Scanning For Depression

The effect of functional connectivity on major depressive disorder treatment choice

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Abstract

Major depressive disorder (MDD) is still not well treatable. Symptoms disappear in only 37% of the patients after a first treatment course, and only 67% of the patients see their symptoms disappear overall. Functional connectivity, defined as the similarity of activation patterns between brain areas, has been shown to be disrupted in MDD patients. The triple network model of dysfunction proposes that in MDD patients, the default mode network (DMN) activity is increased while the activities of the central executive network (CEN) and the salience network (SN) are decreased. These activity changes decrease the functional connectivity between these networks. Yet, as MDD is a very heterogeneous disorder, it is likely different across patients. These differences could tell something about treatment response. Could functional connectivity help select the right medication for the patient? Though, functional connectivity is not able to tell anything about the etiology of the disease in the patient, differences in functional connectivity have been shown to lead to differences in antidepressant response. Due to inconsistencies of functional connectivity, focusing on specific brain areas will not give great predictions regarding treatment response. Recent computational models, however, use functional connectivity to create a "functional connectivity signature" for every patient, and can make moderately well predictions regarding not just treatment response, but also certain risks like suicide risk. Though these predictions still suffer from certain pitfalls, these computational models will likely improve over the years and could become important assets to the clinical practice.

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1. Introduction

1.1 MDD and symptom-clustering

Major depressive disorder (MDD) has been identified as a leading cause of burden (Ferrari et al., 2013). Not only do patients have a high risk of suicide, but they also have a higher risk to suffer from physiological diseases like ischemic heart disease. Unfortunately, there is still not a reliable way to treat MDD. As there are not any objective measures on selecting antidepressants around, clinicians must rely on a "trial-and-error" approach, which is an inefficient approach. Symptoms only disappear in 37% of the patients after a first treatment course. And only 67% of the patients see their symptoms disappear overall (Rush et al., 2006).

A huge problem to the treatment and research on MDD is the heterogeneity of the disorder. Patients not only show a wide range of symptom patterns, but they also show a wide range treatment responses and course trajectories. Based on the symptom patterns, the Diagnostic and Statistical Manual of Mental Disorder (DSM) has recognized several MDD subtypes. However, these subtypes likely cannot explain the varying treatment responses of the patients, as three depression subtypes (melancholic, atypical, and anxious subtypes) have been shown to respond similar to three antidepressants (Arnow et al., 2015). Thus, the subtypes defined by the DSM provide minimal value on the selection of an antidepressant. Dividing MDD differently into subtypes that do respond differently to antidepressants would get rid of the trial-and-error approach and increase the efficiency of MDD treatment.

A popular approach to finding usable MDD subtypes is to collect large amounts of data and then cluster the symptoms and biological variables (Beijers et al., 2019). Only a few subtypes are created of patients with very similar symptoms and biological variables. This method has shown mixed results and has not yet resulted in creating subtypes usable for the clinical practice. One large study using this data-driven clustering by Ten Have et al. (2016) analyzed a sample of 1388 patients and found four subtypes: severe depression with anxiety (28.0%), moderate depression with anxiety (29.3%), moderate depression without anxiety (23.6%), and mild depression (19.0%). The subtypes varied in symptom severity and could be linked to treatment course and eventual outcomes. There were however not many indications that the subtypes had different etiological mechanisms. Just looking at the symptoms of MDD patients thus does not tell enough to know the underlying mechanisms of the disorder. Which makes it difficult to create a therapy based on the data.

1.2 Neuroimaging

Recently, more focus of MDD research has shifted towards neuroimaging. It allows researchers to objectively measure the brain characteristics, instead of having to rely on overt symptoms. This gives more and more reliable information about the brain and could uncover more about the underlying mechanisms of depression.

Much of the research in MDD patients has focused on functional magnetic resonance imaging (fMRI) during the resting-state. This is the state of the brain when the individual is not occupied with a task. The lack of a task is not very demanding for the patient and therefore the resting-state has the clinical advantage of being usable on a diverse patient population (Lee et al., 2013).

Measuring the activation of the brain through neuroimaging could tell something about the functional connectivity between brain areas. Functional connectivity refers to how similar the patterns of activation are between different parts of the brain. For example, brain areas who are part of the same brain network usually have a high functional connectivity between them, as they show similar

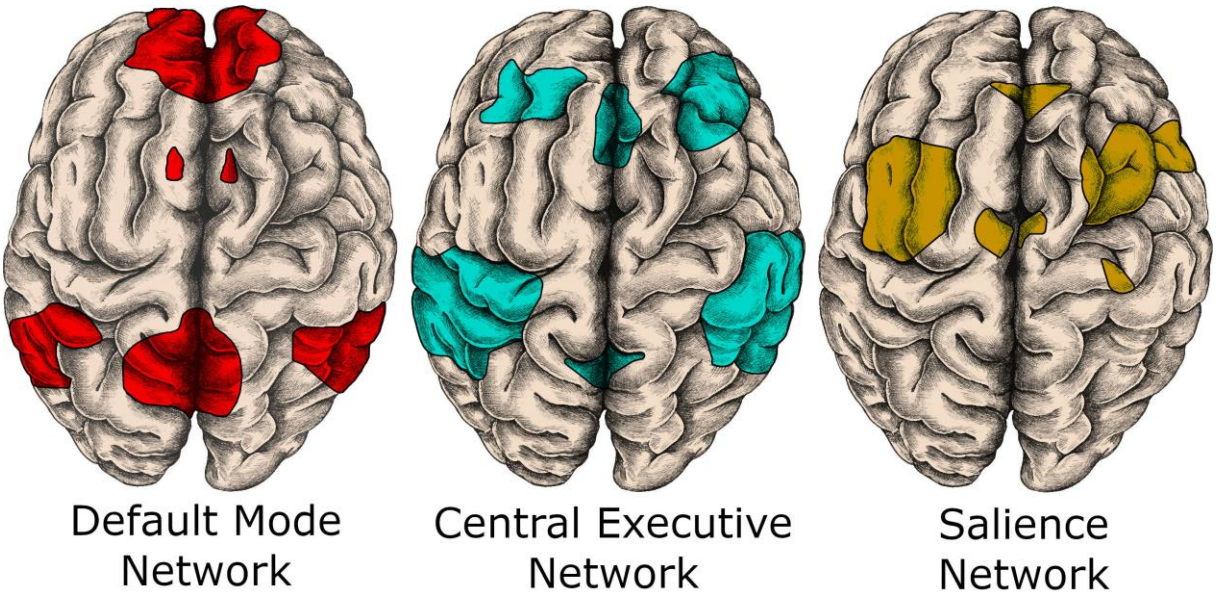

Figure 1: Top view of the three brain networks that are part of the triple network model: default mode network (DMN), central executive network (CEN), salience network (SN). Shown are the areas visible from above. DMN: medial prefrontal cortex (mPFC), angular gyrus, precuneus. CEN: dorsolateral PFC, posterior parietal cortex. SN: anterior cingulate cortex, insular cortex. Brain drawing by: rawpixel.com

activation patterns. Brain networks however have low functional connectivity with brain areas outside of the network, who are likely to show different patterns of activation.

