorsal lateral prefrontal areas, amygdala, putamen, thalamus and the ACC. | Significantly increased connectivity between the left amygdala and the ACC (BA24), between the right insula and the PCC (BA31), and between the right insula and the precuneus (BA7), in patients with refractory depression compared to patients with nonrefractory depression. No significant differences in FC between any of the other seeds and the rest of the brain. |
| Wu et al. (2011)     | Whole-brain ReHo and ROI: bilateral amygdala, hippocampus, insula, putamen, caudate, globus pallidus and thalamus. | Whole-brain analysis: Significantly higher ReHo in the right MTG (BA32/21), right insula (BA13) and the middle cingulate (BA24)/PCC (BA31) in TRD compared to NDD. Significantly lower ReHo in the left precuneus (BA7) and left IFG (BA9/6) in TRD compared to NDD. ROI analysis: No significant differences in ReHo between TRD and NDD in any of the ROI regions. |

(continued on next page)
| Lead author and year | Main outcome measure(s) | Main findings |
|----------------------|--------------------------|---------------|
| Abdallah et al. (2015) | Hippocampal volume. | Significantly lower hippocampal volume in TRD compared to non-TRD, independent of hemisphere. |
| Careceller-Sindreu et al. (2015) | Total habenular volume, gray and white matter habenular volumes and TIV. | No significant differences in TIV, total habenular volume and gray and white matter habenular volumes between groups. Significantly reduced total grey matter habenular volume in female chronic MDD compared to female first-episode MDD. No significant differences between female chronic MDD and female remitted-recurrent MDD. |
| Liu et al. (2012) | Whole-brain gray matter volume. | No significant differences in total gray/white matter volumes between TRD and healthy controls were segmented: left anterior cingulate, right SFG, bilateral medial frontal gyrus, left insula. |
| Carceller-Sindreu et al. (2013) | Hippocampal volume and gray/white matter proportions. | Significantly lower bilateral hippocampal volumes in treatment-resistant/chronic depression compared to first-episode depression. Significantly lower proportion of gray matter in the left hippocampus and higher proportion of white matter in the left and right hippocampus in treatment-resistant/chronic depression compared to remitted-recurrent depression. |
| Shah et al. (2002) | Bilateral anterior and posterior hippocampal volumes, bilateral caudate and putamen volumes, bilateral prefrontal and posterior frontal tissue volumes and bilateral temporal lobes volumes. | No significant differences in hippocampal volumes between TRD and healthy controls. Significantly lower total hippocampal volume in treatment-resistant/chronic depression compared to first-episode depression. |
| Zhou et al. (2011) | Whole-brain gray and white matter volume and concentration. | No significant differences between groups. Whole-brain: No significant differences between groups (FWE corrected). Reduced grey matter volume in left pre-central gyrus (BA4), left medial frontal gyrus (BA6), right insula (BA 13), right transverse-temperal gyrus (BA 41), right IPL (BA 40) and left posterior cingulate (BA 30/31) in the treatment-resistant/chronic group compared to the first-episode group (p < 0.0001 uncorrected). Segmentations: Significantly reduced gray matter volume in the right medial frontal gyrus and the left insula in the treatment-resistant/chronic group compared to the first-episode group. Significantly reduced gray matter volume in the bilateral medial frontal gyrus in the treatment-resistant/chronic group compared to remitted-recurrent group. No significant difference in left anterior cingulate volume between groups. |
| Serra-Blasco et al. (2013) | TIV and whole-brain gray matter volume. Areas showing significant decreased volumes between TRD and healthy controls were segmented: left anterior cingulate, right SFG, bilateral medial frontal gyrus, left insula. | No significant differences in TIV between groups. Whole-brain: No significant differences between groups (FWE corrected). Reduced grey matter volume in left pre-central gyrus (BA4), left medial frontal gyrus (BA6), right insula (BA 13), right transverse-temperal gyrus (BA 41), right IPL (BA 40) and left posterior cingulate (BA 30/31) in the treatment-resistant/chronic group compared to the first-episode group (p < 0.0001 uncorrected). Segmentations: Significantly reduced gray matter volume in the right medial frontal gyrus and the left insula in the treatment-resistant/chronic group compared to the first-episode group. Significantly reduced gray matter volume in the bilateral medial frontal gyrus in the treatment-resistant/chronic group compared to remitted-recurrent group. No significant difference in left anterior cingulate volume between groups. |
