SUNDHEDSSTYRELSEN

# Form 2: Project description

**Table 1: Project description**

**1. Aim, patient perspective and novelty value**

Electroconvulsive therapy (ECT) is the most efficacious treatment for patients with severe depression, psychotic depression, as well as for patients with depression, who have not benefitted from other treatments, or have a high risk of suicide (UK Review group, 2003, Fink et al., 2007). ECT is generally considered an effective and safe treatment resulting in significant improvement and is widely and uniformly practiced in Denmark (Bjørnshauge et al., 2019). However, despite decades of research, there is still debate about potential adverse effects, particularly on cognition.

A large meta-analysis of almost 3000 ECT-treated patients (Semkovska et al., 2010), found that the ECT-associated cognitive disturbances subsided, or even improved two weeks after the treatment. Despite this encouraging result, some patients continuously complain of persistent cognitive disturbances. We do not know how prevalent this is, and there is currently no way to predict beforehand, who will experience these very unpleasant or even debilitating side-effects, and who will not. Finally, we often see a discrepancy between the side-effects the patients experience (subjective effects) and the impairment that can be measured using neuropsychological tests (objective effects). We have no scientific explanation for this phenomenon, which is extremely unsatisfactory from a patient perspective.

Further investigation of these matters is urgently needed and would enable clinicians to better advise patients about the treatment. Such scientific knowledge could also help to clarify cases where patients seek economic compensation from "Patienterstatningen".

***AIM**:* The aim of DANSECT is to investigate the adverse effects of ECT in general, and on cognition in particular. Specifically, the research project aims to examine:

- Prevalence, extent and persistence of adverse cognitive effects following ECT
- Prediction of adverse effects of ECT by combining sensitive neuropsychological tests, cutting edge structural neuroimaging (MRI) and other neurobiological measures
- Associations between neuroimaging findings and clinical and cognitive effects (e.g. memory disturbances)
- Short- and long-term objective and subjective cognitive effects of ECT

***BACKGROUND**:* The adverse cognitive effects observed after ECT include disturbances of several cognitive functions, such as attention, executive functions and memory. The effects on memory are often the most pronounced and include memory loss for events before (anterograde amnesia) and/or after (retrograde amnesia) the treatment. As mentioned, the cognitive disturbances are on average regarded as transient (subsiding within 2 weeks) but may in an unknown number of individual cases persist for longer periods, and even become permanent. The field is generally characterized by studies with discrepancies between findings and several methodological weaknesses. The use of insensitive neuropsychological tests by previous studies have possibly led to a systematic overestimation of the cognitive function of ECT-patients due to ceiling and practice effects. In some of the better studies, the patients have furthermore been treated with what today must be considered out-dated equipment resulting in more severe effects on cognition (Sackeim et al., 2007). Additionally, improvements in the level of depressive symptoms need to be controlled for, as depression itself is associated with cognitive disturbances. It is therefore impossible to disentangle the effects of the disease and the treatment on cognition without a proper control group.

The relationship between ECT-associated structural brain changes, clinical outcome and potential adverse cognitive effects has only been studied a few times and in small samples. More knowledge about this would help answer burning questions about why some people experience cognitive side-effects while others do not, and potentially enable us to predict these side-effects in individual cases.

These important questions stresses the need for new investigations based on cutting edge neuroimaging technology as we have in Glostrup, comprehensive neuropsychological assessments and large study populations. Furthermore, we have at our disposal a very realistic *Foerst driving simulator* enabling transference of the results from sensitive neuropsychological tests done in the lab to a performance measure of daily cognitive function i.e. car driving ability. Moreover, proper control groups are of huge importance to ensure that the adverse cognitive effects of ECT are not masked by improvements in affective state.

The results of this study will thus be of paramount importance to the several thousand patients who every year receive ECT in Denmark and will also raise international awareness.

## 2. Method

The project is divided into Work Package 1 (WP1) and Work Package 2 (WP2).

*WP1* is a prospective follow-up study with the aim of examining why cognitive side-effects of ECT occur and potentially find predictors for who they affect by investigating the ECT-associated cognitive disturbances, structural brain changes and clinical outcomes. WP1 comprises an ECT-group (45 patients) and a clinical control group (45 patients). The former consists of patients with depression receiving ECT, and the latter consists of matched patients with depression treated pharmacologically. The examinations will take place at three time-points; before, immediately after ECT or just before discharge, and 6 months after.

