Learning from reward and prediction

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General discussion

Chapter 07

Summary of main findings

This dissertation aimed to contribute to knowledge regarding: (1) reward-related impairments in acute and remitted (recurrent) MDD, and (2) the predictive properties of clinical tools and neuroimaging to predict insufficient response to treatment. As described in the introduction, we differentiated five stages of illness development and severity in MDD: (i) the prodromal, or at risk stage, (ii) the first depressive episode, (iii) residual symptoms following an episode, (iv) the occurrence of relapses and (v) a stage of chronic and/or treatment-resistant depression (Peeters et al., 2012). This dissertation focused on acute MDD (stage ii/iv/v) and remitted recurrent MDD (stage iii).

Both for scientific and for clinical purposes, developing a better understanding why people who suffer from MDD do not respond to treatment, why depressive episodes tend to relapse or recur and how to predict these two major issues are highly relevant. Prevention of non-response and recurrence through knowledge of underlying etiopathogenetic mechanisms will help clinicians to improve treatment strategies and relieve the burden of MDD for patients, relatives and society. Moreover, identifying distinct profiles of depressive symptomatology or underlying etiological mechanisms, called profiling, can be helpful in prediction of course and treatment.

In this chapter we will first summarize the main findings of this dissertation, followed by an interpretation of our findings. Thereafter, methodological considerations will be discussed and finally, clinical implications and future perspectives will be given.

Part I: pathophysiological mechanism behind reward processing and reward-related learning

Although still under development, computational approaches of brain processes can represent the complexity of the brain better than just activity during certain tasks. This especially holds for reward and aversive processing and adjustment of behavior (i.e. learning) by positive/aversive events. The first part of this dissertation focused on pathophysiological mechanism behind basic reward processing and reward- and aversive related learning in (recurrent) depression, by applying computational approaches.

MDD is characterized by impaired reward circuitry connectivity during reward anticipation
In the first study (chapter 2) we explored whether alterations in connectivity between elements of the reward circuitry can be linked to acute MDD. We explored this because, despite promising findings regarding the involvement of individual brain areas in basic reward processing, it remains largely unexplored how circuitry alterations are involved in the complex characteristics of MDD. We demonstrated that MDD is indeed characterized by alterations in reward circuit connectivity rather than isolated activation impairments in brain areas underlying the reward-system. We found decreased connectivity between the VS and frontal brain areas (ACC, mPFC, superior/middle frontal gyrus), the insula, thalamus, and precuneus. Furthermore, we found decreased connectivity between the VTA and the insula. These findings were specific to reward anticipation, not to reward consumption and suggest an overall decrease in reward circuit connectivity during reward anticipation.

Impaired Reward-Learning in the VTA in Remitted Recurrent Depression

Where chapter 2 provides evidence for a dysfunctional reward-system in depressed patients, clinicians often observe that anhedonia remains as residual symptom during remission. The ability to experience reward and to learn from rewarding events is important in adjustment of behavior, which is expected to be associated with resilience against recurrence. Moreover, it remains unknown whether a dysfunction in processing of reward related-learning is associated with residual anhedonia. We therefore conducted a second study (chapter 3) in which we explored reward-related learning in remitted MDD patients, who were at high risk of recurrence (rrMDD). Apart from comparing patients and controls, we investigated this link between abnormalities in reward-related learning and anhedonia levels. The rrMDD patients, compared to healthy controls, showed impaired reward-related learning activation in the ventral tegmental area (VTA) which is a key area in the dopaminergic reward-related learning network. Moreover, in the rrMDD-patients, VTA-activation decreased when anhedonia levels increased, while in controls this relation was the other way around. These findings suggest impaired reward-related learning signals in the ventral tegmental area VTA during remission in depression rrMDD-patients. Moreover, the inverse association between reinforcement learning and anhedonia in rrMDD patients implies an additional disturbing influence of anhedonia on reward-related learning or vice versa.