| Ma et al. (2012) | Whole-brain gray matter volume. | No significant gray or white matter volume differences between the groups (FWE corrected). Reduced gray matter in the right supramarginal gyrus (BA40), right IPL (BA39/40), left MTG (BA21), left ITG (BA20) and right caudate nucleus in TRD compared to TSD (p < 0.001 uncorrected). Increased gray matter in the left MFG (BA8), left superior occipital gyrus (BA18) and left calcarine fissure (BA17) in TRD compared to TSD (p < 0.001 uncorrected). Reduced white matter in the right lingual gyrus (BA17) in TRD compared to TSD (p < 0.001 uncorrected). Increased gray matter in the right medial frontal gyrus (BA11), right MFG (BA8/9), left anterior cingulate gyrus (BA32), bilateral median cingulate gyrus (BA24), left precentral gyrus (BA6), left supramarginal gyrus (BA40), left precuneus (BA7), left PG (BA23/31), left lingual gyrus (BA17/18) and left MOG (BA18) in TRD compared to TSD (p < 0.001 uncorrected). |
| Portella et al. (2011) | Bilateral anterior and posterior hippocampal volumes, bilateral caudate and putamen volumes, bilateral prefrontal and posterior frontal tissue volumes and bilateral temporal lobes volumes. | No significant differences between groups. A repetition of the whole-brain analysis by Shah et al. (1998) with the number of ECT treatments administered as an additional covariate: only reductions in gray matter density in the left hippocampus in TRD compared to the recovered from depression group remained. Significantly reduced left STG/lateral IFG gray matter density in TRD compared to the recovered from depression group. Significantly increased right cuneus/precuneus gray matter density in TRD compared to the recovered from depression group. Reduced left hippocampus/parahippocampal gyrus gray matter density in TRD compared to the recovered from depression group, but this difference was no longer significant after multiple comparison correction. |
| Serra-Blasco et al. (2013) | Whole-brain gray matter volume. | No significant differences in gray/white matter volumes between TRD and healthy controls. Areas showing significant decreased volumes between TRD and healthy controls were segmented: left anterior cingulate, right SFG, bilateral medial frontal gyrus, left insula. |
| Zhou et al. (2011) | Whole-brain gray and white matter volume and concentration. | No significant differences between groups. Whole-brain: No significant differences between groups (FWE corrected). Reduced grey matter volume in left pre-central gyrus (BA4), left medial frontal gyrus (BA6), right insula (BA 13), right transverse-temperal gyrus (BA 41), right IPL (BA 40) and left posterior cingulate (BA 30/31) in the treatment-resistant/chronic group compared to the first-episode group (p < 0.0001 uncorrected). Segmentations: Significantly reduced gray matter volume in the right medial frontal gyrus and the left insula in the treatment-resistant/chronic group compared to the first-episode group. Significantly reduced gray matter volume in the bilateral medial frontal gyrus in the treatment-resistant/chronic group compared to remitted-recurrent group. No significant difference in left anterior cingulate volume between groups. |
| Shah et al. (1998) | Whole brain-gray matter density. | No significant differences between groups. A repetition of the whole-brain analysis by Shah et al. (1998) with the number of ECT treatments administered as an additional covariate: only reductions in gray matter density in the left hippocampus in TRD compared to the recovered from depression group remained. Significantly reduced left STG/lateral IFG gray matter density in TRD compared to the recovered from depression group. Significantly increased right cuneus/precuneus gray matter density in TRD compared to the recovered from depression group. Reduced left hippocampus/parahippocampal gyrus gray matter density in TRD compared to the recovered from depression group, but this difference was no longer significant after multiple comparison correction. |
| de Diego-Adelino et al. (2013) | Gx (glutamate + glutamine), NAA (N-acetylaspartate + N-acetylaspartate-glutamate) and Cho (glycerophosphocholine and phosphocholine compounds) in bilateral hippocampus. | Significantly higher Cho levels in treatment-resistant/chronic depression compared to first-episode depression in the left and right hippocampus, regardless of tissue composition or hippocampal volume. No significant differences for any of the metabolites between the treatment-resistant/chronic depression and remitted-recurrent depression. |
| Price et al. (2009) | GABA (y-aminobutyric acid) and Gtx (glutamate + glutamine) in the OCC and ACC. | Regions analyzed separately: Significantly reduced OCC GABA in TRD compared to nTRD. No significant difference in ACC GABA in TRD compared to nTRD. No significant differences in Glx between TRD and nTRD in OCC and ACC. Regions analyzed together: Significantly lower GABA in TRD compared to nTRD independent of region. No significant differences in Glx/GABA ratios in the OCC and ACC in TRD compared to nTRD. Exploratory TRD definition analysis: Significantly reduced OCC GABA in TRD compared to nTRD for the 4 failed trials definition, but no significant difference in OCC GABA for the 2 or 5 failed trials definition. |