fMRI studies have shown that MDD patients have a functional connectivity dysfunction during the resting-state. This dysfunction is often focused on three brain networks (Figure 1; Menon, 2011). There is the default mode network (DMN), a brain network which gets activated with introspection and during rumination. It comprises largely of the medial prefrontal cortex (mPFC), posterior cingulate cortex (PCC), bilateral inferior parietal cortex, angular gyrus, and the precuneus. The second network, the central executive network (CEN), is associated with working memory and attention. It includes mainly the dorsolateral PFC (dlPFC) and the posterior parietal cortex. And then there is the salience network (SN), which is important for processing salient external inputs. It includes the anterior cingulate cortex (ACC), the insular cortex, and the ventrolateral PFC (Andrews-Hanna et al., 2014). The SN and CEN are both activated during cognitive tasks. Reversely, the DMN is mainly getting activated during the resting-state. This triple network model of dysfunction proposes that depressed individuals tend to show an increased activity in the DMN, while the activity in the SN and CEN are reduced. This increase in DMN activity expresses itself in an increased amount of rumination, while the decrease in CEN activation causes a lower working memory availability and attention.

MDD has shown to affect the functional connectivity of the brain. As overt symptoms fail to provide the information that help predicting the right medication for the patient, it could perhaps be underlying biological mechanisms like functional connectivity that offer better information. Could functional connectivity help to select the right medication for the patient? Given the fact that MDD is a very heterogeneous disorder, this review aims to explore the differences in functional connectivity between MDD patients. Can MDD subtypes be created based on functional connectivity? Could functional connectivity differences have any significant impact on the clinical practice and research?

2. Functional connectivity-based subtyping

A popular approach to explore differences in functional connectivity between MDD patients is comparable to the approach used by the articles that cluster the overt symptoms. Based on data, it is tried to create homogeneous groups, and each of these groups have their own symptoms and treatment outcome. The difference, however, is that with neuroimaging a more objective measure is used that is more related to the underlying biological mechanisms, instead of using symptoms. A popular article using this approach is a work of Drysdale et al. (2017). Based on distinct patterns of dysfunctional connectivity in limbic and frontostriatal networks, Drysdale et al. showed that MDD patients can be clustered into four subtypes. With these subtypes, they could link functional connectivity patterns to symptoms, by showing that the subtypes had distinct clinical-symptom profiles and had responded differently to treatment. For instance, subtype 1 was three times more likely to improve using repetitive transcranial magnetic stimulation (TMS) than subtypes 2 and 4. Furthermore, subtypes 1 and 4 were characterized in part by increased anxiety, and the subtypes 3 and 4 were associated with increased anhedonia and psychomotor retardation.

Though these MDD subtypes are based partly on underlying biological mechanisms, they too are not actual etiological different MDD subtypes. Even when just using the data from Drysdale et al., alternative solutions to the MDD subtyping exist. This suggests that the observed subtypes were not objective measures, but partly created by decisions. This is strengthened by Dinga et al. (2019), who replicated the procedure followed in the Drysdale et al. study. Like the original study, they found high correlations between functional connectivity and clinical symptoms, yet an optimal solution which featured 3 subtypes. And upon further investigation, they found that the same solution could be made if the data would have come from a single Gaussian distribution. This implies that there is still no proof of the existence of distinct functional connectivity based MDD subtypes. And if there are any existing etiological MDD subtypes, they likely cannot be found using functional connectivity pattern differences in resting-state fMRI.

The previous articles linked functional connectivity patterns directly to symptom patterns and treatment outcome, suggesting that symptom patterns could be related to treatment outcome. It could be argued that it would not be possible to create homogeneous groups of patients. A text-mining study of patient narratives found that patients rarely share subjective experiences (Ghosh et al., 2021). 95% of the 228 individuals whose narratives they analyzed, did not have a similar narrative with anyone else in the study. With such a heterogeneous pool, any attempt to group the experiences of patients would struggle to find a convincing typology. Any attempt to place an individual in a particular category group would be repeating the mistakes of the traditional systems. Categorization leads to a substantial loss of information and diagnostic instability.

Even though it will be difficult to create objective homogeneous groups of MDD patients based on functional connectivity, these patterns do have a considerable effect on treatment outcome and symptoms. As mentioned, Drysdale et al. found considerable differences in each of his subtypes that were based on functional connectivity. He found for instance that a reduced connectivity in frontoamygdala networks resulted in increased anxiety. A hyperconnectivity in thalamic and frontostriatal networks were associated with increased anhedonia and psychomotor retardation. There are also considerable differences between MDD patients who have a hyperconnectivity within the DMN and the MDD patients who have a hypoconnectivity within the DMN (Figure 2; Liang et al., 2020).

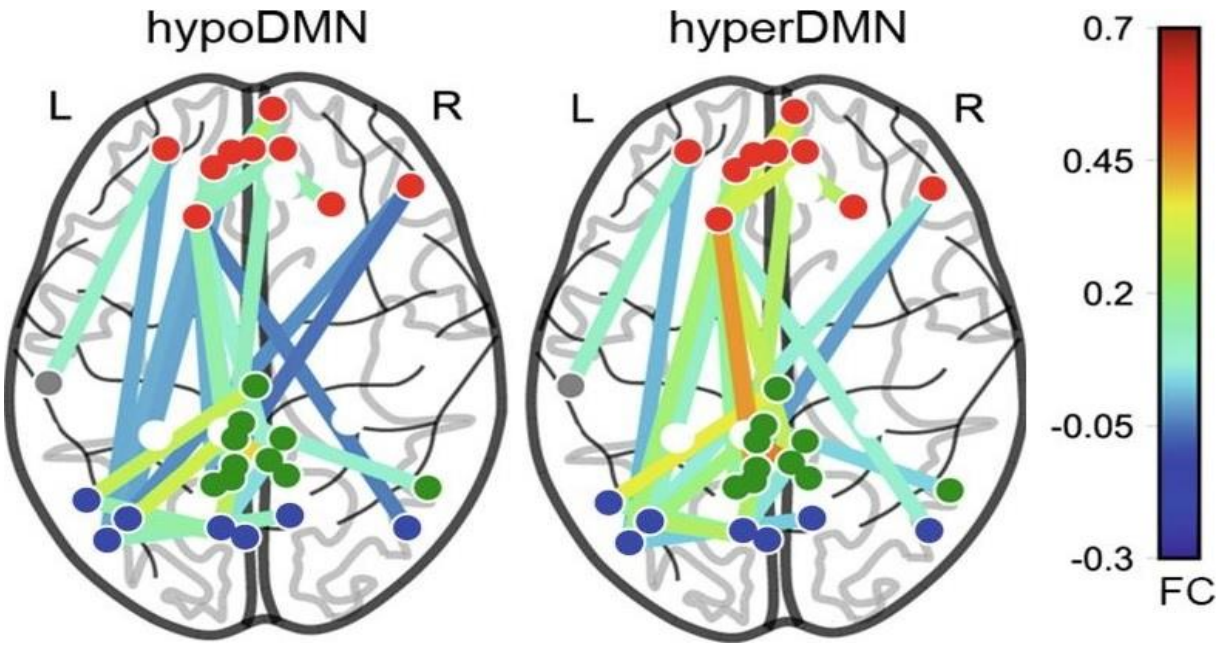

Figure 2: Difference in functional connectivity (FC) between MDD patients with a hypoconnectivity within the DMN (hypoDMN) vs patients with a hyperconnectivity within the DMN (hyperDMN). From: Liang et al. (2020). Red dots represent the frontal regions. Grey dots represent the temporal regions. Blue dots represent the occipital and parietal regions. Green dots are the posterior cingulate cortex (PCC) and the precuneus, both part of the DMN. HyperDMN has increased FC within the DMN, thus the green dots have larger FC between each other than in the hypoDMN group, and the connection between the green dots and the red dots (frontal regions) is larger in the hyperDMN group.

