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## Electrically induced neuroplasticity

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# CHAPTER 7

A general discussion and summary of the thesis

## DISCUSSION

The research presented in this thesis was directed at elucidating the effects of electroconvulsive therapy on the brains and cognitive abilities of patients with a severe depressive disorder. This chapter summarizes the main findings of each study presented, and provides a general discussion regarding relevant literature, (methodological) considerations, clinical applications and future directions.

### COGNITION

Impairment in cognitive abilities is one of the main side effects of ECT. These cognitive impairments have long been recognized as troubling and are experienced as quite daunting by patients and their families. In **Chapter 2**, research into the effects of bilateral ECT is presented. The main finding was that ECT caused significant cognitive side effects in the short-term. In the long-term, however, the patients recuperated.

Specifically, cognitive impairment was measured after ten ECT sessions for verbal memory and learning, as well as for word fluency. For all cognitive tests, the scores returned to baseline levels six months after treatment, indicating no long-term cognitive impairment. For visuospatial abilities, an improvement in test scores was seen from pre-treatment to follow-up. Improvement in depression scores was not related to a change in cognitive scores. This suggests that cognitive impairment develops independent of the antidepressant properties of ECT (although responders showed a greater decrease than non-responders in one subtest of verbal fluency at post-treatment, but not at follow-up). Note that these results pertain to averages. When looking at an individual level, a decrease in test scores at follow-up was observed for five patients on a test for verbal memory, two patients for verbal fluency, three for visual attention, and two for visual attention and task switching. Additionally, in spite of the positive effect on depression, cognition scores were not improved at end of treatment or follow-up, except for in one subtest measuring visuospatial abilities. As depression is associated with cognitive impairment (Rock, Roiser, Riedel, & Blackwell, 2014) it would be expected that when the depression remits, cognition scores will improve as well. Given that cognition scores did not increase beyond pre-ECT levels, it is not possible to fully exclude more persisting cognitive deficits caused by ECT. However, it should be noted that cognition is impaired even in remitted patients who have never had ECT (Semkovska et al., 2019).

Together these results suggest that bilateral ECT causes short term cognitive impairment in the verbal domain, and that patients recuperate six months after treatment.

### DENTATE GYRUS VOLUME

In recent years, increased volume of the hippocampus after electroconvulsive therapy has been a robust and consistent finding. The exact nature of this increase remains unknown. In animals, the analogue of ECT known as electroconvulsive stimulation (ECS) strongly stimulates neurogenesis in the dentate gyrus. In **Chapter 3**, findings are presented from an ultra-high

field MRI study into the effects of ECT on the subfields of the hippocampus. We found that ECT has specific effects on the dentate gyrus, leaving the other subfields unaffected.

Specifically, after ten ECT sessions a strong increase in volume of the dentate gyrus was found. This effect pertained to the dentate gyrus (DG) specifically (i.e. no effects were found in the other hippocampal subfields). No volumetric changes were found in controls who were also scanned twice, five weeks apart. The increase in DG volume was significantly greater than the increase in volume in the largest other subfield (CA1). Interestingly, there was a strong negative correlation (within-subjects) between an increase in volume in the left and right DG and a decrease in depression scores, suggesting that the larger the increase in volume, the greater the effect of ECT on depression. Furthermore, baseline volume of the left and right DG predicted the antidepressant effect of ECT post-treatment.

The exact mechanism and nature of this volumetric increase remains unclear. As preclinical literature shows a strong and robust increase in neurogenesis after ECS in the dentate gyri of animals (Madsen et al., 2000; Nakamura et al., 2013; Perera et al., 2007), the present finding could reflect neurogenesis as well. Other functional recovery processes, such as synaptogenesis, dendritic arborization, and angiogenesis may also contribute to the volume increase, yet these processes cannot explain why growth only pertained to the DG. Less beneficial processes, such as the formation of edema, may also explain the effect, although (again) these would be expected to affect all subfields equally.

## COLLECTION OF LETTERS

While the finding of volume increases in the DG of the hippocampus on 7T MRI points into the direction of neuroplasticity (and in particular, neurogenesis) as being the effect of ECT, a lot of questions remain. For example, do we really need ultra-high field MRI to measure these effects? Are DG volume increases also found on conventional 3T MRI scanners? **Chapter 4** discusses these and other questions in two letters.