(continued on next page)
Table 2 (continued)

| Lead author and year | Main outcome measure(s) | Main findings |
|----------------------|-------------------------|---------------|
| DTI de Diego-Adelino et al. (2014) | Whole-brain and VMPFC ROI white matter FA. | Significantly lower whole-brain mean FA values in treatment-resistant/chronic MDD compared to first-episode MDD. No significant differences in whole-brain mean FA values between treatment-resistant/chronic MDD compared to remitted-remittent MDD. Whole-brain analysis: Significantly lower FA values in treatment-resistant/chronic MDD compared to first-episode MDD, affecting the body of the corpus callosum, bilateral superior longitudinal fasciculus, forceps minor, forceps major, bilateral cingulum and bilateral inferior longitudinal fasciculus. No significant differences in FA values between treatment-resistant/chronic MDD compared to remitted-remittent MDD. ROI analysis: Significantly lower FA values in the VMPFC in treatment-resistant/chronic MDD compared to first-episode MDD and remitted-remittent MDD patients, affecting the uncinate fasciculus and corpus callosum within this region. |
| Zhou et al. (2011) | Whole-brain white matter FA. | Significantly lower FA in the bilateral hippocampus in TRD compared to MDD. |
| ASL Lui et al. (2009) | Whole-brain rCBF and ROI: bilateral hippocampi, lentiform nuclei and thalamus. | No significant difference in global rCBF between the groups. Whole-brain analysis: Significantly lower rCBF in the paracentral lobule, the occipital lobes, the right hippocampus, the left and right lentiform nucleus and the ACC, in the RDD compared to the NDD. ROI analysis: Significantly lower rCBF in the left and right hippocampus, and in the right lentiform nucleus in RDD compared to NDD. No significant differences between RDD and NDD in the left lentiform nucleus and the bilateral thalamus. |
| MTI Jia et al. (2017) | Whole-brain MTR. | Significantly lower MTR in the bilateral precentral gyrus, the left middle occipital lobe and the left precuneus, in TRD compared to non-TRD. The TRD tended to show lower MTR in the left temporal lobe compared to non-TRD, but this difference was no longer significant after multiple comparison correction. |
| PET Li et al. (2015) | Whole-brain rCMglu (18F-FDG PET) and ROI: prefrontal cortex (a priori) and bilateral DLPFC (non a priori). | Whole-brain analysis: Significantly decreased rCMglu in the bilateral DLPFC (BA9) and the supplementary motor area (BA6) in MRD compared to non-MRD. ROI analysis: Significantly decreased prefrontal cortex rCMglu in MRD compared to non-MRD. Significantly decreased rCMglu in the bilateral DLPFC in MRD compared to non-MRD. |
| SPECT Baeken et al. (2012) | 5-HT2A receptor BI in four bilateral cortical VOIs and four bilateral prefrontal cortical VOIs: frontal cortex, temporal cortex, parietal cortex, OCC, DPFC, VMPFC, OFC, ACC. | Significantly lower 5-HT2A receptor BI in the frontal cortex in TRD compared to ADN. No significant differences in 5-HT2A receptor BI between TRD and ADN in temporal cortex, parietal cortex and OCC. Significantly lower 5-HT2A receptor BI in the DLPFC in TRD compared to ADN. Trend-like lower BI in the ACC in TRD compared to ADN (p = 0.07). No significant differences in 5-HT2A receptor BI between TRD and ADN in the VMPFC and OFC. No significant difference in SERT residual availability and DAT availability between responders and nonresponders to antidepressant therapy. |
| Cavanagh et al. (2006) | SERT-availability in brainstem ROI comprised of the thalamus-hypothalamus, midbrain and pons. DAT-availability in bilateral striatum ROI comprised of the head of the caudate and putamen. Reference ROI: bilateral medial and lateral occipital lobe. | No significant differences in 5-HT2A receptor BI between TRD and ADN in temporal cortex, parietal cortex and OCC. Significantly lower SERT availability in the VPFC and OFC. |
| ERP Qiao et al. (2017) | P300 amplitude and latency. | Significantly longer P300 latency in TRD compared to NTRD. No significant difference in P300 amplitude. |
| Wang et al. (2009) | S1-P50 amplitude and latency (conditioned stimulus wave) and S2-P50 (testing stimulus wave), S1/S2 (amplitude), S1/S2/S1 (100x(1-S2/S1)) (%) | No significant differences in S1-P50 and S2-P50 latency and amplitude and S1-S2 between TRD and NTRD. Significantly higher S2/S1 and lower 100x(1-S2/S1) in the TRD compared to NTRD. No main effect of age. |

Abbreviations: rs-fMRI, resting-state functional magnetic resonance imaging; (f)ALFF, (fractional) amplitude of low-frequency fluctuations; RSN, resting state network; DMN, default mode network; DLPFC, dorsolateral prefrontal cortex; TRD, treatment-resistant depression; FC, functional connectivity; ROI, region of interest; TSD, treatment-sensitive depression; IPL, inferior parietal lobe; PCG, posterior cingulate gyrus; SPG, superior parietal gyrus; MFG, middle frontal gyrus; IFG, inferior frontal gyrus; OCC, occipital cortex; nTRD, nontreatment-resistant MDD; DTI, diffusion tensor imaging; FA, fractional anisotropy; (CoHe-)ReHo, (coherence-based) regional homogeneity; ACC, anterior cingulate cortex; MTG, middle temporal gyrus; SFG, superior frontal gyrus; BA, brodmann area; NDD, non-refractory MDD; sMRI, structural MRI; TIV, total intracranial volume; MDD, major depressive disorder; FWE, familywise error; ECT, electroconvulsive therapy; MRS, magnetic resonance spectroscopy; OCC, occipital cortex; nTRD, nontreatment-resistant MDD; DTI, diffusion tensor imaging; FA, fractional anisotropy; ASL, arterial spin labeling; rCBF, regional cerebral blood flow; RDD, refractory depressive disorder; MTI, magnetization transfer imaging; MTR, magnetization transfer ratio; PET, positron emission tomography; rCMglu, regional cerebral glucose metabolism; MRD, medication-resistant depression; SPECT, single photon emission computed tomography; BI, binding index; VOI, volume-of-interest; DPFC, dorsal prefrontal cortex; VPFC, ventral prefrontal cortex; ADN, antidepressant-naïve; SERT, serotonin transporter; DAT, dopamine transporter; ERP, event-related potential; NTRD, non-treatment-resistant depression.
values in the right lingual region and increased fALFF in the middle occipital gyrus in TRD patients compared to non-TRD patients.