3. Using functional connectivity as a biomarker?

The heterogeneity of MDD has led to slow improvement on MDD research. This has led to the increasingly popularity of personalized medicine the past decade. Personalized medicine targets the individual and tries to improve treatment by integrating data from the person's genetic makeup, epigenetic modifications, clinical symptoms, biomarker changes, and environmental exposures (Ozomaro et al., 2013). Using this approach, one can regard functional connectivity as a biomarker that could help signal whether a treatment option would work on the patient or not.

3.1 functional connectivity DMN

As previously mentioned, the DMN is one of the most mentioned networks that shows a dysfunction in MDD patients. While generally MDD patients seem to show an increased connection within the DMN, there are also MDD patients who show a hypoconnectivity within the DMN. It is generally found in the literature that patients with a DMN hyperconnectivity during the resting-state respond better to antidepressants (Chin Fatt et al., 2020; Korgaonkar et al., 2020). There however have been studies that have gotten different results (Guo et al., 2013; Tokuda et al., 2018). Results are thus not always consistent.

The connectivity of the DMN with other brain regions has also been found to be a potential biomarker for antidepressant response. Treatment responders could be distinguished from non-responders by an increased connectivity between the DMN and the fronto-parietal, somatomotor, visual, limbic,

auditory, and ventral attention network (Korgaonkar et al., 2020). A higher connectivity between the DMN and the CEN also predicted better outcomes to SSRI treatment (Chin Fatt et al., 2020).

fMRI studies that have focused on cognitive and emotional processing give more details on the role of the DMN in MDD patients. Normally, during emotional processing or when performing a demanding cognitive task, the DMN is being deactivated, while CEN and the SN getting activated. However, it has been shown that MDD patients cannot deactivate the DMN well during a cognitive or emotional task (Spies et al., 2017). This deficiency in deactivating the DMN could result in the DMN interfering during the emotional or cognitive task, which results in rumination, or cognitive deficits. Spies et al. found that the MDD patients that were better at deactivating the DMN during an emotional task were also more likely to be responders to SSRI treatment. This same effect can likely be applied to ketamine as well (Figure 3; Stippl et al., 2021), making this effect not specific to a particular antidepressant. The CEN followed an opposite correlation and treatment-sensitive MDD patients had more activation in the dlPFC during emotional working memory tasks than treatment-resistant MDD patients. Thus, MDD patients appear to be less able to control the DMN. They have a lower connectivity than controls during the resting-state when the DMN should be getting activated. And MDD patients are worse than controls at deactivating the DMN during emotional processing or cognitive tasks when the DMN should be getting deactivated. The MDD patients that are better at activating the DMN during the resting-state or deactivating the DMN during a cognitive task seem to respond better to antidepressants. Yet, they seem to be treatment-sensitive in general, and are not sensitive to a particular antidepressant.

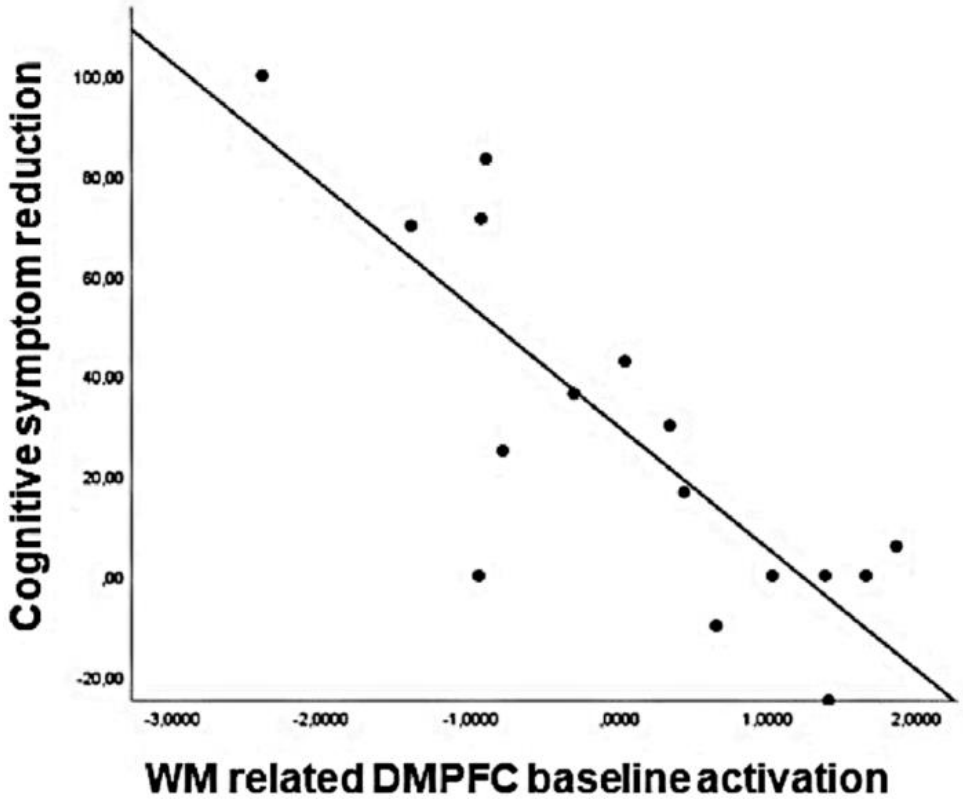

Figure 3: Lower activation of working memory (WM) in dorsomedial prefrontal cortex (DMPFC) at baseline is associated with cognitive symptom reduction after ketamine infusion (Stippl et al., 2021). Each dot represents one subject. The DMPFC is part of the DMN. This graph thus shows that patients who are better at suppressing their DMN during WM, have more symptom reduction after ketamine infusion.

3.2 Effects of antidepressants on functional connectivity

But how exactly do antidepressants affect the functional connectivity? Why do antidepressants improve the symptoms of patients with a hyperconnectivity in the DMN, but work less on patients with a hypoconnectivity? The effect of an SSRI depends on the activation of the serotonin system. The SSRI can increase the activation of the serotonin system by blocking the serotonin transporter (SERT). At an approximately 80% occupancy of the SERT, there is a maximum SSRI effect, and no further improvements can be found even when using higher dosages of SSRI (Ruhé et al., 2009). This effect can also be seen in the functional connectivity. It was found that SSRIs reduce the functional connectivity within the DMN and several other regions which includes the ACC (Table 1; Schrantee et al., 2018). The amount of this reduction in connectivity correlates with the effect of SSRI. Once the SERT has reached an 80% occupancy, the functional connectivity of the DMN cannot be decreased further. This could suggest that MDD patients with a minor increase of DMN functional connectivity would need smaller dosages of SSRI than patients who have a major increase in DMN functional connectivity. Furthermore, as SSRI reduces the DMN functional connectivity, this might explain why the MDD patients who already have a reduction in DMN functional connectivity are less likely to respond to SSRI treatment.