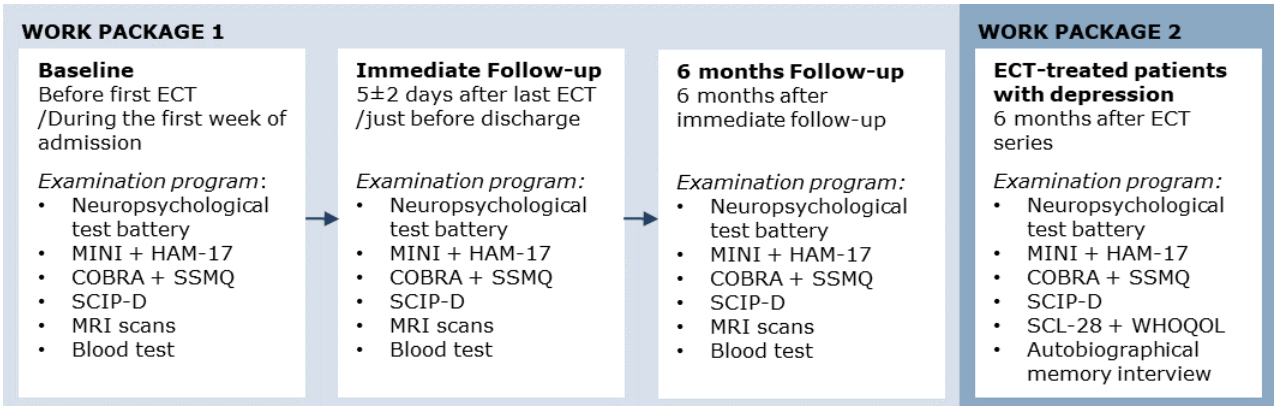
*WP2* is a cross sectional study with the aim of investigating the prevalence and severity of cognitive disturbances in an ECT-treated population of patients with depression 6 months after the treatment. WP2 additionally aims to evaluate the validity of the objective and subjective cognitive disturbances by examining the associations between cognition measured by neuro-psychological tests and self-rating questionnaires, and how they transfer to a performance measure of daily cognitive function using a driving simulator. In WP2 approx. 200 patients will be included from the different participating Mental Health Centres.

See below for an overview of the research project.

### Participants

*WP1:* In-patients (age 18-95) referred to ECT or pharmacological treatment due to moderate to severe depression (according to ICD-10) are eligible. The exclusion criteria include severe psychotic symptoms or suicidal impulses. Additionally, patients who currently receive maintenance ECT or have received ECT during the past 6 months will be excluded. Patients who receive a new series of ECT within the follow-up period will be analysed separately. Special exclusion criteria regarding the MRI scans include: first trimester pregnancy, claustrophobia and severe restlessness; other contraindications to MRI; severe somatic disease.

*WP2:* All patients treated with ECT for depression at the participating Mental Health Centres are eligible for inclusion in WP2.




### Power calculation

In a two-sample paired design, including 45 patients in each group in WP1, with 80% power and a significance level of 0.05, we can detect an effect size of 0.595. This is a clinically significant effect size in line with deficits found on e.g. the Spatial Working Memory test from Cambridge Neuropsychological Test Automated Battery (CANTAB). According to Semkovska et al. (2010) several neuropsychological tests show an even greater effect size comparing before and after treatment. Considering that the prevalence and severity of these subjective cognitive

disturbances 6 months after ECT are neither known nor well-researched, it is not possible to predict the necessary sample size for WP2. Nevertheless, a conservative estimate is that 200 included patients in WP2 will be sufficient to examine the main effects on cognition (e.g. memory) and also correlations with objective measures, given that there is a clinically relevant deficit present.

**Examination programme**

Examinations in *WP1* will take place at three time points:

1. Baseline: Before the first ECT for the ECT-group and at admission for the clinical control group.
2. Immediate follow-up: 5±2 days after completion of the ECT series for the ECT-group, and immediately before discharge from the hospital for the clinical control group. The decisions to terminate the ECT series, or discharge the pharmacologically treated patients, are both made after a significant clinical improvement. The two groups will therefore be comparable in their disease course at these time points.
3. 6 months follow-up: 6 months after immediate follow-up for both groups.