### 3.3.3. Other findings

In addition to the above, the results of the included studies also implicate altered FC and spontaneous neuronal activity in various other brain regions in TRD compared to TSD/non-TRD patients, albeit supported by fewer studies. For example, Wu et al. (2011) found increased ReHo in the right insula (BA13) in TRD patients. Furthermore, as described above, TRD patients showed decreased FC between the right insula and the left calcarine cortex (Guo et al., 2013b), and increased FC between the insula and the PCC and precuneus (posterior DMN) (Lui et al., 2011). In contrast, de Kwaasteniet et al. (2015) did not find any impairment in FC between the anterior insula (salience network) and the DMN or cognitive control network.

De Kwaasteniet et al. (2015) did, however, find decreased FC between the left motor cortex and the left IFG in TRD patients, whereas Ma et al. (2012) found increased FC between the right caudate and the right IFG. Additionally, the significant network of reduced FC in TRD patients centered on the olfactory cortex found by He et al. (2016), had a reduced connection with the right IFG. Furthermore, this region was found to have increased fALFF values in TRD patients (Yamamura et al., 2016), whereas Wu et al. (2011) found decreased coherence-based ReHo in the left IFG. De Kwaasteniet et al. (2015) also found decreased FC between the bilateral motor cortex and the bilateral STG in TRD patients. Furthermore, both decreased FC between the right MTG and the right STG (Ma et al., 2012) and decreased interhemispheric FC in the STG (Guo et al., 2013b) were found in TRD.

Lastly, a significant cluster of increased ALFF values was found in TRD patients in the posterior lobes of the cerebellum (Guo et al., 2012b), with the coordinates of the primary peak being close to one of the executive network seeds used by Guo et al. (2013a) (partially overlapping sample). In contrast, in the same sample as Guo et al. (2013a), Guo et al. (2012a) found decreased coherence-based ReHo in TRD patients in a cluster with the primary peak being close to a different executive network seed in the cerebellum.

A small number of findings from the rs-fMRI studies could not be reviewed in the same context as the other studies and were not discussed here. For a complete overview of all rs-fMRI findings, see Table 2.

### 3.4. Structural MRI

Nine studies used structural MRI to study gray and white matter volume differences in TRD patients compared to TSD/non-TRD patients. Abdallah et al. (2015) and de Diego-Adelino et al. (2013) found significantly reduced hippocampal volumes in TRD patients compared to non-TRD patients. In addition, although de Diego-Adelino et al. (2013) did not find a significant difference in hippocampal volumes overall between TRD patients and TSD patients, they did find a significantly lower proportion of grey matter in the left hippocampus and higher proportion of white matter in the left and right hippocampus. Furthermore, Shah et al. (1998) found reduced left hippocampus/parahippocampal gyrus gray matter density in TRD patients compared to TSD patients, although this difference was no longer significant after multiple comparison correction. In a later analysis of manually segmented hippocampal volumes in the same sample, Shah et al. (2002) did not find a significant difference in hippocampal volume either. Shah et al. (2002) then repeated their earlier whole-brain analysis while controlling for age and the number of ECT treatments administered, which then did result in a significant reduction in gray matter density in the left hippocampus.

Abnormalities in gray and white matter volumes between TRD and non-TRD/TSD patients were also found in a variety of other brain regions. Shah et al. (2002) and Ma et al. (2012) found reduced right and bilateral caudate volumes, respectively, in TRD patients compared to TSD patients. In addition, an ROI-analysis by Serra-Blasco et al. (2013) revealed significantly reduced gray matter volume in the right medial frontal gyrus and the left insula in TRD patients compared to non-TRD patients, and significantly reduced gray matter volume in the bilateral medial frontal gyrus in TRD patients compared to TSD patients, but no significant volume differences in the anterior cingulate were found. In contrast, Shah et al. (2002) did not find any abnormalities in their manually segmented putamen, prefrontal and posterior frontal regions or the temporal lobe. Furthermore, although Careceller-Sindreu et al. (2015), in a predominantly overlapping sample with Serra-Blasco et al. (2013), found significantly reduced white matter habenular volumes in female TRD patients compared to female non-TRD patients but not female TSD patients, no significant differences in habenular volumes were found when males were included in the analysis. The whole-brain analysis by Shah et al. (1998) found significantly reduced left superior temporal/lateral inferior frontal gyrus gray matter density and increased right cuneus/precuneus gray matter density in TRD patients. However, none of these effects remained significant after Shah et al. (2002) repeated this analysis with the number of ECT treatments administered as an additional covariate. Additionally, in partially overlapping samples with Ma et al. (2012) and de Diego-Adelino et al. (2013), respectively, whole-brain analyses by Liu et al. (2012) and Serra-Blasco et al. (2013) revealed no significant differences in gray matter volume between patient groups that survived multiple comparisons corrections (for uncorrected differences, see Table 2). Notably, only Zhou et al. (2011) investigated whole-brain gray and white matter volumes and concentrations in prospective TRD and TSD patients, and they did not find any significant differences either.