The first letter concerns the question whether the volume increases in the DG and its association to the decrease in depression scores will hold when measured with a conventional, more readily available, 3T MRI scanner. To address this question, we collaborated with a group from Keio University (Tokyo, Japan), and reanalyzed their data set that was acquired using 3T MRI using similar methods as presented in Chapter 3. This reanalysis indeed revealed that a significant increase in the DG (and only the DG), is related to a decrease in depression score within subjects. Future studies can thus adopt these methods to further investigate the role of the DG in ECT using 3T MRI. This makes it easier to study larger samples to investigate whether these volume changes are necessary and sufficient for the antidepressant response.

The second letter addresses a commentary written by Koch and colleagues concerning Chapter 3 (Koch, Morey, & Roelofs, 2019). Koch et al., raised the possibility that neurogenesis plays a role in all stress-related disorders (not limited to depression). Pertaining to our study, they questioned whether pretreatment DG volume differs between patients and controls. In response we reanalyzed our data and did not find a significant difference between

patients and controls for the left or right DG. Furthermore, Koch et al., suggested that the association between baseline volume and treatment severity could explain the predictive effect of the DG, but such an association was not found when reanalyzing the data. Furthermore, including treatment severity at baseline did not change the results of the regression model predicting the antidepressant effect of ECT.

### **EDEMA, ANGIOGENESIS, NEUROPLASTICITY**

The volumetric increases of the dentate gyrus presented in this thesis, and the robust finding of volume increases after ECT in the entire hippocampus reported by others, raise the question whether the biological basis of this volume increase can be found in beneficial processes (e.g. neuroplasticity, angiogenesis) or less beneficial processes (e.g. edema). **Chapter 5** sets out to investigate this question by employing diffusion weighted imaging to study edema or broad neuroplastic effects, and intravoxel incoherent motion analysis (IVIM) and arterial spin labeling (ASL) to study perfusion. If vasogenic edema is responsible for the volume increase seen in the hippocampus, one would expect that the mean diffusivity (MD) value increases (i.e. due to the accumulation of fluid in the extracellular space), yet when neuroplastic effects are implicated it will decrease the MD (i.e. due to the decrease in extracellular space as an effect of new cells/axons/dendrites/synapses). Additionally, an increase in perfusion parameters would be expected when angiogenesis takes place after ECT.

In the current study we found decreased MD after ECT in the left and right hippocampus in patients, but not in controls. Within the IVIM framework, the perfusion fraction  $f$  also decreased significantly after ECT in the left hippocampus, but not in the right (no differences were found in controls). The pseudo-diffusion component  $D^*$  (estimated from IVIM data) and the ASL maps did not change significantly after ECT. Together, albeit preliminary, these results suggest that cell density increased and thus imply that neuroplastic effects (and not vasogenic edema) play a role in the volume increases of the dentate gyrus.

### **THE LATERAL VENTRICLES**

In adult rodents, neurogenesis also takes place in the subventricular zone of the lateral ventricles. Whether this happens in humans is an open question with contrasting findings and views. Studies report ablation of neurogenesis in the lateral walls of the ventricles after two years of age while others report neuroblasts and (quiescent) stem cells up until later in adulthood. Given the neurogenesis enhancing potential of ECT, **Chapter 6** sets out to investigate if shape changes of the lateral ventricles occur in the neurogenic niches (suggesting neurogenesis), or along the entire ventricle.

We found a significant decrease in volume of the ventricles in patients, but not in controls. The decrease in ventricle volume was associated within subjects to the increase in DG volume (reported in Chapter 3), and to a decrease in Hamilton score. Shape analysis showed significant shape changes over time along the entire ventricle, not restricted at the lateral wall of the lateral ventricles. In addition, shape changes associated to the antidepressant

properties of ECT were also not restricted to the subventricular zone. These findings suggest that although the ventricles decrease in volume, this will likely not be entirely due to neurogenesis in the SVZ.

## GENERAL DISCUSSION

In the following, a brief general discussion will be presented regarding literature relevant to the studies included in this thesis.