The examination program for both groups in WP1 is mentioned in the above figure. Each examination in WP1 will last approximately 3 hours, and breaks will be included. As these patient groups are severely ill and often have an increased fatiguability, not all patients will be able to complete the entire examination program. In these cases, a prioritisation of the examinations will be made, and missing data will be handled in the statistical analyses.

The examination program in *WP2* will include the same assessment tools as WP1, with the exception of the MRI scans and blood tests. In addition to this, WP2 will include a semi-structured interview assessing autobiographical memory, and assessments of functional capacity and quality of life.

**Recruitment**

Patients will be recruited from Mental Health Centres in the Capital Region (WP1+2) and other participating centres in Denmark (WP2). This ensures a sufficiently large patient base for inclusion.

**Statistical Analyses**

Based on data from *WP1* we will: 1) Investigate the effects of ECT vs. pharmacological treatment on both clinical and cognitive outcome using *propensity score matching*. 2) Explore the relationship between the cognitive side-effects, structural brain changes, other neurobiological measures, and clinical outcome across the three timepoints in both groups. 3) Evaluate the short- and long-term objective and subjective cognitive effects of ECT vs. pharmacological treatment.

Based on data from *WP2* we will: 1) Analyse the prevalence and severity of cognitive disturbances 6 months after ECT-treatment. 2) Evaluate the validity of and relationship between the objective, subjective, and performance-based measures of the cognitive effects of ECT. Additionally, we plan to use machine-learning to predict adverse cognitive effects by combining information obtained from neuropsychological tests, MRI, and blood samples. This plan is perfectly aligned with the National strategy for personalised medicine which has the overall goal to improve Danish healthcare by using a technological infrastructure that links directly into the clinical setting.

## 3. Regulatory and ethical requirements

The participants will receive information about the project orally and in writing. Regardless of inclusion in the project, there will be no changes in the patients' treatment, which will follow the department's usual treatment guidelines. Usually, the examinations do not lead to any particular discomfort and none of the planned examinations are assumed to affect the course of the disease. As the patients may experience the assessments as tiring, breaks will be included to minimize attrition. Additionally, we believe any disadvantage will be outweighed by the extra care and attention the patients receive by participating in the study.

Participation in the examination program is voluntary. The patients can withdraw from the study or opt out of parts they do not wish to participate in at any time. The patients are covered by The Danish Act on the Right to Complain and Receive Compensation within the Health Service (Patientforsikringsloven). The protocol fulfils the Helsinki Declaration II.

The protocol will be submitted for approval to The Regional Committees on Health Research Ethics (National Videnskabsetisk Komité). The project will be reported to The Danish Data Protection Agency (Datatilsynet). These approvals will be applied for in April 2019 and are assumed to be obtained during the following months, at the latest in August in time for the project.

**4. Patient perspective**

Professor Poul Videbech (PV) has for several years participated in meetings and events with patient organizations, where he has discussed their experiences with the effects and side-effects of their ECT treatments. PV has also treated many patients with psychotherapy after they have received a series of ECT. Additionally, he has been in dialogue with patients in Facebook groups for ECT patients who experience cognitive side-effects. Furthermore, PV has participated in hearings at Christiansborg with concerned members of the Danish parliament and representatives from patient groups. In this way, the involvement of patients has been an integral part of the project from its very conception, and continuously throughout its development. The very idea for the project thus stems from the patients' experiences with side-effects and their wish for better scientific evidence. Consequently, the patients have been profoundly involved in the formulation of the project's aims and objectives. The continued involvement of patients will be ensured by patient representatives from Depressionsforeningen on the advisory board.

The need for more scientific knowledge about the side-effects of ECT, especially on the cognitive functions, is clear as they cause the most concern for patients and represent a large impediment for their recovery. Furthermore, knowledge about these matters will profoundly influence the patients' possibilities for seeking economic compensation from "Patient-erstatningen", which is of great importance for the individuals suffering from ECT-associated side-effects.

**5. Expected results, communication and implementation**

We expect to provide new knowledge about the prevalence of cognitive effects of ECT. Furthermore, we strive to be able to predict the risk of these adverse effects to improve the clinical counselling of the patients with regards to choosing the treatment or not. The results of this project will make it possible for the doctor and the patient directly to compare the adverse effects of antidepressant medications with those of ECT.