In summary, there is limited evidence for structural brain abnormalities TRD. Most notably, TRD may be associated with reduced caudate volumes compared to TSD. The evidence also suggests reduced hippocampal volumes in TRD patients, but only compared to non-TRD patients. Evidence for reduced hippocampal volumes in TRD compared to TSD is extremely limited and circumstantial. Although there are some findings of structural differences in other brain areas, the majority of studies seem to indicate no structural differences, especially in TRD compared to TSD.

### 3.5. Diffusion tensor imaging

Diffusion tensor imaging (DTI) is a widely used MRI technique to study white matter microstructure, by measuring the diffusion of water molecules through neuronal tissue (Taylor et al., 2004). Water diffusion in white matter is anisotropic, meaning that it is not the same in all directions. The degree of anisotropic diffusion provides information about the white matter microstructure. The most commonly used DTI measure for the degree of anisotropic diffusion is fractional anisotropy (FA). We identified two studies that used this measure to study differences in white matter microstructure in TRD. An ROI analysis of the VMPFC by de Diego-Adelino et al. (2014) revealed significantly lower FA values in TRD patients compared to both non-TRD patients and TSD patients, affecting the uncinate fasciculus and corpus callosum within this region. Their whole-brain analysis revealed significantly lower whole-brain mean FA values in TRD patients compared to non-TRD patients. In addition, TRD patients exhibited significantly lower FA values compared to non-TRD patients, affecting the body of the corpus callosum, bilateral superior longitudinal fasciculus, forceps minor, forceps major, bilateral cingulum and bilateral inferior longitudinal fasciculus. No significant FA value or whole-brain mean FA value differences were found between TRD patients compared to TSD patients. On the other hand, a whole-brain analysis by Zhou et al. (2011) showed a significant reduction in FA in the white matter within the bilateral hippocampus in TRD patients compared to TSD patients.

### 3.6. Magnetic resonance spectroscopy

Proton magnetic resonance spectroscopy (MRS) allows for the non-
invasive in-vivo quantification of various brain metabolites and neurotransmitters. Price et al. (2009) used this technique to study γ-aminobutyric acid (GABA) and glutamate + glutamine (Glx) in the occipital cortex (OCC) and ACC in TRD and non-TRD patients. TRD patients showed a significant reduction in OCC GABA levels, but no significant difference in the ACC. However, when the OCC and ACC GABA levels were analyzed together, significantly reduced GABA levels were found in TRD patients, independently of region. Remarkably, the TRD group in this study included MDD patients with at least three failed adequate antidepressant trials in the current episode. Consequently, the non-TRD group in this study included MDD patients who had had two antidepressant trial failures in the current episode, which would have been categorized as treatment-resistant in most of the other included studies. The association between reduced OCC GABA and treatment resistance was further explored using alternative categorical definitions of TRD. Notably, this association was no longer significant when TRD was categorized as a failure of at least two antidepressant trials, suggesting that this effect is restricted to more severe TRD.

Portella et al. (2011) assessed glutamate (Glu), total N-acetylaspartate (total NAA) and Choline-containing compounds (Cho) in the VMPFC of TRD patients. They found significantly lower Glu and total NAA values and higher Cho values in the VMPFC in TRD patients compared to non-TRD patients, but no significant differences were found between TRD patients and TSD patients. Notably, the groups were not matched on gender. However, multivariate analyses showed no main effect of gender or gender x group interaction effect. Later on, the same group conducted a similar study focusing on the hippocampus (de Diego-Adelino et al., 2013) using a partially overlapping sample. They found significantly higher choline levels in TRD patients compared to non-TRD patients in the left and right hippocampus, regardless of tissue composition or hippocampal volume. There were no significant differences for any of the metabolites between TRD patients and TSD patients.

Taken together, the current MRS studies do not provide clear evidence for a relationship between treatment resistance in MDD and altered brain metabolites or neurotransmitters. So far, the data suggests that OCC and possibly ACC GABA levels are reduced but only in more severe TRD patients (Price et al., 2009). Other differences in brain metabolites were found in comparison with non-TRD patients but not TSD patients (de Diego-Adelino et al., 2013; Portella et al., 2011), suggesting that these differences are not related to treatment resistance.

3.7. Magnetization transfer imaging

Magnetization Transfer Imaging (MTI) is an MRI technique to measure macromolecular density in the brain, reflected by the magnetic transfer ratio (MTR). Higher and lower MTR’s are associated with remyelization and demyelization of white matter respectively (Chen et al., 2008; Kumar et al., 2014). In gray matter, MTR might reflect changes in cell structure, number of cells, or dendritic density (Khalili et al., 2008). Jia et al. (2017) used the MTR to study alterations in brain macromolecules in TRD patients compared to TSD patients. They observed significantly lower MTR in the bilateral precentral gyrus, the left middle occipital lobe and the left precuneus, in TRD patients. TRD patients additionally tended to show lower MTR in the left temporal lobe, but this difference was no longer significant after multiple comparison correction.