Impaired Aversive-Learning in the Habenula in Remitted Recurrent Depression

Besides learning from rewarding events, the ability to learn from aversive events is also important in resilience against recurrence. The ability to learn new behavior that decreases hypersensitivity to aversive events plays an important role in resilience against recurrence by providing protection against symptoms like daily stress. In acute MDD, it has been demonstrated that impairments in aversive-learning are associated with hyperactivity of the habenula. It remains largely unexplored whether this dysfunction persists in remitted depressed individuals who were at high risk of recurrence. In chapter 4, we therefore explored habenula activation and connectivity during aversive learning in order to elucidate possible aversive-learning impairments and dysfunctions in the circuitry associated with aversive events in subjects vulnerable for recurrence. Impaired neural responses, specifically during processing of conditioned stimuli, were found in the form of hyperactivity of the habenula in remitted MDD patients, suggesting that impaired aversion-related learning signals persist during remission. Furthermore, we demonstrated aberrant connectivity between the habenula and the VTA during aversive learning in rrMDD patients. Considering the (indirect) inhibitory influence of the habenula on the VTA, hyperactivity of the habenula could result in an increased inhibition of the VTA, leading to lower temporal correlation between these two areas and therefore lower connectivity.

Part II: prediction of response to treatment in MDD

The second part of this dissertation focused on the prediction of (insufficient) response to treatment in mdd.

The maudsley staging method is a reliable and valid tool to predict poor outcome in depressed patients irrespective of treatment

Early prediction of pooroutcome is important for the development of more targeted treatment strategies. One promising tool that is aimed at predicting outcome of depression is the Maudsley Staging Method (MSM). However, the MSM has only been investigated using a relatively small sample of patients who were treated in a tertiary care setting. In chapter 5, the predictive property of the MSM was explored in a larger naturalistic cohort of the Netherlands Study of Depression and Anxiety (NESDA). We aimed to further validate the predictive value of the MSM and indeed confirmed that the MSM is a valid and reliable tool to predict poor outcome in a broad spectrum MDD. Interestingly, this prediction appeared to be independent of whether treatment was offered.

Decreased functional connectivity of the insula with the salience network is a potential biomarker for prospective insufficient response

Besides clinical prediction models, neuroimaging studies have also showed promising features to predict clinical outcomes. In Chapter 6, we used the neuroimaging cohort of the NESDA-study for an explorative approach to investigate whether baseline alterations in neural connectivity were an indicator of the need of a switch of antidepressants during two years of naturalistic follow-up. We considered this need for a switch as a proxy for insufficient treatment response, thereby probing this imaging marker as an indicator for insufficient treatment response. We observed that lower connectivity of the insula with the salience network was associated with prospective insufficient response to antidepressants.

Interpretation of findings

Impairments in the circuitry associated with rewarding and aversive events

Over time, research has expanded from a search for impairments in isolated brain areas to a search for interacting brain circuits. Chapters 2, 3 and 4 also do so, and provide findings that point to abnormalities in the circuitry associated with rewarding and aversive events in (recurrent) depression.

Cortico-striatal circuitry

An overall decrease in reward circuit connectivity was observed in patients with acute MDD during reward anticipation (chapter 2). Generally, regardless of task design, decreased activity in cortico-striatal regions, including the striatum, putamen, thalamus, insula and ACC, has been previously observed in MDD (Zhang et al., 2013). These brain areas are part of the mesocorticolimbic reward pathway and have long been considered as the essential regions in reward processing. Studies specifically investigating monetary reward anticipation and consumption showed decreased activation in the caudate during both reward anticipation and consumption stages and increased activation in the ACC, middle frontal gyrus and frontal

lobe during reward anticipation (Zhang et al., 2013). Our findings of decreased connectivity between the VS and frontal areas (the ACC/mPFC and superior/middle frontal gyrus) confirm cortico-striatal involvement in MDD pathology and provide evidence that MDD is characterized by alterations in reward circuit connectivity rather than isolated activation impairments. The ACC plays an important role in actions needed to obtain a reward, also called action–outcome associations (Chudasama et al., 2013). Frontal regions play a central role in reward seeking and reward effort (Tzschentke and Schmidt, 2000). Interactions between these areas have been suggested to strongly modulate the mesocorticolimbic dopamine circuit (Tzschentke and Schmidt, 2000) and are specifically related to reward anticipation (Balleine et al., 2007; Knutson, Fong et al., 2001; Wittmann et al., 2007). These current results substantiate the notion that dysfunctions in the cortico-striatal circuitry during reward anticipation are an important marker of MDD (Zhang et al., 2013).