### NEUROPLASTICITY

Two studies presented in this thesis suggest that neuroplasticity (and possibly neurogenesis) in the dentate gyrus of the hippocampus (but not in the subventricular zone) plays a role in the antidepressant effects of ECT. In animal research ECS has been shown to induce neurogenesis in the dentate gyrus of the hippocampus (Ito et al., 2010; Madsen et al., 2000; Nakamura et al., 2013; Olesen, Wörtwein, Folke, & Pakkenberg, 2017; Parent, 2007; Perera et al., 2007), together with other neuroplastic effects outside the dentate gyrus such as angiogenesis, synaptogenesis and dendritic arborization (Chen, Madsen, Wegener, & Nyengaard, 2009; Ekstrand, Hellsten, Wennström, & Tingström, 2008; Newton, Girgenti, Collier, & Duman, 2006; Vaidya, Siuciak, Du, & Duman, 1999; Wennström, Hellsten, Ekdahl, & Tingström, 2003). The volumetric increases of the dentate gyrus (Chapter 3), together with the absence of an indication of vasogenic edema (Chapter 5), indicate that ECT also has neuroplastic effects in the human brain, which in turn are associated with the antidepressant effects of ECT. In Chapter 6, no clear evidence was found that ECT stimulates neurogenesis in the other neurogenic region of the brain: the subventricular zone.

Although correlative in nature, these findings are in line with the neurogenic hypothesis of depression. In its simplest form the neurogenic hypothesis states that 1) decreased neurogenesis in the hippocampus is at least partially responsible for depression and that 2) reversing this decrease (by stimulating neurogenesis) would lead to remission of depressive symptoms (Eisch & Petrik, 2012; Miller & Hen, 2015; Petrik, Lagace, & Eisch, 2012). Especially studies testing if decreased neurogenesis is responsible for depression have yielded conflicting results (Anacker & Hen, 2017; Petrik et al., 2012) and therefore it is not likely that the neurogenic hypothesis will hold in its current form. However, the idea that neuroplasticity contributes to the antidepressant action of various therapies receives support. Studies show that some antidepressant effects do rely on neurogenesis (i.e. preventing neurogenesis prevents antidepressant response), but not all (Anacker & Hen, 2017). For ECT, it may also be the case that only some of the effects are explained by neurogenesis.

Acknowledging that depression is a heterogenous disorder with (most likely) a complex interplay of causal mechanisms, it could be that some (if not all) forms of depression will (in part) be due to decreased neurogenesis (or hippocampal/DG dysfunction) and that especially these types of depression will benefit from neurogenesis enhancing treatments. If

7

this is true, it would be important to study which patients fall in this category, and provide them with treatments that are potent neurogenesis enhancers. A possible way to find out if patients have dentate gyrus dysfunction resulting from aberrant neurogenesis is to test for DG-dependent cognitive processes. The DG has been identified to be of crucial importance in pattern separation (a process enabling the ability to discriminate between highly similar events) and cognitive flexibility in the context of learning and memory (Bakker, Kirwan, Miller, & Stark, 2008; Epp, Silva Mera, Köhler, Josselyn, & Frankland, 2016; Leutgeb, Leutgeb, Moser, & Moser, 2007). Neurogenesis, in turn, has also been identified to play a key role in regulating and mediating these processes (Anacker & Hen, 2017; Clelland et al., 2009; Epp et al., 2016). Consequently, difficulties in tasks relying on pattern separation and/or cognitive flexibility, such as the Mnemonic Similarity Task or the Picture Recognition task, might reflect DG dysfunction and aberrant neurogenesis (Anacker & Hen, 2017; Bakker et al., 2008; Brock Kirwan et al., 2012; Das, Ivleva, Wagner, Stark, & Tamminga, 2014; Déry et al., 2013; Kirwan & Stark, 2007; Stark, Yassa, Lacy, & Stark, 2013; Wesnes, Annas, Basun, Edgar, & Blennow, 2014; Yassa & Stark, 2011). If true, research could set out to assess the possible predictive properties of these processes for the antidepressant response in neurogenesis enhancing treatments. In effect, ECT might be targeted to patients showing DG-dependent cognitive impairment without having them to be scanned with an MRI scanner. Being able to predict which patients will respond to treatment will reduce the risk of administering ECT without results. This will not only prevent people from being exposed to the risk of developing cognitive side effects without a beneficiary effect of the ECT treatment, it will also prevent the huge disappointment experienced by patients who did not respond to ECT. In addition, it will also be cost-effective.