3.8. Arterial spin labeling

Arterial spin labeling (ASL) MR imaging is one of several imaging techniques that allows the detection of regional cerebral blood flow (rCBF) in the brain, which is another way to measure regional spontaneous neuronal activity. Liu et al. (2009) applied this technique in TRD and TSD patients. Their whole-brain analysis indicated that TRD patients had significantly lower rCBF in the paracentral lobule, the occipital lobes, the right hippocampus, the left and right lentiform nucleus and the anterior cingulate cortex. Consecutive ROI analysis confirmed the significantly lower rCBF of TRD patients in the left and right hippocampus, and in the right but not the left lentiform nucleus. In addition, no significant differences in rCBF were observed between the two groups in the bilateral thalamus.

3.9. Positron emission tomography

PET can use specific radioactive tracers to allow detection of certain metabolic processes in the brain. Like rs-fMRI and ASL, 18F-FDG PET can be used to detect regional spontaneous neuronal activity by measuring regional cerebral glucose metabolism (rCMglu) at rest. A whole-brain analysis by Li et al. (2015) showed significantly decreased rCMglu in the supplementary motor area and the bilateral DLPPC in TRD patients compared to TSD patients, the latter finding being confirmed by post-hoc DLPPC ROI analysis. The ROI analysis also revealed significantly decreased rCMglu in the prefrontal cortex in general in TRD.

3.10. Single photon emission computed tomography

Two studies were identified that used SPECT to look into different aspects of the serotoninergic system in TRD. Cavanagh et al. (2006) used SPECT with [123I]-β-CIT to study SERT availability in the brain stem and dopamine transporter (DAT) availability in the bilateral striatum of TRD compared to TSD patients, but found no significant differences. Instead of looking into the presynaptic SERT, Baeken et al. (2012) studied the postsynaptic 5-HT2A serotonin receptor binding index (B1) with 123I-1-T-R91150 SPECT in melancholic TRD and non-TRD patients. The 5-HT2A receptor B1 in TRD patients was significantly lower in the frontal cortex overall and in the DPPC specifically. They also found a lower B1 in the ACC in TRD patients, but the difference failed to reach significance (p = .07). No significant differences were found in the temporal cortex, parietal cortex, occipital cortex, ventral prefrontal cortex and orbitofrontal cortex.

3.11. Event-related potentials

We identified two studies that studied two different event-related potentials (ERP): the P50 (Wang et al., 2009) and the P300 (Qiao et al., 2017). Although Wang et al. (2009) did not find any differences in amplitude or latency of the conditioning stimulus (S1-P50) or the testing stimulus (S2-P50) of their auditory P50 test, they did find increased S2/S1 ratios (and decreased 100x(1-S2/S1)) in TRD patients compared to TSD patients. As a repeating stimulus (i.e., the testing stimulus/S2-P50) is normally suppressed through the process of sensory gating, these findings suggest impaired sensory gating in TRD. Notably, the TRD and TSD groups were not matched on age. However, multivariate analyses showed no main effect of age. During an auditory oddball paradigm, Qiao et al. (2017) found significantly longer P300 latencies in TRD patients compared to non-TRD patients. The P300 latency is the time required for recognition and the preliminary processing of the stimulus, which thus may be impaired in TRD patients. There was no significant difference in the P300 amplitude between the groups.

4. Discussion

This systematic review aimed to determine the neurobiological differences of TRD compared to non-TRD and TSD. We hypothesized that TRD may be considered a distinct MDD sub-type based on these neurobiological differences. Our main finding is that alterations in the DMN appear to be an important neurobiological feature that differentiates treatment resistance from treatment responsiveness in MDD. Additionally, there is insufficient evidence for structural brain abnormalities specific to treatment resistance, which suggests that TRD may be mostly related to functional abnormalities. Lastly, we found that besides rs-fMRI and sMRI studies, there is a paucity of studies...
Our review indicates that TRD is associated with hypoconnectivity of the DMN. We found decreased FC between different brain regions within the DMN and between DMN regions and other brain areas (i.e., sensory (association) areas and regions within the executive and affective limbic networks). In addition, we found that TRD was associated with hyperactivity in several DMN regions. The opposite effects on connectivity and activity within the DMN seem contradictory at first glance, but may be explained by different cellular mechanisms underlying long-range FC and local neuronal activity. Although there is a wide variety of neurons in the brain, they can be broadly categorized into projection neurons and local interneurons. Whereas projection neurons contain the excitatory neurotransmitter glutamate, local interneurons contain the inhibitory neurotransmitter GABA (Kandel et al., 2013). These neurotransmitter systems may be differentially affected in TRD and may cause different effects on local and long-range connectivity.

In line with our review, a previous systematic review on resting-state fMRI also shows the involvement of the DMN in treatment resistance in MDD (Dichter et al., 2015). However, Dichter et al. (2015) concluded that TRD may be associated with hyperconnectivity of the DMN. A likely explanation for this difference in findings is the number of available rs-fMRI studies in 2015 compared to this review (n = 7 vs. 11). Moreover, we used an interpretation of which brain regions belong to the DMN based on a recent, more comprehensive definition (Alves et al., 2019). According to this interpretation, the results of six out of the seven studies included DMN regions, while according to Dichter et al. (2015), the results of three out of those seven studies included DMN regions. Of note, using a more conservative definition of the DMN in the current review appears to lead to similar results compared to when the more comprehensive definition is used, albeit less cogent.