In addition to the proposed involvement in reward, the cortico-striatal circuitry may also play a role in treatment response. Admon et al. (2015) found that relative to HC, less deviant cortico-striatal connectivity at baseline during monetary gain vs. penalty, predicted greater improvement in symptoms 12 weeks later. These findings should however be interpreted with caution considering their modest sample size of 14 MDD-patients. Nevertheless, cortico-striatal regions have been associated with prognostic value before (Fu et al., 2013). A meta-analysis by Fu et al. (2013) including a variety of functional neuroimaging paradigms, demonstrated that increased baseline activity in the anterior cingulate cortex was as a promising predictor of both pharmacological as well as (cognitive) behavioral treatment response, while increased activation of the insula and striatum was demonstrated to be a predictor of poorer clinical response. Despite these promising predictive properties of neural activity of isolated brain areas, the importance of dysregulated cortico-striatal connectivity as a neuroimaging predictor of response should be studied more extensively. Later on in the discussion we will discuss in more detail how a good predictor (i.e. biomarker) is defined.

VTA-Habenula circuitry

Besides impairments in acute MDD, we found that reward related abnormalities are also apparent when patients are in remission. Chapters 3 and 4 show impaired reward-related learning signals in the VTA and impaired aversion-related learning signals in the habenula, respectively. Chapter 4 also shows aberrant habenula-VTA connectivity during aversive-learning. Collectively, these findings emphasize the involvement of a circuitry associated with rewarding and aversive events comprising the VTA and the habenula that is specific for learning.

Usually, individuals make decisions that maximize reward and minimize loss by making efforts for rewards, by avoiding aversive events, and by adapting behavior after the experience of an event. This appears important in providing resilience against recurrence (Dutcher and Creswell, 2018). Positive emotional responses decrease stress-sensitivity (Wichers et al., 2007), and predict recovery during antidepressant treatment (Wichers et al., 2009). The impaired VTA function during remission (chapter 3), may cause difficulties in learning new behaviors that might improve mood or keep patients well (Vrieze et al., 2013). Moreover, persisting overactivity of the habenula during remission (chapter 4), specifically during processing of conditioned stimuli, may suggest that the habenula is triggered more easily, even when aversive events are minor. Impairments in learning from aversive events can cause an increase in encountering of aversive events. Ultimately, this increased frequency may cause

an increase in avoidance-behavior. Considering the involvement of the VTA and habenula in both reward (Chase et al., 2015; Garrison et al., 2013; Matsumoto and Hikosaka, 2007) and aversive learning (Hennigan et al., 2015), the aberrant connectivity between the habenula and the VTA during aversive learning may suggest an overall learning impairment. Aberrant connectivity between habenula and VTA, while learning (aversive) associations can lead to impaired (pavlovian) learning from aversive stimuli, which might be associated with learned helplessness (Pryce et al., 2011), which has previously been identified as a vulnerability-factor for recurrence (Bockting et al., 2006). Rodent studies have shown enhanced synaptic activity of VTA-projecting habenula neurons in learned helplessness models (Li et al., 2011). Although we did not test this, we speculate that in recurrent depression, earlier episodes can cause sensitization of the brains reinforcement learning system, and/or habenula-VTA decoupling, therefore making the brain more prone to learn worse from rewards and aversive events, associated with increasing risk of developing future episodes, a concept known as kindling (Monroe and Harkness, 2005). These speculations however remain to be investigated in future analyses of this and other datasets.

Although MDD is primarily being considered as a mood disorder, these findings suggest that disrupted reinforcement learning might underlie core features of MDD like anhedonia and negative bias (Eshel and Roiser, 2010; Pizzagalli, 2014). Over the past decade, reinforcement learning impairments have been linked to the pathophysiology of depression (Chen et al., 2015). However, this is the first study exploring reinforcement learning during remission. Previous studies conducted in subjects at risk for depression and with sub-threshold depression indeed have demonstrated that abnormalities in processing of wanting and liking aspects of reward are a trait marker for major depressive disorder (McCabe et al., 2009; McCabe et al., 2012; McCabe, 2016; Pan et al., 2017; Stringaris et al., 2015). Findings from this dissertation corroborate that, in addition, reinforcement learning abnormalities also point to a trait-like abnormality, which subsequently, if replicated, might be of importance with regard to vulnerability for recurrence. In order to answer if reward related impairments indeed predict a higher risk of recurrence, a longitudinal study design is necessary including information about recurrence status in the sample.

Can we predict response to treatment in MDD?