Ketamine is an antidepressant that is effective for patients with treatment resistant MDD. Its mechanism of action is complex and not yet fully understood. One of its actions that is known is that it works as an NMDA receptor antagonist (Zorumski et al., 2016). Its actions are further associated with an increase in glutamate release. Interestingly, there were findings of a reduction of plasma glutamate levels following treatment with SSRI (Küçükibrahimoğlu et al., 2009). Its effect on functional connectivity also seem to differ to the effects seen by SSRIs. There has been reported an increase in functional connectivity within the DMN (Fleming et al., 2019). The functional connectivity was also increased between the DMN and several other brain regions, including the insula and the ACC, regions which are part of the SN. An increase in the SN has shown it can lessen the DMN activity. The connectivity between the dlPFC and the DMN did not change. The insula is part of the SN. This network is important for the integration of external emotional stimuli and regulates the switching between the central executive network and the DMN.

Antidepressants are not limited to pharmacological compounds. Transcranial magnetic stimulation of the dlPFC has emerged as a promising tool for the treatment of MDD and is a useful alternative for patients that do not respond to pharmacotherapy. Instead of using medication, TMS positions a magnetic coil at the head of the patient. This will create an electric current at the specific location of the brain so that nearby nerve cells at the cortical surface become activated. This activation could modulate the functional connectivity within the region that is stimulated, but it can also modulate the functional connectivity of more distant regions. TMS of the dlPFC has been found to normalize hyperconnectivity within the DMN of MDD patients (Table 1; Liston et al., 2014). It further influences the salience network by attenuating a hyperconnectivity of the DMN and CEN with the subgenual anterior cingulate cortex (sgACC). This in turn further helps to improve the interactions and switching between the DMN and CEN. TMS however does not improve any hypoconnectivity within the CEN. Nor is the connectivity between the dlPFC and the CEN or DMN related to treatment response.

Liston et al. further found that a sgACC hyperconnection with the DMN and CEN predicts treatment effect. Another study further elaborated on this using TMS on different sites within the dlPFC and found that these different sites yield different responses (Weigand et al., 2018). A larger hyperconnection between the TMS site and the sgACC predicted better clinical outcomes in individual patients. A larger hyperconnection in a patient also predicted a better antidepressant response.

Table 1: The main findings for the effects of each antidepressant on the functional connectivity.

SSRI	Ketamine	TMS
Decreases functional connectivity within DMN (Schrantee et al., 2018)	Increases functional connectivity within the DMN (Fleming et al., 2019)	SgACC connectivity with DMN and CEN predicts treatment effect (Liston et al., 2014)
Decreases functional connectivity between DMN and ACC (salience network) (Schrantee et al., 2018).	Increases functional connectivity between DMN and ACC, and between DMN and insular cortex (salience network) (Fleming et al., 2019)	Larger connection between TMS site of stimulation and sgACC predicted better outcome (Weigand et al., 2018).
Significant increase in dlPFC and mPFC activity (Cheng et al., 2016)	No changes in dlPFC connectivity with DMN (Fleming et al., 2019)	Normalizes hyperconnectivity within DMN (Liston et al., 2014)

3.3 Inconsistency

Antidepressants thus have a considerable effect on the functional connectivity of both MDD patients and healthy individuals. This raises the question whether the differences in functional connectivity that are being seen in MDD patients can partially be attributed to antidepressants. A recent clinical trial investigated this and followed 41 first-episode drug-naïve MDD patients for 8 weeks that were either given an SSRI (escitalopram) or a serotonin-norepinephrine reuptake inhibitor (SNRI; duloxetine) during the clinical trial (Figure 4; Li et al., 2021). At baseline and after treatment, their functional connectivity was compared with the functional connectivity of healthy controls. Interestingly and controversially, the functional connectivity at baseline was not significantly different between the MDD patients and the healthy controls. As expected however, the functional connectivity of the MDD patients did decrease after 8 weeks of SSRI treatment, affecting almost all brain networks. Antidepressants thus did not normalize the functional connectivity of the patients, rather it pushed the functional connectivity to abnormal levels.

Researchers should therefore be careful making conclusions on functional connectivity that is based on data from MDD patients who have had prior antidepressant treatment. It is still unknown how much their functional connectivity is altered by previous antidepressant use. Many articles discussed in the current review however have used patients that were either treatment-naïve or had not received treatment for several months and these articles did find differences between healthy controls and MDD patients at baseline. The differences between healthy controls and MDD patients is thus inconclusive and inconsistent. This could have several explanations. Firstly, as mentioned MDD is a very heterogeneous disorder. As every article uses a different set of MDD patients, the sets themselves could be very different, resulting in very different results. Secondly, the set-up of the experiments tends to vary a lot. Not only is there an inconsistency regarding the brain regions that are looked upon, but there are also location differences within a brain region. Also, what brain regions are part of what brain network tend to vary with each article. As functional connectivity seems very reactive, small