It has been shown that MDD in general (without distinguishing between non-TRD and TRD) is associated with increased connectivity within the anterior DMN and with increased and decreased connectivity between the anterior and posterior DMN (Mulders et al., 2015). Our review showed an association between TRD and decreased FC between different components of the DMN (Guo et al., 2013b; He et al., 2016; Ma et al., 2012), including between the anterior and posterior DMN (de Kwaasteniet et al., 2015). These findings suggest that although altered connectivity within the DMN may be a neurobiological feature of MDD in general, decreased connectivity within the DMN might specifically be a feature of treatment resistance in MDD. This finding is in line with pharmacotherapy studies showing that lower baseline FC between the posterior and anterior DMN is associated with antidepressant non-response (Andreescu et al., 2013; Goldstein-Piekarski et al., 2018). However, note that these associations of decreased anterior-posterior DMN FC with antidepressant non-response were found in the PCC, whereas the decreased FC found by de Kwaasteniet et al. (2015) in patients with TRD was located in the adjacent cuneus/precuneus and left superior parietal gyrus.

Next to decreased FC within the DMN, treatment resistance is also associated with decreased FC between DMN components and regions outside the DMN. These regions include the motor cortex and sensory (association) areas (Heschl’s gyrus, olfactory cortex, cuneus, STG) (de Kwaasteniet et al., 2015; He et al., 2016; Ma et al., 2012), and regions within the executive and affective limbic networks (de Kwaasteniet et al., 2015; Guo et al., 2013a). These reductions in FC may reflect widespread reduced FC in TRD, but may also be related to specific aberrations in the resting state of MDD. For example, an important symptom of MDD is depressive rumination, which is the repetitive, self-reflective and passive focus on depressive symptomatology and its causes and consequences (Morrow and Nolen-Hoeksema, 1990; Nolen-Hoeksema, 1991). Depressive rumination is thought to have a maladaptive (brooding) and adaptive (reflective pondering) component (Treynor et al., 2003). Adaptive rumination has been shown to be associated with lower levels of depressive symptoms over time compared to maladaptive rumination (Treynor et al., 2003). Dominance of the DMN over the executive network has been linked with higher levels of maladaptive rumination and lower levels of adaptive rumination in MDD (Hamilton et al., 2011). Switching between the DMN and executive network is thought to be regulated by the salience network (Sridharan et al., 2008). Previous research in MDD patients has shown increased FC between the salience network and the anterior/posterior DMN (Manoliu et al., 2014; Mulders et al., 2015) as well as decreased FC between the posterior DMN and the executive network (Manoliu et al., 2014; Mulders et al., 2015; Ye et al., 2012). Our review suggests that these alterations are not only present in the general MDD population, but also specifically in TRD compared to TSD (de Kwaasteniet et al., 2015; Guo et al., 2013a; Lui et al., 2011). Although the number of studies showing these alterations is limited, they suggest that TRD may be associated with impaired salience network mediation of interactions between the DMN and the executive network, which may result in increased and decreased levels of maladaptive and adaptive rumination, respectively.

Decreased FC between the DMN and sensory (association) areas in TRD may reflect impaired integration of sensory information during self-referential processing, in particular sensory information concerning positive life events. According to the two-factor sensitization model proposed by Farb et al. (2015), fixation on negative life events followed by rumination creates abstract dysphoric schemas about one’s self, future and role in the world in MDD. These dysphoric schemas then further enhance fixation on negative life events over positive life events. Whether decreased FC between the DMN and sensory (association) areas in TRD is indeed associated with this process is speculative and further research would have to look into this. However, previous research does show that lower registration of sensory input is positively correlated with depression severity (Serafini et al., 2017) and negative affect (Engel-Yeger and Dunn, 2011), which is a core symptom of MDD. Moreover, the two ERP studies we included in this review also suggest impairments of sensory processing specific to TRD (Qiao et al., 2017; Wang et al., 2009).

In contrast to our finding of hypoconnectivity of the DMN, we additionally found that TRD is associated with hyperactivity in mostly cortical DMN regions (Guo et al., 2012b; Wu et al., 2011; Yamamura et al., 2016; Zhang et al., 2019). This may be related to increased rumination as well. For example, a recent meta-analysis showed consistently increased activity in DMN regions during rumination in healthy individuals (Zhou et al., 2020). Furthermore, several studies show abnormally increased activity in DMN regions during rumination in MDD compared to healthy controls (Burkhouse et al., 2017; Cooney et al., 2010).