Besides improving our understanding of the neurobiology of MDD, determination of pathophysiological mechanisms underlying MDD can also be used in prediction of treatment response. Accurate prediction of non-response is necessary in order to overcome the stepwise trial-and-error approach currently used for treatment selection in psychiatry. In the second part of this dissertation we attempted to identify clinical and neuroimaging predictors for insufficient response to treatment (chapter 5 and 6). Early recognition and prediction of non-response can result in faster and more targeted treatment strategies and reduce suffering.

Definition of a biomarker

In order to investigate predictive properties of clinical tools and neuroimaging, we first have to define what makes a good predictor/biomarker. In medical literature, a biomarker is defined as a characteristic that can be objectively measured as an indicator of a normal biological or a pathogenic processes or a response of an individual to a therapeutic exposure or intervention (FDA-NIH Biomarker Working Group, 2016). Biomarkers can be divided in

two categories, i.e., the diagnostic biomarker which determines the presence or absence of a disorder and the prognostic biomarkers which predicts response to treatment or longitudinal course of illness (Hacimusalar and Esel, 2018). In the literature, prognostic biomarkers are also referred to as treatment biomarkers or treatment predictors. Alternatively, a biomarker can be a trait biomarker (i.e. present before onset of the disorder, during and after remission), a state biomarker (i.e. present during the disorder but not after remission), or an endophenotype marker (i.e. includes besides trait marker characteristics, also a heritability component) (Gottesman and Gould, 2003). In order to be clinically useful, the specificity and sensitivity of a biomarker should be high (more than 80%) (Schneider and Prvulovic, 2013). Furthermore, a biomarker should be reliable, inexpensive and non-invasive in order for it to be used in everyday clinical practice (Hacimusalar and Esel, 2018).

Clinical predictors

The Maudsley Staging Method (MSM), that we validated in chapter 5 in a large naturalistic cohort of primary and secondary care patients with depression, had already been proven to be a reliable tool in predicting poor outcome and course of MDD by Fekadu et al. (2009). However, this was in a relatively small sample of patients who were treated in highly specialized tertiary care. In chapter 5 we show that the MSM is generalizable to a much larger community-based population of depressed patients attending primary and secondary care. Generalizability of clinical predictor tools are required to maximize the utility of tools for predicting remission, episode persistence and/or future treatment resistance. An alternative instrument, extending the MSM, the Dutch Measure for Quantification of Treatment Resistance in Depression (the DM-TRD), has also been shown to be a feasible tool to assess failed biological, psychotherapeutic, and supportive treatments (Peeters et al., 2016). In a previous comparison the DM-TRD was suggested to be slightly more sensitive (Peeters et al., 2016). Unfortunately, the NESDA-data-set did not allow concurrent determination of the DM-TRD in the same study, allowing a further comparison. The DM-TRD was recently validated again in a large cohort of MDD outpatients (van Dijk et al., 2018) and was suggested to be a solid long-term predictor of symptom severity over time as well. Future studies are needed to establish whether these tools are sensitive and specific for predictions of treatment outcome in individual patients. This will be the next step to fully validate these clinical tools as a profiling tool to guide treatment.

Neuroimaging predictors

Consistent with results from recent reviews and a meta-analysis (Fonseka et al., 2018; Fu et al., 2013; Hacimusalar and Esel, 2018), chapter 6 demonstrates that neuroimaging can also be valuable in providing predictors for insufficient response to treatment. Structural imaging studies show that increased volume of the hippocampus predicts better response to treatment (MacQueen et al., 2008; Vakili et al., 2000), and that decreased hippocampal volume predicts insufficient response in MDD (Fu et al., 2013; Samann et al., 2013). Although biomarkers identified with task-based fMRI paradigms have been shown to be unreliable (Fonseka et al., 2018; Nord et al., 2017), resting state connectivity provides potential neuroimaging biomarkers as well (Salomons et al., 2014). For example, lower fronto-thalamic, fronto-striatal, and fronto-limbic connectivity were associated with better treatment outcomes (Salomons et al., 2014). Our finding that lower connectivity of the insula with the salience network was associated with prospective insufficient response to treatment might provide an additional biomarker. However, these reviews and meta-analysis consistently conclude

that although the identification of neuroimaging predictors of treatment response seems promising, before these biomarkers can be translated into clinical practice they require replication and validation in large, independent samples. Subsequently, randomized controlled trials investigating biomarker-based treatment versus treatment as usual are necessary to investigate the true advantage of implementation of these potential biomarkers.