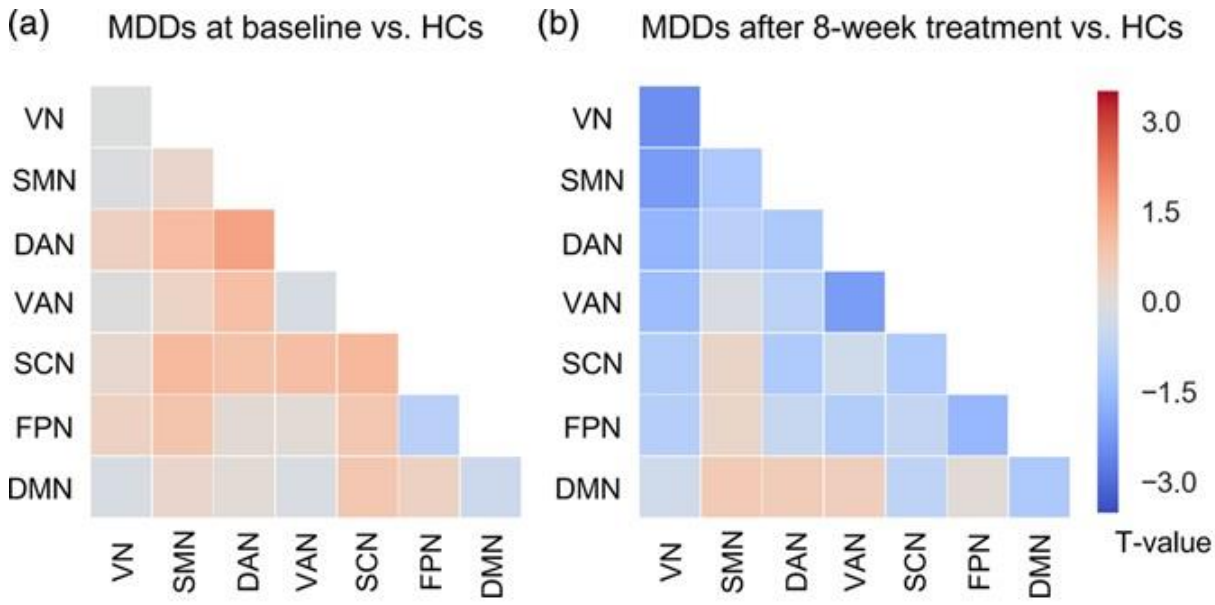

Figure 4: Heatmap showing the differences in functional connectivity between MDD patients and healthy controls on (a) baseline and (b) after an 8-week treatment with SSRI or SNRI (Li et al., 2021). Li et al. did not find significant differences between HC and MDD at baseline. After 8 weeks of treatment, the functional connectivity of the MDD patients were significantly lowered. VN = visual network, SMN = somatosensory-motor network, DAN = dorsal attention network, VAN = ventral attention network, SCN = subcortical network, FPN = frontoparietal network, DMN = default mode network

changes in set-up could have large effects on the outcomes. Thirdly, fMRI tend to vary at every location. These locational differences could have a large effect on the outcomes. Despite all the inconsistencies, many articles have shown that patients that are sensitive to a particular treatment, have a different functional connectivity than the patients that are resistant to the treatment. And though inconsistent, patients reacting to different treatment seem to have small differences in their functional connectivity. Would it be able to determine what patient should receive what treatment?

4. Predicting antidepressant treatment?

Research on each antidepressant seems to focus on a certain biomarker that is characteristic for the antidepressant. Research on SSRIs are focusing on an increase of the functional connectivity with or within the DMN in MDD patients. Research on ketamine focuses on an increase of the functional connectivity in the insula or the salience network. The focus of TMS research is mainly on the connectivity between the dlPFC and the sgACC. But how characteristic are these biomarkers for each of these antidepressants? Or do patients who respond to SSRIs share the same functional connectivity with the patients who respond to ketamine? Is it possible to use functional connectivity to distinguish patients based on which treatment they are likely to respond to?

For example, a hyperconnection between the dlPFC and sgACC seems to predict TMS response in medication treatment resistant MDD patients. And though a hyperconnection between the dlPFC and sgACC is mainly investigated in the context of TMS, the few articles that have focused on pharmaceutical compounds seem to suggest that this connection could also signal a sensitivity towards pharmacological treatment in treatment-naive patients. With magnetoencephalography (MEG) it was found that the functional connectivity between the dlPFC and the sgACC is useful to predict

pharmaceutical treatment outcome (Wang et al., 2019). A higher α band of the dlPFC-sgACC connection was associated with less severe depressive symptoms and a better treatment outcome. α band connectivity was also associated with rumination, a symptom that is also seen with increased DMN activation. This could suggest that the patients with an increased α band connectivity would also likely have an increased functional connectivity within the DMN, which was also associated with an increased response to SSRIs. More support for the involvement of the serotonin system in the dlPFC-sgACC connection has been shown using the SERT binding rate. SERT can decrease postsynaptic serotonin levels. Lower serotonin levels have been found to increase neuronal activation (Morris et al., 1999). It was found that the MDD patients that responded well to SSRI treatment had a higher SERT binding in the sgACC (Lanzenberger et al., 2012). And thus, have lower serotonin levels, and therefore likely an increase in neuronal activation of the sgACC.

Another study tested the dlPFC activity during cognitive tasks (Fales et al., 2009). Increasing the dlPFC activity is one of the main points of TMS treatment. During cognitive tasks, MDD patients show reduced activity in the dlPFC. Fales et al. found that SSRI treatment significantly increased the dlPFC activity during cognitive tasks. The dlPFC activity is thus not just affected by TMS treatment but could also be affected by pharmacological treatment.

4.1 Computational models

A couple of the main characteristics of TMS treatment are thus also being seen with SSRI treatment. Focusing on a particular brain area or connection would probably not give enough information to differentiate between treatment. To find differences, it would likely require investigating many regions.

Recently, an increasing amount of research have used computational models that use machine-learning algorithms to predict treatment response. Machine-learning algorithms have become an important topic in computer science, and they are increasingly being used in other fields. Machine-learning algorithms are programmed to analyze any data that it is being given, and change its behavior based on the data that has been analyzed. They could for instance be used for email filtering, where the algorithm could learn which emails to filter out based on experience. Machine-learning algorithms could potentially be used to predict treatment response in MDD patients by comparing a patient his data to all the previous data that is collected (Figure 5). Such an algorithm could thus become more precise when given more experience.

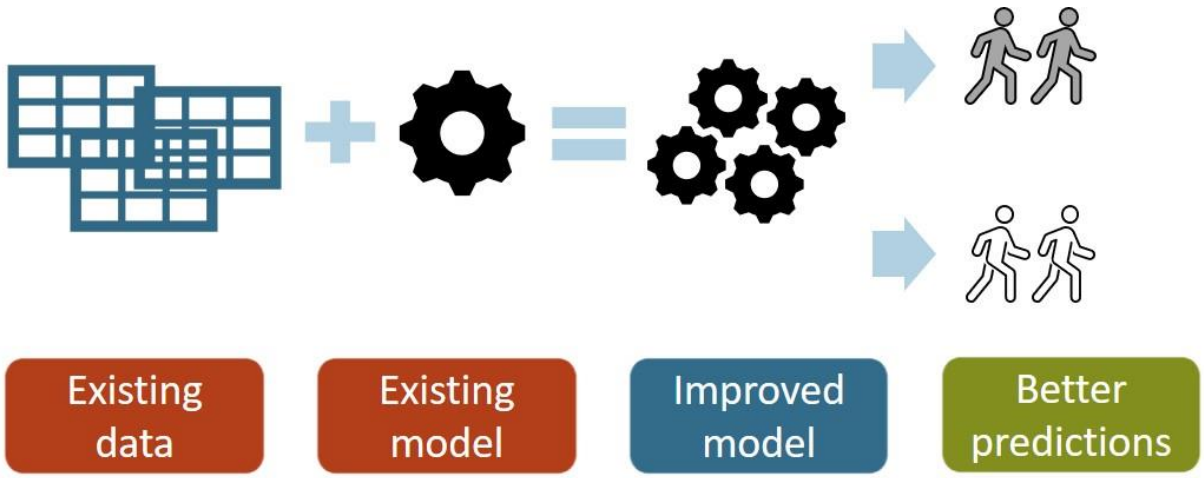

Figure 5: Basic representation how machine learning increases prediction accuracy. Existing data is being fed to a machine learning model. The model will process the data and change its behavior based

on the data. This means that the more data is being fed to the model, the more the model can change its behavior, and the more it can improve its algorithm. This improved model will in turn thus be able to make better predictions.

Using computational models to determine what antidepressant would likely be helpful for the patient allows to combine the information of many brain regions, instead of only using the information of a select few regions. Further, grouping patients into groups that are sensitive to a specific antidepressant allows to choose the antidepressant that is likely the right kind. It might group patients together who could be etiological different, but that might not matter as they both are likely to respond to the selected antidepressant.