When considering ECT as a potent neurogenesis enhancing treatment, it should be noted that a time-gap is observed between the antidepressant effects of ECT (which begin to emerge after just a few sessions, i.e. within a few weeks), and for the newborn neurons to become functionally integrated in the hippocampal circuitry. For example, it takes 2-3 weeks for newborn neurons to be integrated in the rodent hippocampus, yet more than 8 weeks for them to be fully matured (Anacker & Hen, 2017). Patients, on the other hand, may report significant changes in mood before the moment that the new born neurons are fully matured. Therefore, the antidepressant effects of ECT are likely not fully attributable to matured newborn neurons. Other neuroplastic processes (such synaptogenesis, gliogenesis, dendritic arborization, spine formation and maturation), might also contribute to the working mechanism of ECT. In future work it will be important to disentangle the effects caused by neurogenesis from the effects caused by different (neuroplastic) processes in order to create a better understanding of ECT as an antidepressant treatment.

## **SIDE EFFECTS**

Cognitive impairment after ECT is temporary for most people (Chapter 2; Vasavada et al., 2017). However, at the individual level, some people may experience more lasting side effects (Chapter 2; Hebbrecht et al., 2020). Cognitive side effects, together with memory impairment

are disturbing side effects for patients, causing anticipatory fear before, and ruminative stress, after ECT (Frank Koopowitz, Chur-Hansen, Reid, & Blashki, 2003; Griffiths & O'Neill-Kerr, 2019; Rush, McCarron, & Lucey, 2007; Vann Jones & McCollum, 2019). Alleviating and/or preventing these side effects [(for example with the use of acetylcholinesterase inhibitors (Henstra et al., 2017; van Buel et al., 2017))] will greatly improve the tolerability of ECT and improve patients' perception of ECT.

Retrograde amnesia (amnesia for previously stored memories) is one of the most troubling and hard-to-study side effects of ECT (Fraser, O'Carroll, & Ebmeier, 2008; Prudic, Peyser, & Sackeim, 2000; Sackeim, 2014; Semkowska & McLoughlin, 2013, 2014). Patients suffering from this type of amnesia have trouble recalling personal events, which can be distressing. Several groups found that objective memory performance on autobiographical memory measures was impaired up until six months after ECT, yet performance on subjective memory measures showed impairments that were more persistent (Fraser et al., 2008). However, these findings have been contradicted showing also improvements in subjective memory (Vann Jones & McCollum, 2019).

The exact causes of these memory impairments remain unknown. Given that much of the ECT related anxiety and worry is related to memory and cognitive impairment (Obbels, Verwijk, Bouckaert, & Sienaert, 2017), it is important to get a better understanding of the causes of, and ways to counteract or prevent, memory impairment. Considering ECT as a potent neurogenesis enhancing treatment it could be that neurogenesis might play a role in this side effect (Akers et al., 2014; Anacker & Hen, 2017). New neurons that are added to the existing hippocampal circuits, remodel these circuits, compete with existing neurons, form new synaptic connections and may even replace previously formed synaptic connections of 'old' neurons (Akers et al., 2014; Toni et al., 2008, 2007; Yasuda et al., 2011). Memory engrams [populations of cells that become active during formation and recall of memories (Tonogawa, Liu, Ramirez, & Redondo, 2015)] may therefore also be disturbed by the addition of new neurons to these engrams (Anacker & Hen, 2017). This is also predicted by computational models of memory and neurogenesis (Weisz & Argibay, 2012) and believed to be the underlying mechanism of infantile amnesia [the natural process of forgetting memory from infancy (Akers et al., 2014)]. Corroborating these results, it has been shown that increasing neurogenesis in adult mice promotes forgetting of newly learned memories (Akers et al., 2014). Given that ECT may increase neurogenesis in humans, it could be that these newly formed neurons integrate in memory engrams and thereby induce retrograde amnesia. Although speculative, future studies are warranted to investigate this possibility.

## CONSIDERATIONS

The studies presented in this thesis have some inherent methodological limitations that deserve attention. First, the sample size used in the analyses conducted in this thesis (Chapters 2, 3, 5 and 6) is relatively small. Therefore, the results presented in this thesis should function



as a stepping stone for future more adequately powered studies, rather than as confirmatory studies that can easily be generalized. In addition, although the use of an ultra-high-field MRI scanner enabled us to delineate the hippocampus with increased resolution (Chapter 3), the imaging technique remains suboptimal when it comes to studying direct neurochemical and neuroplastic effects. Ultra-high field MRI, while cutting edge, precludes us from directly observing cells, synapses and axons. Positron Emission Tomography may provide a mean to elucidate the effects of ECT on synaptic density, but a tracer for neurogenesis is not yet available. At present, only post-mortem research can provide direct information on all these cellular mechanisms, but this type of research has limitations of its own. Therefore, although volumetric increases (Chapter 3) and diffusivity decreases (Chapter 5) point into direction of neuroplasticity, it is important to keep in mind that directly observing these processes remain challenging in humans.

Another limitation is that the findings in the current thesis are based on two (Chapter 3, 5 and 6) or three (Chapter 2) measurement points. Given that ECT causes very rapid changes in mood and changes in brain structure and function, a time interval of 5 weeks (i.e. 10 ECT sessions) may be too coarse for us to portray a detailed timeline implying causation. This leaves an important question unanswered: do volumetric increases precede improvements in mood, or vice versa? If the structural changes in the brain precede the antidepressant effects, causality would be implied. However, the sparsity of measurement point prevents us to draw definitive conclusions regarding the causal link between brain changes and mood improvements.

As alluded to in previous paragraphs, (major) depression is a heterogenous disorder. Given that a major depressive disorder (as classified by the DSM-5), consist of a combination of either depressed mood or anhedonia, together with at least four other symptoms (as depicted in Fig. 1, Chapter 1), it could be that the etiology of this disorder varies considerably. Differences in the pathogenesis of depression might also call for different treatment strategies, and possibly more importantly, it may be that the effects of ECT differ when different etiologies are present, which may be the case in our sample. Elucidating which clusters of symptoms have shared etiology (or the other way around: grouping etiological similarities regardless of the phenotype), may result in the opportunity to more effectively target treatments to patients.

## CLINICAL IMPLICATIONS

Since the findings presented in this thesis come from a small sample and warrant replication, the direct clinical implication of this work is limited. However, the results do give rise to some potential clinical implications. In Chapter 3, we showed that the volume of the DG increased after ECT, that this increase correlated with symptom improvement and that baseline DG (specifically, the asymmetry index of the left and right DG) could predict clinical effect. If these effects hold in larger samples, and especially if the predictive effect of the DG asymmetry index holds when measured using more readily available clinical MRI scanners, it could

be used as a potential marker to give a better estimation of who is likely to respond and who is not.

Another scientifically interesting way forward is to see whether DG volume (for example relative to the total intracranial volume) at baseline is correlated with certain cognitive tasks that rely on adequate DG functioning [such as pattern separation and cognitive flexibility (Anacker & Hen, 2017; Bakker et al., 2008)]. If so, do impairments in DG related cognitive tasks also predict ECT efficacy? Clinically, this will make prediction of ECT efficacy more feasible and cost-effective compared to using an MRI scanner.

Together with other predictors still being investigated, a more informed advice can be given to the patient opting for ECT. Additionally, when prediction (of both the antidepressant effect, but also the side effects) is more accurate, ECT could be used earlier in the process of treating depression with a reduced risk of administering it without beneficial and/or with severe side effects.

Finally, if neurogenesis indeed plays an important role in the high efficacy of ECT, as this thesis suggests, it would be key to develop new interventions that stimulate neurogenesis but lack the necessity for anesthesia. Examples are sustained physical activity, intermitted fasting, cognitive training, or, better yet, a combination of these three methods.

## GENERAL CONCLUSION

Electroconvulsive therapy is a treatment with a long history. It is effective, safe and used in severe and persisting depressive disorders. The exact effects of ECT on the brain, and more specifically, its mechanism in alleviating depression remain not fully understood. In this thesis, research is presented aiming to elucidate some of the effects of ECT on the brain while simultaneously investigating the relevance of these effects for the efficacy of ECT. The studies presented in this thesis show that ECT is associated with short term cognitive deficits, and that brain changes suggest neuroplasticity occurring after ECT. Important next steps would be to test whether the findings hold in larger samples using more feasible techniques (i.e. 3T MRI). Furthermore, the neurobiological correlates of brain volumetric changes should be further investigated, together with their relevance to ECT's positive effect on mood and adverse effects on cognition and memory.

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