Other promising predictors

Besides these neuroimaging findings, also decreased brain-derived neurotrophic factor (BDNF), increased cytokines, and increased hypothalamo-pituitary-adrenal axis activity are mentioned as promising biomarker candidates for MDD (Hacimusalar and Esel, 2018). Although promising, the authors also conclude that in general, isolated biomarkers are low in specificity and sensitivity. They suggests that a multimodal, multivariable approach, integrating clinical and neuroimaging markers with data from other biological modalities (e.g. genetic, proteomic, metabolomics), might be able to provide a more comprehensive assessment of treatment prediction (Hacimusalar and Esel, 2018; Schmidt et al., 2011).

Can we predict recurrence?

As the incidence of relapses and recurrences may be as high as 80% within 5 years (Bockting et al., 2009), prediction of relapse and recurrence is important as well. Although only inferences can be made whether finding of this dissertation are associated with patients at high risk of recurrence, chapter 3 and 4 point to a possible involvement of impaired reward- as well as aversive-learning in recurrence vulnerability. Previous studies have shown promising insights into the prediction of recurrence. Clinical characteristics (number of previous episodes, coping style, and residual depressive symptoms) have been found to be predictive of recurrence in remitted depressed patients (Bockting et al., 2006; Mocking et al., 2016; ten Doesschate et al., 2010). Furthermore, neuroimaging studies have suggested to provide important prognostic markers for relapse and recurrence in MDD (Hacimusalar and Esel, 2018). For example, structural imaging revealed that decreased gray matter volume in neural regions involved in executive function, emotional regulation and salience processing (the insula, dorsolateral prefrontal cortex and middle frontal gyrus) predicted a relapsing course in MDD (Zaremba et al., 2018). In addition, larger hippocampal volume was associated with lower relapse rates (Kronmuller et al., 2008). Functional imaging studies demonstrated that relapse can be predicted by mood linked reactivity of the medial prefrontal cortex (Farb et al., 2011). Whether the current result can attribute to these findings should become apparent in future studies. A confirmation of a link between impaired reinforcement learning (both reward and aversive learning) and recurrence, investigated in future longitudinal studies, would indicate a pathogenic process and could suggest a potential prognostic biomarker. However, following the definition of a biomarker, high specificity and sensitivity are required for this to be a potential trait biomarker for recurrence vulnerability. Therefore, replication and validation in independent samples are required.

In conclusion, prediction of recurrence and non-response with clinical tools and neuroimaging holds promise; however, before this can be clinically useful, research must be directed towards improvement of the predictive vales of these biomarkers and increase of specificity and sensitivity. At this stage, we can non-invasively and objectively measure normal biological processes, pathogenic processes or a response to a therapeutic exposure or intervention, however, accurately measuring these processes at the level of an individual remains challenging.

Methodological Considerations

MRI

Although fMRI has been proven to be a valuable tool in research, there are some methodological considerations that one should be aware of. Firstly, fMRI cannot directly measure neurotransmitter signaling. This is especially important regarding our study on (expected dopamine-firing) abnormalities in the VTA, where we measure VTA activation as a proxy for phasic DA-bursts. However, evidence suggests that blood oxygen level-dependent measurements in reward related brain areas are indicative of DA release (Knutson and Gibbs, 2007; Pessiglione et al., 2006). Additional acquisitions of PET scans or even multimodal PET/MRI scans (Cecchin et al., 2017), might offer more detailed insights on the dopaminergic reward system and the involvement in recurrence and non-response in MDD. Secondly, resolution of fMRI is spatially low which makes it difficult to study small structures like the VTA and the habenula and to distinguish different parts of these structures like medial/lateral parts. Thirdly, with fMRI it is not possible to distinguish whether observed activity is caused by underlying dopaminergic signaling or perhaps from another neurotransmitter system. This is especially important for chapters 3 and 4 because besides dopamine, the VTA and habenula also receive and project GABAergic and glutamatergic neurons.

Experimental task

The experimental task described in chapter 3 and 4 lacked an active response to the appearance of the pictures on the screen. This excludes the possibility of any behavioral confound in the Pavlovian learning. Although this passive conditioning task was specifically used to assess particular aspects of learning, participants might have lost their engagement or attention to the task and we were not able to assess individualized learning rates. In new experiments, an active response (e.g. button press) will be embedded in the task, which will facilitate the possibility to fit the model to the data and select parameters that show the best overall fit to the signals.

Study design

Chapter 3 and 4 lacked inclusion of a currently depressed group, and scanning of depressed subjects was not incorporated in the design. This hampers the ability to draw inferences about persistence of impaired reward-related learning during remission, and thereby prediction of recurrence. Nevertheless, in its present form, the study can be very helpful for the identification of factors that remain impaired during remission in depressive patients with a history of recurrence.

Clinical implications and future perspectives

It is sometimes considered challenging to relate neuroimaging findings to clinical practice. However, this dissertation presents findings that provide a greater understanding of neural correlates and, more importantly, complex neural circuitry underpinnings of depression and recurrence vulnerability. Insights that may be useful in mental health care practice.

Behavioural and neuromodulation therapy

Chapter 3 and 4 point to a possible involvement of impaired reward- as well as aversive-learning in the vulnerability for recurrence. Follow up studies should point out whether these observed impairments in reinforcement learning are indeed associated with recurrence. A link between recurrence and impaired reinforcement learning (both reward and aversive learning) could suggest that the focus of therapy should lie on enhancing positive affect by training patients to focus attention on positive reinforcers as well as diminishing negative affect (Servaas et al., 2017; Wichers et al., 2010; Wichers et al., 2012). Focusing on positive experiences could train the ability to make associations between behaviour and pleasurable outcomes and reinforce repetition of reward provoking behaviour (operant conditioned learning). Training the ability for (rr)MDD patients to learn about rewarding and aversive feedback in daily life should therefore be investigated in future studies. This type of training could for example be examined in a prospective randomized controlled trial offering behavioural activation therapy (Soucy Chartier and Provencher, 2013) to MDD patients vulnerable to recurrence.

Reward in TRD sample

Besides the demonstrated reward related dysfunctions in currently depressed and remitted recurrent MDD patients in this dissertation, evidence emerges that treatment resistance, especially to first choice antidepressants, may also be caused by an underlying dysfunction in reward (i.e. dopamine-related functioning) and punishment processing. A logical follow up of this dissertation would be to extrapolate the findings from both parts of this dissertation in a study that investigates pathophysiological mechanism behind reward and punishment processing in a treatment resistant group of patients.

Role of neurotransmitters other than dopamine

Two of the three studies in part one of this dissertation focused on dopaminergic reward-related system. It is plausible though, that the γ-aminobutyric acid (GABA) and glutamate system play an additional role, as these systems have also been considered to be involved in treatment non-response and risk for recurrence (Lener et al., 2017; Li et al., 2019). GABA is the major inhibitory and glutamate the major excitatory neurotransmitter in the brain. In addition to dopamine, VTA neurons also co-release other neurotransmitters, including GABA and glutamate (Yoo et al., 2016). Furthermore, GABA/glutamate co-release controls the output of the habenula which is modified by antidepressant treatment (Shabel et al., 2014). Therefore, it is possible that the reinforcement learning activity in the VTA and habenula we demonstrated in chapter 3 and 4, is partly attributable to underlying GABA and glutamate

dysfunction. However, this cannot be derived from the current study design and should be investigated in future studies, presumably with 7T magnetic resonance spectroscopy (MRS), given the small volumes of these regions and the difficulty of obtaining reliable MRS-scans. Such MRS-scans could determine the in vivo concentration of brain metabolites such as GABA and glutamate non-invasively. Although quantification of chemical profiles like GABA and glutamate from the brainstem are technically challenging, studies have demonstrated promising methods (Deelchand et al., 2015; Emir et al., 2012; Oz and Tkac, 2011).

Machine learning and normative modeling

Psychiatry could benefit from the application of neuroimaging biomarkers in combination with other variables (i.e. biomarkers from neuropsychological measurements and genes) in order to improve diagnostic sensitivity and specificity and prediction of treatment/disease outcomes (Hacimusalar and Esel, 2018). Ideally, for new patients, stratification to distinct subgroups (e.g. responders or non-responders) should be possible based on individualized prediction. There is evidence that machine learning is a promising technique that can be valuable in developing prognostic and diagnostic tools in psychiatry by providing such individualized stratification (Bzdok and Meyer-Lindenberg, 2018). Depending on the type of machine learning (i.e. unsupervised), these techniques could even aim at a transdiagnostic approach that cuts across traditional disease boundaries.