We will strive to ensure a smooth and swift implementation of the research outcomes generated by this project into the clinic, to generate a true precision medicine approach to future ECT patients. We thus expect the results of DANSECT to be important for the treatment of the most severely affected sufferers from depression. The results of the research project will be communicated to scientists and clinicians through national and international conferences and publications in scientific journals. Additionally, results will be communicated through articles published in trade magazines and popular science media, such as Ugeskrift for Læger, Psykolog Nyt and Videnskab.dk, as well as in the daily press. Furthermore, presentations will be held for relevant health care professionals at Mental Health Centres and at various assemblies, such as the Danish Psychiatric Society' annual meeting. The acquired knowledge will also be communicated to patients and relatives through patient groups and -associations, including SIND and Depressionsforeningen. In addition, the communication of results will be directed at decision makers to ensure that the results of the research project will be utilized. This is planned to be attained through networks and organizations such as the Danish Psychiatric Society and Psykiatrifonden.

**6. Selected key references relevant to the project**


- Fink M, Taylor MA. *JAMA*. 2007; 298:330–332.
- The UK Review Group. *Lancet*. 2003; 361:799–808.
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- Sackeim HA et al. Neuropsychopharmacology. 2007;32(1):244-54.
- Gbyl K, Videbech P. Acta Psychiatr Scand. 2018;138(3):180-195.
- Hermida AP et al. Psychiatr Clin North Am. 2018;41(3):341-353.
- Dong M et al. Psychogeriatrics. 2018 Nov;18(6):468-475.


**Table 2: Project group and the organisation**

## 7. Qualifications of the project group

The research project will be conducted at Centre for Neuropsychiatric Depression Research (CNDR) located at Mental Health Centre Glostrup (MHCG) in collaboration with other Danish ECT departments. Numerous PhD-projects has been and are currently carried out in the research environment at MHCG, which has the necessary clinical and scientific expertise, as well as the necessary facilities to carry out the present research project. The MRI scans are carried out in the Functional Imaging Unit at Glostrup Hospital headed by professor Henrik Larsson with whom we already have a close collaboration in another ECT project.

The CNDR and professor Poul Videbech have long-term experience in performing research in ECT and in neuroimaging. Furthermore, we are already conducting an ECT project that is recruiting patients receiving ECT. This project will end the inclusion of patients in September 2019 and the DANSECT project can then continue to use the existing organisation to recruit patients. We thus have the necessary experience and infrastructure to conduct a complicated study like the present.

See enclosed CVs for Poul Videbech, Henrik Larsson, Christina Blanner Kristiansen, and Didde Bjørnshauge.

## 8. The organisation of the project group

The research project will be carried out as a neuropsychological PhD study and will involve collaborators from the Mental Health Centres of The Capital Region and other Mental Health Centres in Denmark.

The PhD-student Didde Bjørnshauge, cand.psych., will be heading the project and conducting the neuropsychological assessments. Christina Blanner Kristiansen, MD, PhD, will conduct the MRI scanning and blood sampling.

The Psychiatric department in Vejle has already offered to participate in the study and assist with the inclusion of patients.

**Advisory Board**

Leading psychiatric experts on ECT from Vejle, Skejby, Aalborg, Odense and Copenhagen has accepted to participate in an advisory board. Additionally, patient representatives from Depressionsforeningen is participating.

**Supervisors and associated experts**

- Poul Videbech, Primary supervisor, Professor at University of Copenhagen, CNDR, Mental Health Centre Glostrup.
- Birgitte Fagerlund, Project supervisor, PhD, Senior researcher, cand.psych, Center for Neuropsychiatric Schizophrenia Research, Mental Health Centre Glostrup.
- Kamilla Miskowiak, Project supervisor, Professor of Cognitive Neuropsychiatry, Department of Psychology, University of Copenhagen, and leader of the Neurocognition and Emotion in Affective Disorders Group (NEAD), Mental Health Centre Copenhagen.
- Professor Henrik Larsson, Functional Imaging unit, Glostrup

**Time plan**

The project is anticipated to start September 1st, 2019 if the necessary approvals has been obtained. The project will last 3 years according to the following plan: