Towards a neurobiological view of depression

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General Discussion

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Over the past decades the pathophysiology of MDD has been a topic of intensive research. Different hypotheses have been put forward, including reduced neurogenesis, blunted HPA-axis response, altered neuroimmune functioning, and monoaminergic dysfunctions (chapter 2). However, to which extent each of these alterations is causatively related to symptoms of depression is not completely understood. It is generally believed that increased knowledge of the pathophysiological mechanisms underlying depression will eventually give rise to improved treatment strategies and diagnostic opportunities.

Future perspective for a biomarker-based test for depression

We started our research by an investigation of potential serum and urine biomarkers for MDD, with the aim of developing a biomarker-based test for depression (chapter 3). Our results, although still awaiting validation, indicate that a panel of biomarkers can successfully discriminate between MDD patients and control subjects. During the course of this project, several other papers were published indicating the success of biomarker panels to diagnose depression [1-6].

Although these are important steps towards the development of a biomarker- based test for depression, certain criteria will need to be fulfilled before such a test can be used in a clinical setting. Firstly, while most current studies on this subject have investigated the potential of biomarker panels to separate pre- selected groups of confirmed MDD patients and healthy controls, in a clinical setting it will be more relevant to be able to separate between MDD and other psychiatric and/or somatic disorders that have a symptomatic overlap with MDD. It is likely that symptomatic overlap between such disorders is partly a result of overlapping pathophysiological mechanisms. The biomarker profile of MDD may therefore show similarities to the biomarker profile of related disorders (chapter 2). Only if a panel can separate between MDD patients and patients with closely related disorders with sufficient accuracy, it can be introduced as a method for diagnosing depression.

Another question that should be asked is what the added value of a biomarker- based test for depression would be. In order to be of added value, a newly developed diagnostic test should have certain advantages compared to the tests that are currently available. For example, a new test may be more accurate, less invasive or less costly than previous diagnostic methods. In the case of MDD, current diagnostic methods are already relatively inexpensive and non-invasive. As regards accurateness, it seems unlikely that a laboratory test can fully replace psychiatric evaluation.

While the clinical usefulness of a biomarker-based diagnostic test for depression might therefore be limited in psychiatric settings, in a non-psychiatric setting the demand for such a test could be more pronounced. Medical personnel in such settings are less well trained to recognize depression. Indeed, Su *et al*. [7] demonstrated that the accuracy of a depression diagnosis by non-psychiatric physicians was only 31.4% compared to diagnosis by a psychiatrist. Thus, for non-psychiatrist physicians, a laboratory test could be a helpful tool for determining the likelihood of an MDD diagnosis. In that sense, the fact that final symptomatic evaluation by a psychiatrist

will probably remain necessary should not nullify the demand for a biomarker-based test for depression.

In addition, MDD biomarkers could have other applications besides diagnostic ones, for example identification of those at risk of developing depression, diagnosis of pathophysiological subtypes of depression, or prediction of clinical response to different treatment strategies. However, studies of biomarker panels for MDD, including our own study (chapter 3), currently mainly focus on the separation of patients with a confirmed MDD diagnosis from healthy controls [1,2,4,5]. Whether biomarkers identified in such studies may have other applications as well remains to be investigated.

Arnold *et al.* [3] have investigated both the diagnostic and predictive potential of a large set of biomarkers in patients with Alzheimer's disease / Mild Cognitive Impairment with or without depressive symptoms. Remarkably, the biomarkers that were found to have predictive potential showed only minimal overlap with the biomarkers that were found to have diagnostic potential. This suggests that predictive biomarkers do not necessarily have diagnostic potential as well, and thus studies that focus solely on the potential of biomarkers to separate MDD patients and controls might discard biomarkers with possible predictive potential.