An alternative approach that has been suggested is the implementation of normative modeling (Marquand et al., 2016). Normative modeling is based on the idea that biologically, clinical groups are often highly heterogeneous and that healthy variation is a prerequisite to understanding disease variation. Normative modeling allows to determine where an individual lies within a common range for the population. First, a normative model is defined that links biological (e.g. functional brain activity) and clinical variables (e.g. questionnaire scores) with the estimation of predictive confidence, to quantify the fit of each point to the normative model. Second, for each individual, the deviation from the normative model is calculated. Next, an index of abnormality is calculated (Marquand et al., 2016). Marquand and colleagues used normative modelling to predict reward-related brain activity in a large healthy cohort. They provided promising insights that normative modeling can be used in studying disorders at the individual level without dichotomizing samples. Instead, disorders can be thought of as extremes within a certain (normal) range (Marquand et al., 2016).

Towards individualized treatment

Refinement of predictivity of clinical and neuroimaging methods by machine learning or normative modeling techniques are crucial in order to achieve individualized stratification. Several lines of evidence point to the possibility of predictive models that can be applied to and obtain answers for a single patient (Browning et al., 2019; Gao et al., 2018; Szegedi et al., 2009).

June 2040:

At the department of psychiatry, a patient Mrs. R. (female, 37 years old) is seen by a psychiatrist for a second depressive episode. The first episode (4 years ago) she experienced remission without treatment. The current episode she shows remission after treatment with psychotherapy and one antidepressant. Although in remission now, Mrs. R. reports that she still experiences difficulties in sleeping, concentrating and experiencing pleasure and reward. Since her improvement, she noticed an oversensitivity to negative events, i.e. despite having experienced positive events related to her own efforts, she irrationally doesn't value those and instead sticks to a few small negative events that occurred irrespectively of any action by herself.

With the results of this dissertation in mind, and subsequent research based on our and other's findings, we can speculate what steps can be taken when a patient comparable to Mrs. R. seeks treatment. With additional work and new developments in profiling of patients, the predictivity of clinical and neuroimaging markers will have improved, and a multivariable approach and intelligent self-learning algorithm will be applied before initiating treatment. This approach will integrate clinical (i.e. new versions of the MSM) and neuroimaging markers (i.e. resting-state), in order to predict outcome of various treatment options against depression, and these measurements will also assess the level of vulnerability for non-response. Furthermore, in order to explore if residual symptoms are caused by impairments of reward- and aversion-related processing and learning, a Pavlovian classical conditioning task will be used to assess reward and aversive learning. Based on subsequent work it will have been established that if these impairments in reward- and aversive processing are identified, intervention with a specific cognitive reward-training and positive-affect focused behavioral activation therapy will significantly improve Mrs. R.'s resilience against recurrence.

Conclusion

Treatment outcomes for major depressive disorder (MDD) need to be improved as both non-response rates after treatment and relapse/recurrence rates following remission are high. Ideally, early prediction of nonresponse and recurrence would either facilitate the choice, shortening the time to change to an adequate treatment or intensify treatment e.g. by combination of pharmacotherapy and psychotherapy. This dissertation has attempted to provide insight in mechanisms relevant for recurrence vulnerability and non-response to treatment. Moreover, we aimed to predict this non-response to treatment.

We conclude that acute MDD is characterized by impairments in reward response and reward connectivity and that temporal difference modeling of reward-related PE-signals give a more accurate representation of reward processing. During remission but still at high risk of recurrence, impairments in learning from rewarding and aversive events persist. These dysfunctions could represent trait rather than state-dependent abnormalities, and may be of importance for recurrence vulnerability. With regard to prediction of treatment outcome and non-response we confirmed that the MSM is a valid and reliable tool to predict poor outcome in MDD. When examining prediction of non-response with a more neurobiological, mechanistic approach, we provide evidence that differences in functional connectivity of the insula with the salience network is indicative for non-response which might encourage the choice for alternative treatment at an early stadium. These findings may contribute to enhanced understanding of pathophysiological mechanisms of (recurrent) MDD and prediction of non-response, ultimately improving the quality of life of people that suffer from MDD.