As computational models are relatively new, their approach vary significantly between each other. Some articles used solely fMRI to predict treatment, whereas other articles did not use any fMRI measurements to predict treatment. However, many of these articles found some degree of success, independent of their choice of methods. Zhang et al. (2020) used functional connectivity patterns within the CEN and the DMN as the basis of their algorithm, using a method called power envelope connectivity (PEC), which is based on resting-state MEG data. They trained their algorithm of three datasets and tested it on the fourth. They found that the MDD patients whose functional connectivity differed most from the controls were less likely to respond to antidepressant medication, yet they were just as likely to respond to TMS. This suggests that the algorithm could improve the choice of antidepressant for the patient.

Using another algorithm, the same group could predict whether the symptoms of patients would improve with sertraline (Wu et al., 2020). This time, the algorithm was based on resting-state EEG data, where each patient got its own EEG signature. Like Wang et al. (2019), Wu et al. found that the α frequency was an important indicator of treatment response. A greater α wave was indicative for a better outcome. A higher α wave could suggest that the patients who responded better have a higher dlPFC activity. This however does not influence the severity of the MDD. The prediction of the model was not related to the severity of the disease. Patients that were less likely to respond to sertraline, were more likely to respond to rTMS of the dlPFC.

(Xue et al., 2021) used diffusion tensor imaging (DTI) of 90 cortical and subcortical regions for its computational model. DTI is an MRI technique that measures the connectivity within white matter tracts and uses the diffusion of water molecules to create the images. It is not a much-researched technique in MDD research, but it has shown to be able to predict antidepressant response (Korgaonkar et al., 2014). Xue et al. went a step further and designed their model to use DTI to discriminate SSRI responders from serotonin norepinephrine reuptake inhibitors (SNRI) responders. Their model had a 70% success rate in an out-of-sample test site. Two neural networks were especially important in discriminating the treatment choice. The emotion regulation circuit, centered on the hippocampus and the amygdala, was important for determining the efficacy of SSRI treatment. The emotion regulation circuit and the reward circuit, especially the putamen and the superior frontal gyrus, were important for determining the efficacy of SNRI treatment.

Computational models and functional connectivity could potentially be used on areas other than treatment response. They could for instance predict the likelihood of certain risk factors. (Dai et al., 2020) found that their computational model, which was based on fMRI, correlated with the suicide risk determined by the Nurses' Global Assessment of Suicide Risk. This proves that it is possible to rate suicide risk using functional connectivity. It could be applied as an objective measure where otherwise

a clinician could only depend on subjective factors. Improvements to computation models in the future could make them even more reliable and add critical information to a clinical diagnosis.

4.2 Pitfalls

Computational models are still a relatively new subject in MDD research, and they are bound to have pitfalls still. A big pitfall currently is the big variance between imaging sites. Functional connectivity is very depended on the imaging site, which makes it difficult to create computational models that are very accurate on multiple sites. For clinical application, it would be necessary that the differences between imaging sites will be minimized. These site differences are caused by measurement biases due to differences in fMRI protocols and magnetic resonance (MR) scanners. They are also caused by a sampling bias simply due to a different population (Yamashita et al., 2020). Yamashita et al. tried to correct for these differences by measuring the differences on each site and use these to correct their fMRI results. To harmonize the imaging sites, they used so called traveling subjects, healthy controls who perform an MRI at the different sites. Based on these measurements, an algorithm can be written, and differences can be minimized. When Yamashita et al. used this algorithm on an independent imaging site without any traveling subjects, the algorithm could distinguish MDD patients from healthy controls with an accuracy of 69%. The algorithm thus does work moderately well, but accuracy could still be improved. Both better methods to decrease site biases need to be made, as improvements to the machine learning algorithms.

5. Discussion

The functional connectivity of a patient thus has a considerable effect on symptoms and treatment outcome. However, it is unlikely it could uncover the etiology of the depression of a patient, and it is unlikely it could uncover any possible etiological MDD subtypes. It seems functional connectivity is not so much a source of depression, rather a symptom.

Even so, differences between patients in functional connectivity have uncovered that functional connectivity could be used to tell whether a patient is treatment-sensitive or whether the patient is treatment-resistant to a specific antidepressant treatment. What these differences however are exactly, is very inconsistent and seems to be relying on the testing site as well as on the MDD testing population.

To be able to improve treatment choice in MDD patients, it should also be known what antidepressant would work on the patient, something that is not possible now in clinical practice. By looking at several studies, patients who respond to different antidepressants also seem to have a different functional connectivity. Yet, these results are also inconsistent, and often not enough is known on the functional connectivity across the brain, as many articles on a specific antidepressant tend to research the same regions. For instance, research on SSRIs is focusing on changes in the DMN, while research on TMS is focusing on changes in the dlPFC-sgACC connection. But SSRIs have likely also been shown to influence the dlPFC-sgACC connection, making it difficult for this connection to be used as a biomarker. It is therefore important that not one of several regions is looked at, but a wide area is being researched.

This could be possible using computational models. Recent literature on computational models suggests that by just looking at functional connectivity, some predictions can be made about whether a patient would be able to respond to a particular antidepressant. They could suggest even what antidepressant medication might be more suitable. Now, many different algorithms and imaging techniques are being tried out with computational models with all having some sort of success. Yet, as functional connectivity tends to be very inconsistent across sites, it is still difficult to make consistent predictions about antidepressant sensitivity across sites.

Despite functional connectivity being inconsistent across sites, it seems that computational models can already predict antidepressant treatment well with just using functional connectivity. To make these models usable for clinical practice, these models just need to become more reliable. These could be done by increasing the functional connectivity reliability across different sites. The algorithms and the usage of imaging techniques could still also be improved. Future studies could also look at combining functional connectivity with other symptoms to improve the predictions, something that has not been done much yet. These seem to be two different fields now but combining the data would increase the information and therefore likely increase the prediction quality. Once reliable, these computational models could significantly impact the choice for treatment and would be a better option than the contemporary trial-and-error method.

6. Bibliography

Andrews-Hanna, J. R., Smallwood, J., & Spreng, R. N. (2014). The default network and self-generated thought: component processes, dynamic control, and clinical relevance. *Annals of the New York Academy of Sciences*, *1316*(1), 29–52. https://doi.org/10.1111/nyas.12360

Arnow, B. A., Blasey, C., Williams, L. M., Palmer, D. M., Rekshan, W., Schatzberg, A. F., Etkin, A., Kulkarni, J., Luther, J. F., & Rush, A. J. (2015). Depression subtypes in predicting antidepressant response: A report from the iSPOT-D trial. *American Journal of Psychiatry*, *172*(8), 743–750. https://doi.org/10.1176/appi.ajp.2015.14020181

Beijers, L., Wardenaar, K. J., van Loo, H. M., & Schoevers, R. A. (2019). Data-driven biological subtypes of depression: systematic review of biological approaches to depression subtyping. *Molecular Psychiatry*. https://doi.org/10.1038/s41380-019-0385-5

Cheng, Y., Xu, J., Arnone, D., Nie, B., Yu, H., Jiang, H., Bai, Y., Luo, C., Campbell, R. A. A., Shan, B., Xu, L., & Xu, X. (2016). Resting-state brain alteration after a single dose of SSRI administration predicts 8-week remission of patients with major depressive disorder. *Psychological Medicine*, *47*(3), 438–450. https://doi.org/10.1017/S0033291716002440

Chin Fatt, C. R., Jha, M. K., Cooper, C. M., Fonzo, G., South, C., Grannemann, B., Carmody, T., Greer, T. L., Kurian, B., Fava, M., McGrath, P. J., Adams, P., McInnis, M., Parsey, R. V., Weissman, M., Phillips, M. L., Etkin, A., & Trivedi, M. H. (2020). Effect of intrinsic patterns of functional brain connectivity in moderating antidepressant. *American Journal of Psychiatry*, *177*(2), 143–154. https://doi.org/10.1176/APPI.AJP.2019.18070870

Dai, Z., Shen, X., Tian, S., Yan, R., Wang, H., Wang, X., Yao, Z. J., & Lu, Q. (2020). Gradually evaluating of suicidal risk in depression by semi-supervised cluster analysis on resting-state fMRI. *Brain Imaging and Behavior*, 1–10. https://doi.org/10.1007/s11682-020-00410-7

Dinga, R., Schmaal, L., Penninx, B. W. J. H., van Tol, M. J., Veltman, D. J., van Velzen, L., Mennes, M., van der Wee, N. J. A., & Marquand, A. F. (2019). Evaluating the evidence for biotypes of depression: Methodological replication and extension of Drysdale et al. (2017). *NeuroImage: Clinical*, *22*, 101796. https://doi.org/10.1016/j.nicl.2019.101796

Drysdale, A. T., Grosenick, L., Downar, J., Dunlop, K., Mansouri, F., Meng, Y., Fetcho, R. N., Zebley, B., Oathes, D. J., Etkin, A., Schatzberg, A. F., Sudheimer, K., Keller, J., Mayberg, H. S., Gunning, F. M., Alexopoulos, G. S., Fox, M. D., Pascual-Leone, A., Voss, H. U., … Liston, C. (2017). Resting-state

connectivity biomarkers define neurophysiological subtypes of depression. *Nature Medicine*, *23*(1), 28–38. https://doi.org/10.1038/nm.4246

Fales, C. L., Barch, D. M., Rundle, M. M., Mintun, M. A., Mathews, J., Snyder, A. Z., & Sheline, Y. I. (2009). Antidepressant treatment normalizes hypoactivity in dorsolateral prefrontal cortex during emotional interference processing in major depression. *Journal of Affective Disorders*, *112*(1–3), 206–211. https://doi.org/10.1016/j.jad.2008.04.027

Ferrari, A. J., Charlson, F. J., Norman, R. E., Patten, S. B., Freedman, G., Murray, C. J. L., Vos, T., & Whiteford, H. A. (2013). Burden of Depressive Disorders by Country, Sex, Age, and Year: Findings from the Global Burden of Disease Study 2010. *PLoS Medicine*, *10*(11), e1001547. https://doi.org/10.1371/journal.pmed.1001547

Fleming, L. M., Javitt, D. C., Carter, C. S., Kantrowitz, J. T., Girgis, R. R., Kegeles, L. S., Ragland, J. D., Maddock, R. J., Lesh, T. A., Tanase, C., Robinson, J., Potter, W. Z., Carlson, M., Wall, M. M., Choo, T. H., Grinband, J., Lieberman, J., Krystal, J. H., & Corlett, P. R. (2019). A multicenter study of ketamine effects on functional connectivity: Large scale network relationships, hubs and symptom mechanisms. *NeuroImage: Clinical*, *22*, 101739. https://doi.org/10.1016/j.nicl.2019.101739

Ghosh, C. C., McVicar, D., Davidson, G., & Shannon, C. (2021). Measuring diagnostic heterogeneity using text-mining of the lived experiences of patients. *BMC Psychiatry*. https://doi.org/10.1186/s12888-021-03044-1

Guo, W., Liu, F., Xue, Z., Gao, K., Liu, Z., Xiao, C., Chen, H., & Zhao, J. (2013). Abnormal resting-state cerebellar-cerebral functional connectivity in treatment-resistant depression and treatment sensitive depression. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *44*, 51–57. https://doi.org/10.1016/j.pnpbp.2013.01.010

Korgaonkar, M. S., Fornito, A., Williams, L. M., & Grieve, S. M. (2014). Abnormal structural networks characterize major depressive disorder: A connectome analysis. *Biological Psychiatry*, *76*(7), 567–574. https://doi.org/10.1016/j.biopsych.2014.02.018

Korgaonkar, M. S., Goldstein-Piekarski, A. N., Fornito, A., & Williams, L. M. (2020). Intrinsic connectomes are a predictive biomarker of remission in major depressive disorder. *Molecular Psychiatry*, *25*(7), 1537–1549. https://doi.org/10.1038/s41380-019-0574-2

Küçükibrahimoğlu, E., Saygın, M. Z., Çalışkan, M., Kaplan, O. K., Ünsal, C., & Gören, M. Z. (2009). The change in plasma GABA, glutamine and glutamate levels in fluoxetine- Or S-citalopram-treated female patients with major depression. *European Journal of Clinical Pharmacology*, *65*(6), 571–577. https://doi.org/10.1007/s00228-009-0650-7

Lanzenberger, R., Kranz, G. S., Haeusler, D., Akimova, E., Savli, M., Hahn, A., Mitterhauser, M., Spindelegger, C., Philippe, C., Fink, M., Wadsak, W., Karanikas, G., & Kasper, S. (2012). Prediction of SSRI treatment response in major depression based on serotonin transporter interplay between median raphe nucleus and projection areas. *NeuroImage*, *63*(2), 874–881. https://doi.org/10.1016/j.neuroimage.2012.07.023

Lee, M. H., Smyser, C. D., & Shimony, J. S. (2013). Resting-state fMRI: A review of methods and clinical applications. *American Journal of Neuroradiology*, *34*(10), 1866–1872. https://doi.org/10.3174/ajnr.A3263

Li, L., Su, Y., Wu, Y., Castellanos, F. X., Li, K., Li, J., Si, T., & Yan, C. (2021). Eight-week antidepressant treatment reduces functional connectivity in first-episode drug-naïve patients with major depressive disorder. *Human Brain Mapping*, hbm.25391. https://doi.org/10.1002/hbm.25391

Liang, S., Deng, W., Li, X., Greenshaw, A. J., Wang, Q., Li, M., Ma, X., Bai, T. J., Bo, Q. J., Cao, J., Chen, G. M., Chen, W., Cheng, C., Cheng, Y. Q., Cui, X. L., Duan, J., Fang, Y. R., Gong, Q. Y., Guo, W. Bin, … Li, T. (2020). Biotypes of major depressive disorder: Neuroimaging evidence from resting-state default mode network patterns. *NeuroImage: Clinical*, *28*, 102514. https://doi.org/10.1016/j.nicl.2020.102514

Liston, C., Chen, A. C., Zebley, B. D., Drysdale, A. T., Gordon, R., Leuchter, B., Voss, H. U., Casey, B. J., Etkin, A., & Dubin, M. J. (2014). Default mode network mechanisms of transcranial magnetic stimulation in depression. *Biological Psychiatry*, *76*(7), 517–526. https://doi.org/10.1016/j.biopsych.2014.01.023

Menon, V. (2011). Large-scale brain networks and psychopathology: A unifying triple network model. In *Trends in Cognitive Sciences* (Vol. 15, Issue 10, pp. 483–506). Trends Cogn Sci. https://doi.org/10.1016/j.tics.2011.08.003

Morris, J. S., Smith, K. A., Cowen, P. J., Friston, K. J., & Dolan, R. J. (1999). Covariation of activity in habenula and dorsal raphe nuclei following tryptophan depletion. *NeuroImage*, *10*(2), 163–172. https://doi.org/10.1006/nimg.1999.0455

Ozomaro, U., Nemeroff, C. B., & Wahlestedt, C. (2013). Personalized medicine and psychiatry: dream or reality? *Psychiatric Times*, *30*(10), 26–26. https://go-gale-com.proxy-ub.rug.nl/ps/i.do?p=AONE&sw=w&issn=08932905&v=2.1&it=r&id=GALE%7CA344603303&sid=googleScholar&linkaccess=fulltext

Rush, A. J., Trivedi, M. H., Wisniewski, S. R., Nierenberg, A. A., Stewart, J. W., Warden, D., Niederehe, G., Thase, M. E., Lavori, P. W., Lebowitz, B. D., McGrath, P. J., Rosenbaum, J. F., Sackeim, H. A., Kupfer, D. J., Luther, J., & Fava, M. (2006). Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: A STAR*D report. *American Journal of Psychiatry*, *163*(11), 1905–1917. https://doi.org/10.1176/ajp.2006.163.11.1905

Schrantee, A., Lucassen, P. J., Booij, J., & Reneman, L. (2018). Serotonin transporter occupancy by the SSRI citalopram predicts default-mode network connectivity. *European Neuropsychopharmacology*, *28*(10), 1173–1179. https://doi.org/10.1016/j.euroneuro.2018.07.099

Spies, M., Kraus, C., Geissberger, N., Auer, B., Klöbl, M., Tik, M., Störkat, I. L., Hahn, A., Woletz, M., Pfabigan, D. M., Kasper, S., Lamm, C., Windischberger, C., & Lanzenberger, R. (2017). Default mode network deactivation during emotion processing predicts early antidepressant response. *Translational Psychiatry*, *7*(1), e1008–e1008. https://doi.org/10.1038/tp.2016.265

Stippl, A., Scheidegger, M., Aust, S., Herrera, A., Bajbouj, M., Gärtner, M., & Grimm, S. (2021). Ketamine specifically reduces cognitive symptoms in depressed patients: An investigation of associated neural activation patterns. *Journal of Psychiatric Research*, *136*, 402–408. https://doi.org/10.1016/j.jpsychires.2021.02.028

Ten Have, M., Lamers, F., Wardenaar, K., Beekman, A., De Jonge, P., Van Dorsselaer, S., Tuithof, M., Kleinjan, M., & De Graaf, R. (2016). The identification of symptom-based subtypes of depression:

A nationally representative cohort study. *Journal of Affective Disorders*, *190*, 395–406. https://doi.org/10.1016/j.jad.2015.10.040

Tokuda, T., Yoshimoto, J., Shimizu, Y., Okada, G., Takamura, M., Okamoto, Y., Yamawaki, S., & Doya, K. (2018). Identification of depression subtypes and relevant brain regions using a data-driven approach. *Scientific Reports*. https://doi.org/10.1038/s41598-018-32521-z

van Loo, H. M., de Jonge, P., Romeijn, J. W., Kessler, R. C., & Schoevers, R. A. (2012). Data-driven subtypes of major depressive disorder: A systematic review. *BMC Medicine*, *10*(1), 156. https://doi.org/10.1186/1741-7015-10-156

Wang, Q., Tian, S., Tang, H., Liu, X., Yan, R., Hua, L., Shi, J., Chen, Y., Zhu, R., Lu, Q., & Yao, Z. (2019). Identification of major depressive disorder and prediction of treatment response using functional connectivity between the prefrontal cortices and subgenual anterior cingulate: A real-world study. *Journal of Affective Disorders*, *252*, 365–372. https://doi.org/10.1016/j.jad.2019.04.046

Weigand, A., Horn, A., Caballero, R., Cooke, D., Stern, A. P., Taylor, S. F., Press, D., Pascual-Leone, A., & Fox, M. D. (2018). Prospective Validation That Subgenual Connectivity Predicts Antidepressant Efficacy of Transcranial Magnetic Stimulation Sites. *Biological Psychiatry*, *84*(1), 28–37. https://doi.org/10.1016/j.biopsych.2017.10.028

Wu, W., Zhang, Y., Jiang, J., Lucas, M. V., Fonzo, G. A., Rolle, C. E., Cooper, C., Chin-Fatt, C., Krepel, N., Cornelssen, C. A., Wright, R., Toll, R. T., Trivedi, H. M., Monuszko, K., Caudle, T. L., Sarhadi, K., Jha, M. K., Trombello, J. M., Deckersbach, T., … Etkin, A. (2020). An electroencephalographic signature predicts antidepressant response in major depression. *Nature Biotechnology*. https://doi.org/10.1038/s41587-019-0397-3

Xue, L., Pei, C., Wang, X., Wang, H., Tian, S., Yao, Z., & Lu, Q. (2021). Predicting Neuroimaging Biomarkers for Antidepressant Selection in Early Treatment of Depression. *Journal of Magnetic Resonance Imaging*, jmri.27577. https://doi.org/10.1002/jmri.27577

Yamashita, A., Sakai, Y., Yamada, T., Yahata, N., Kunimatsu, A., Okada, N., Itahashi, T., Hashimoto, R., Mizuta, H., Ichikawa, N., Takamura, M., Okada, G., Yamagata, H., Harada, K., Matsuo, K., Tanaka, S. C., Kawato, M., Kasai, K., Kato, N., … Imamizu, H. (2020). Common brain networks between major depressive disorder and symptoms of depression that are validated for independent cohorts. *BioRxiv*, 2020.04.22.056432. https://doi.org/10.1101/2020.04.22.056432

Zhang, Y., Wu, W., Toll, R. T., Naparstek, S., Maron-Katz, A., Watts, M., Gordon, J., Jeong, J., Astolfi, L., Shpigel, E., Longwell, P., Sarhadi, K., El-Said, D., Li, Y., Cooper, C., Chin-Fatt, C., Arns, M., Goodkind, M. S., Trivedi, M. H., … Etkin, A. (2020). Identification of psychiatric disorder subtypes from functional connectivity patterns in resting-state electroencephalography. *Nature Biomedical Engineering*, 1–15. https://doi.org/10.1038/s41551-020-00614-8

Zorumski, C. F., Izumi, Y., & Mennerick, S. (2016). Ketamine: NMDA receptors and beyond. *Journal of Neuroscience*, *36*(44), 11158–11164. https://doi.org/10.1523/JNEUROSCI.1547-16.2016