Recently, a number of studies have been published that evaluate the potential of biomarker panels to predict the development of depressive symptoms in specific patient groups at high risk for depression. For example, an inflammatory biomarker risk score, based on levels of multiple inflammatory biomarkers in CSF, was found to predict the development of post-traumatic depression in adults with moderate to severe brain injury [8]. Other studies combined serum biomarker levels with clinical or sociodemographic parameters. For example, a combination of serum markers (AXL receptor tyrosine kinase, vascular cell adhesion molecule 1, vitronectin, collagen IV) and clinical variables (Inventory of Depressive Symptomatology, Beck Anxiety Inventory somatic subscale, depressive disorder lifetime diagnosis, body mass index) was shown to predict development of depression in patients with social anxiety disorder [9]. Similarly, serum tetranectin could, together with clinical and sociodemographic parameters, predict the development of depressive episodes in patients with panic disorder [10]. Although promising, one should keep in mind that all of these studies have been performed in highly specific patient groups carrying a particularly high risk for developing depression, and the value of the biomarker panels identified in these studies might be limited outside these specific groups of patients.

Of particular interest is the potential of biomarkers to predict treatment response and thus aid treatment choice. Antidepressant drugs are known to have a delayed onset of action, with clinical improvement becoming evident only after 3-8 weeks of therapy. However, the side effects are evident directly from the start of the therapy. In addition, there is a large subset of patients that does not respond to one or more types of antidepressant drugs. Biomarkers that could predict the relative success of different antidepressant therapies and thus could identify the therapy with the highest chance of success would therefore be very useful.

Although currently no biomarkers or biomarker panels exist that can predict treatment response with sufficient accuracy to be used in a clinical setting, several studies support the existence of biomarkers that are associated with treatment response [11-14]. Such biomarkers include structural and functional alterations in the brain, genetic polymorphisms, gene expression, and peripheral protein levels. For an in-depth discussion of potential biomarkers of treatment response in MDD, the reader is referred to the reviews that have been published on this topic [11-14].

Although all current antidepressant drugs primarily target the monoaminergic system, new antidepressant treatment strategies are currently being investigated. For example, substances targeting the glutamatergic system (e.g. ketamine) or the neuroimmune system (e.g. NSAIDs) have shown promising results in preliminary trials [15]. The introduction of alternative antidepressant therapies will further increase the demand of methods that can predict clinical response to different treatment strategies and thus aid treatment choice.

It is reasonable to assume that patients with different underlying pathophysiological mechanisms, reflected by different biomarker profiles, will react differently to certain treatment strategies. In this respect, it is interesting to note that our panel of biomarkers (chapter 3) includes biomarkers that reflect diverse pathophysiological mechanisms, including neuroimmune activation, HPA axis dysregulation, and reduced neurotrophic support / neurogenesis. Future research should point out if alterations on specific subdivisions of this biomarker panel could potentially be used to predict response to various treatment strategies.

In conclusion, although the clinical applicability of a biomarker-based diagnostic depression test in a psychiatric setting is probably limited, biomarker panels, including the panel described in chapter 3, could provide a useful tool for non- psychiatric medical personnel encountering potential cases of depression. A highly promising development would be the identification of peripheral biomarkers that predict clinical response to different treatment strategies. This would allow for selecting the optimal treatment for each individual patient.

Immunomodulatory effects of electroconvulsive therapy

We continued our research by investigating the mechanisms underlying the antidepressant effects of electroconvulsive therapy (ECT), one of the most effective treatment strategies for MDD. It is well known that ECT induces hippocampal neurogenesis and has profound effects on the neurotrophic system. We have instead focused on a less well-investigated area, namely the effects of ECT on the neuroimmune system.

Chapter 4 reviews the scientific literature regarding the effects of ECT on the neurotrophic and neuroimmune system and proposes a hypothesis of how these systems might interact. The proposed hypothesis states that controlled potentiation of inflammatory responses may elicit neurogenic and neuroprotective effects and thereby contribute to ECT's antidepressant efficacy. This hypothesis is supported by studies demonstrating acute transient immune activation after individual ECT sessions and normalization of inflammatory parameters over multiple ECT sessions,

combined with studies suggesting potential neurotrophic effects of inflammatory cytokines and activated immune cells (chapter 4).

Since publication of the literature review described in chapter 4, several clinical studies have been published supporting an overall anti-inflammatory effect of repeated ECT sessions. Shibasaki *et al*. [16] found altered levels of matrix metalloproteases MMP-2 and MMP-9 in MDD patients, with increased levels of the proinflammatory MMP-9 and decreased levels of the prohomeostatic MMP-2. Levels of both MMPs normalized over a course of ECT. Moreover, MMP-9 levels were found to be negatively correlated with HAM-D scores, while a positive correlation was found between MMP-2 and HAM-D scores. This study suggests an overall anti-inflammatory effect over multiple ECT sessions. This suggestion is further supported by Kartalci et al. [17], who demonstrated that ECT gradually increases levels of the anti-inflammatory cytokines IL-4 and TGF-β in schizophrenia patients. In contrast, in another recent study [18] ECT failed to normalize reduced TGF-β levels and increased IL-6 levels in patients with melancholic depression, despite improvement in clinical symptoms. Interestingly, in line with our hypothesis that acute transient neuroimmune activation by ECT might stimulate neurotrophic effects and thereby contribute to clinical improvement, this study demonstrated an acute surge of the pro- inflammatory cytokine IL-6 directly after the first ECT session. Overall, this paper would suggest that although acute immune stimulation might play a role in the antidepressant effects of ECT, normalization of cytokine levels is not a necessary prerequisite for clinical improvement.

To further elucidate the complex effects of ECT on neuroimmune activation, we studied the effects of ECS on microglial activity in animal models for depression and neuroinflammation, yielding contradictory results (chapter 5-7). In chapter 6, we found that a series of 10 ECS sessions did not affect microglial activity in healthy control mice, nor prevent microglial activation and depression-like behavior by subsequent i.c.v. LPS injection. In line with these findings, a single ECS session did not alter microglial activity under control conditions or after LPS stimulation (chapter 7). In contrast, we demonstrated increased microglial activity in the CA1 and CA3 hippocampal regions after repeated ECS sessions in a chronic social defeat (CSD) x ECS paradigm (chapter 5). In this paradigm, microglial activity was unaffected by CSD.

The origin of this difference in outcome is unclear, although it should be noted that there are quite a few differences in study paradigm. In addition, the CSD study was performed in another animal facility than the other two studies and mice were bred and housed under different conditions. Although speculative, these differences might have influenced the outcome of these studies.
Several other studies have investigated the effects of ECS on number and activational state of microglia (reviewed in chapter 4). Mirroring our own variation in results, these studies have yielded inconsistent results, with some studies demonstrating a short- or longer-term effect on microglial activity, while other studies failed to find any such effect. Overall, these data support the view that ECS might under some circumstances affect microglial activity, although these effects are probably dependent upon additional factors.

Of special interest is a recently published study demonstrating increased baseline microglial activity and normalization over a course of 6 ECS sessions in Gunn schizophrenia rats, a genetic rat model for schizophrenia that has been previously associated with morphological changes indicative of neuroinflammation [19]. No effect was observed on microglial activity in Wistar control rats. This study suggests that although ECS may not affect, or even increase, microglial activity under non-pathological circumstances, repeated ECS sessions may normalize microglial activity under certain pathological conditions characterized by increased baseline microglial activation.

Although our studies, as well as most other animal studies, have focused on the central effects of ECS on the immune system, as far as we are aware there have not been any reports of the effects of ECT on central inflammation in humans. Instead, human studies have focused on alterations in peripheral cytokine levels and changes in the number and activational state of peripheral immune cells. The reason for this is probably that central measurements are particularly difficult to obtain in human studies. Nevertheless, we believe it would be highly relevant to measure central as well as peripheral immune activation in humans.

In order to measure central effects of ECT on immune activation in humans, we would suggest performing a PET study in MDD patients undergoing ECT. PET tracers such as PK11195 are considered reasonably accurate markers of neuroimmune activity. Ideally, PET scans should be performed at several time points during an ECT course, for example previous to the first ECT session, directly after the1st, 5th and 10th session, and two weeks after completion of therapy. In addition, PET scans should be performed in healthy age- and sex- matched controls. Optionally, blood samples could be collected prior to every PET scan to allow for peripheral cytokine measurements. HAM-D scores should be monitored prior to every PET scan as well. Such a study would contribute greatly to our knowledge of ECT-induced central and peripheral immune activation in MDD patients.

Mechanisms underlying cognitive side effects of electroconvulsive therapy

In line with several other rodent studies [20-24], we have found evidence for impaired learning and memory in mice undergoing ECS (chapter 5). Cognitive dysfunction, particularly anterograde and retrograde amnesia, is one of the most common side effects of ECT. Several hypotheses exist regarding the mechanisms underlying memory-related side effects of ECT. Two systems in particular have been implicated in the cognitive side effects of ECT: the cholinergic system and the glutamatergic system.

Evidence for involvement of the cholinergic system in ECT-related memory impairment is provided by rodent studies showing a decrease in hippocampal and striatal acetylcholine after ECS [25,26]. Furthermore, a recent study demonstrated that ECS-induced memory disturbances in rodents could be prevented by the cholinesterase inhibitor physostigmine, and that this effect was mediated at least partly by the α4β2 nicotinic acetylcholine receptors [24]. This study further showed a decrease in α4β2 nicotinic acetylcholine receptors in prefrontal and hippocampal areas

after repeated ECS. Previous studies have found a similar ECS-induced decrease in muscarinic acetylcholine receptors and have suggested the involvement of these receptors in ECS-induced amnesia [27,28].

Our own experiments, demonstrating an ECS-induced decrease in cholinergic fiber density in the hippocampus, which was accompanied by deficits in learning and memory (chapter 5), further support involvement of the cholinergic system in ECT-related cognitive deficits. Future research should be directed at the prevention of cognitive side effects by manipulation of cholinergic signaling. The potential success of such treatment strategies is suggested by a recent study demonstrating the effectiveness of the acetyl cholinesterase inhibitor rivastigmine in preventing ECT-induced memory deficits in schizophrenia patients [29].

The glutamatergic system is implicated in ECT-induced amnesia via effects on glutamate-associated long-term potentiation. It has been suggested that ECT induces saturation of long-term potentiation (LTP), a process mediated by activation of glutamatergic NMDA receptors, thereby reducing further hippocampal plasticity necessary for memory formation. This view is supported by rodent studies demonstrating impaired induction of LTP after repeated ECS, combined with evidence that ECS itself increases LTP [22,30,31]. In addition, LTP could be prevented in rodents by anesthesia with the NMDA receptor antagonist ketamine during ECS sessions [22,32,33]. Human studies confirm a positive effect of ketamine anesthesia on ECT-induced cognitive side effects [34-36].

In line with ECS-induced saturation of hippocampal LTP by massive activation of NMDA receptors, we have demonstrated massive neuronal activity, as evidenced by increased c-fos expression, in the hippocampus and connected areas after a single ECS, but not after repeated ECS (chapter 7).

Although ECT is a highly effective treatment for MDD, cognitive side effects currently form a major impediment to its clinical use. Preliminary studies in animals or small numbers of patients suggest that cognitive side effects can be attenuated by pharmaceutical interventions that influence underlying mechanisms [22,29,33-36]. A further increase in knowledge regarding these mechanisms may give rise to new treatment options for the prevention of ECT- induced amnesia.

Concluding remarks

Major Depressive Disorder is a particularly disabling disease with far-reaching consequences for those affected, their families, and society as a whole. Although significant breakthroughs have been achieved over the past decades regarding the development of new treatment options, for a large subset of patients treatment is still not sufficiently effective. One of the reasons for this might be that, despite a vast increase in scientific literature on the subject, the pathophysiology of MDD is still not completely understood. It is to be expected that increased understanding of the pathophysiological mechanisms underlying MDD, as well as the antidepressant mechanisms underlying the clinical success of effective treatment strategies such as ECT, will result in the development of novel and more effective treatment strategies with less side effects.

A major goal for the upcoming decades is the personalization of antidepressant treatment. This will require additional research into factors predicting the relative success of different treatment strategies. In addition to symptom profiles and patient characteristics, biomarkers have the potential to be a major aid in choosing the treatment with the highest chance of success for the individual patient.

The development of novel treatment strategies combined with methods to choose the best treatment for the individual patient could mean the next major breakthrough in MDD treatment and might revolutionize antidepressant therapy.

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