Taken together, although different regions within the DMN seem to be hyperactive in TRD, communication within the DMN and between the DMN and other brain areas and networks appears to be reduced. It is thought that the DMN consists of several subsystems involved in different aspects of internal mentation, such as memory-based construction, introspection about mental states, and valuation of personally significant affective information (Andrews-Hanna, 2012). Future research should focus on confirming and clarifying the involvement of the DMN in TRD and how the specific DMN alterations relate to these different aspects of internal mentation and depressive symptoms such as rumination. It is crucial to directly probe these and other psychological processes that are widely implicated in MDD, such as reward and affective processes, in TRD. Unfortunately, to date there are no task-based fMRI studies in TRD to address this.

Aside from alterations of the DMN, the rs-fMRI studies in this review suggest an association between TRD and aberrant occipital lobe activity and FC (de Kwaasteniet et al., 2015; Guo et al., 2012a, b; Guo et al., 2013b; He et al., 2016; Yamamura et al., 2016), which is in line with the systematic review by Dichter et al. (2015). Additionally, lower rCBF and MTR were found in the occipital lobe in TRD compared to TSD by the included ASL and MTR studies (Jia et al., 2017; Lui et al., 2009), and one MRS study additionally showed that OCC GABA levels were reduced in
TRD compared to non-TRD (Price et al., 2009). Significantly reduced OCC GABA levels may pose a risk for selective serotonin reuptake inhibitor (SSRI) non-response, as studies have shown that SSRIs elevate OCC GABA levels (Bhagwagar et al., 2004; Sanacora et al., 2002). The occipital lobe is involved in visual processing (Grill-Spector and Malach, 2004) and although there is considerable evidence for an association between depression and impairments in visual processing (Bubl et al., 2010; de Fockert and Cooper, 2014; Deseilles et al., 2009) and altered OCC activity (Li and Wang, 2020; Liu et al., 2013; Teng et al., 2018), its involvement is not often represented in neural circuitry models of MDD. Our findings suggest that these deviations may play an important role in treatment resistance in MDD, and future research on TRD should specifically focus on this aspect of depression.

This review has several limitations. First, both the number of included studies and the sample sizes of the included studies were small. In addition, several of the included studies made use of the same or partially overlapping samples, indicating that part of the previously reported findings were not independent. Moreover, very few studies could be included for the majority of the neuroimaging modalities, which made it difficult to draw any general conclusions on their outcome measures. For the modalities that were represented relatively well (resting-state fMRI and structural MRI) there was a large variety in outcome measures. Taken together, it is important that the findings in this review are replicated in independent studies with larger sample sizes before their merit can be determined.

Second, several confounding effects could not be taken into account in this review. For example, although TRD was defined in the same manner for the majority of the included studies (failure of two or more antidepressant treatments), the actual number of attempted antidepressant therapies was mostly unknown, as only a few studies reported this. Accordingly, this number could have varied greatly and the possibility that patients with less severe treatment resistance may have their own distinctive neurobiological features compared to more severe treatment resistance cannot be ruled out. Additionally, in the majority of included studies treatment resistance seems to entail antidepressant drug resistance. It is unclear to what extent participants were also resistant to psychotherapy, which may be associated with its own distinctive neurobiological features as well.

Third, it is unclear if part of the findings presented here are the effect of treatment resistance or if they are an effect of longer illness duration, higher depression severity and increased antidepressant medication use. However, these clinical characteristics are inherent to TRD and it would be extremely difficult to control for these confounds. Prospective longitudinal studies, where neuroimaging assessments are performed in MDD patients before and after each treatment attempt, would be the preferred method to study the neurobiological features of TRD. However, this type of design is time consuming and expensive. For other study designs, reporting the level of treatment resistance and other important clinical variables of the study subjects is imperative, as well as taking them into account in the data-analysis.

Lastly, the included studies did not control for psychosocial and socioeconomic differences between the TRD and non-TRD/TSD groups. It is largely unknown what exact role factors such as insecure housing, ongoing abusive relationships, social isolation, or systematic discrimination play in developing treatment resistance in depression. Possibly, different underlying psychosocial and socioeconomic differences might result in different alterations of brain activity and connectivity. This could explain different neurobiological treatments might be needed for different neurobiological profiles in addition to targeted interventions to the psychosocial circumstances. Therefore, in the pursuit of preventing TRD and the development of effective interventions for TRD, it is not only important to study neurobiological brain characteristics of TRD, but also to identify psychosocial and socioeconomic risk factors.

In conclusion, the findings of this review suggest that TRD may be an MDD-subtype with its own characteristic neurobiological features, of which dysfunction of the DMN may be the most notable. However, the question remains whether these impairments are specific to TRD or whether they are a more severe version of the impairments present in the general MDD population. Due to the limitations of the included studies, future research should include prospective longitudinal neuroimaging studies to delineate which effects are present in treatment-naive patients and can therefore be seen as treatment resistance biomarkers, and which effects are the result of disease progression. It would also be of interest to investigate the mechanism that causes unresponsiveness to common antidepressant treatments, as differences between TRD and TSD may either reflect an abnormality in TRD causing unresponsiveness, or a protective feature in TSD causing responsiveness. Eventually, these results might lead to early identification of those with a high risk of treatment resistance to common antidepressant treatment options and the ability to offer them alternative and more effective treatments at an early stage.

Data availability
Data will be made available on request.

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Declaration of Competing Interest
The authors report no declarations of interest.

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Appendix A. Supplementary data
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