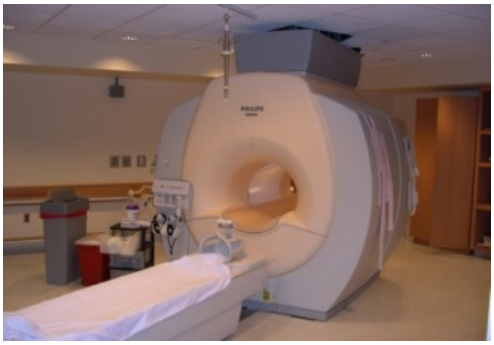
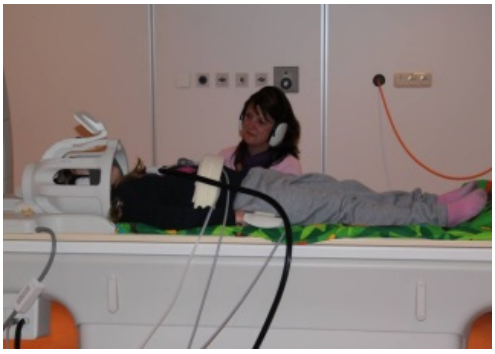
Projectplan samenwerkingsproject projecttoeslag

Bijlage bij aanvraag projecttoeslag

Title

Neuro fM**R**I bi**o**markers for **tre**atment **n**avigation in **d**epression (NEUROTREND)





1. Background, problem formulation, goals, added value

Background

Major depressive disorder (**MDD**), is a mental disorder characterized by at least two weeks of low mood that is present across most situations. It is often accompanied by, loss of interest in normally enjoyable activities, low energy, and pain without a clear cause. People may also occasionally have false beliefs or see or hear things that others cannot. Some people have periods of depression separated by years in which they are free of complaints while others nearly always have symptoms present. Major depressive disorder can negatively affect a person's personal, work, or school life, as well as sleeping, eating habits, and general health.

Depression is the most prevalent neuropsychiatric disorder, and in 15-20% of cases becomes chronic. The costs of depression (directly and indirectly) amount to 3 billion euros in the Netherlands, with high costs and large impact on quality of life. Most of the costs are generated in the group of patients with chronic depression (about 30% of the patients). Furthermore, in that patient group the highest impact on quality of life is found.
A specific focus should be on depression in the elderly, because diagnosis can be difficult (masked depression often occurs) in this specific group of patients and the disease course is often towards chronicity in these patients. Furthermore, older age was found to be an important risk factor for a worse course in MDD in a Dutch longitudinal cohort study (Schaakxs 2018)

Problem statement

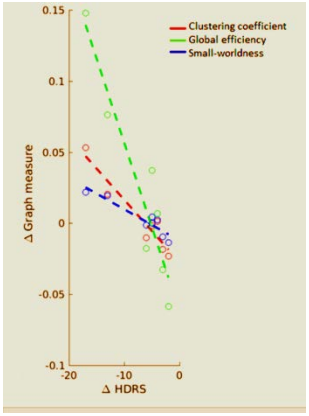
Current diagnostic tests are subjective and inaccurate. The diagnosis is based on the person's reported experiences and a mental status examination. There is no laboratory test for major depression. Especially in elderly there is a great tendency to underreport, with often socially accepted responses on questionnaires.
Objective and accurate biomarkers are therefore urgently needed to improve treatment at lower costs (Swedish council of HTA, 2004).
One of the urgent issues is the selection of patients that will develop a chronic refractory depression. A large group of patients benefit from 'treatment as usual' (psychotherapy, supported by antidepressants). However, in some patients symptoms will not remit or they suffer from side-effects of the medication. This leads to a chronic refractory depression with an increased risk of suicide (Between 2–7% of adults with major depression die by suicide; Bergfeld et al., 2018). A successful 'last resort treatment' is Electroconvulsive Therapy (ECT). The published guidelines on the use of ECT in depression show a general consensus on the efficacy of ECT in the treatment of severe depression, treatment resistance to antidepressants and/or suicidal ideation (Pinna 2018). In the search of a personalized treatment approach in ECT,

several biological determinants of ECT are described, both on a neurotransmitter level and on a genetic level. Moreover, fMRI studies pre and post ECT in MDD patients showed a reduction of functional connectivity which was associated with improvement of depressive symptoms. (Perrin 2012).

The relative success of the method led to a position of neurostimulation in the treatment of patients with depression. Therefore objective criteria are needed for treatment navigation: which patients are at risk to develop chronicity and require early more intensive treatments. Meta-analyses on treatment effects are inconclusive (Swedish council of HTA, 2004). There is consensus that depression is (partially) based on dysfunctional connectivity in brain networks (e.g. Drysdale 2017), although the exact characterization is missing. Meanwhile, biomarkers would be a possible pathway for treatment navigation.

Project goals

Research during the last decade identified MRI-outcomes as potential powerful biomarkers (i.e. the connectome signatures in fMRI Lui et al., 2011). In our own work, connectivity changed as a consequence of neurostimulation (repetitive TMS) showing a functional reorganisation from a high clustered (dense connected) default mode brain network to a more steady state after neurostimulation only in responders.



Courtesy Debby Klooster; TU/e

Figure 8: High correlation between the change in graph parameters and clinical outcome within the DMN.

The goal of our project is to further develop and validate MRI-based biomarkers for diagnosis and treatment stratification of depression. The project will be embedded in a close collaboration and colocation of researchers, and can leverage strongly on ongoing and future e/MTIC projects (such as the Medicaid project presented to the TKI HTSM). The focus of the project is on patient value and industrial valorization, and scientific excellence as well as industrial relevance are both guaranteed through the TU/e-Philips unique way of cooperating in which all project are jointly supervised by the university, the hospitals and industry.

Added value for TKI program and knowledge infrastructure

The project strongly contributes to the HTSM Healthcare roadmap (in particular to its diagnostics and therapy ambitions).

The technology for diagnosis will land in decision support systems for diagnosis and treatment stratification and the selection of therapies.

Strong involvement of Philips, Hobo Heeze, and hospitals/GGZ Eindhoven ensure the essential embedding of the research in the application environments of the manufacturer and end users. Lastly, the project will ensure open access publishing of widely applicable methods.

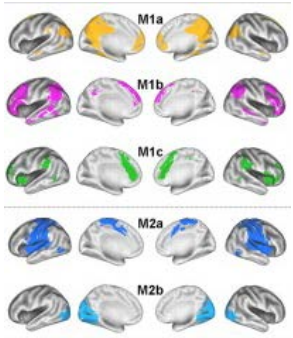
2. Approach

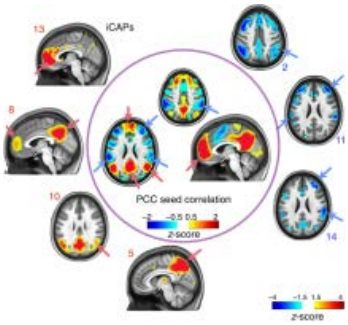
Two PhD students will be appointed in this project, one with a clinical background (psychiatry or clinical psychology) and one with a technical/engineering background. The budget will be provided by the cooperating parties in combination with TKI funding. The combination of a technical and a clinical PhD student is the so-called twin approach with which our groups have worked for MR imaging research since 1999.

- Patients will be selected from the clinical partner GGZ-E, based on a reconfirmed DSM-5 diagnosis. We will aim at a group of 100 patients and 50 controls. Patients and control will be matched group wise. Special attention will be focused on including also geriatric patients.

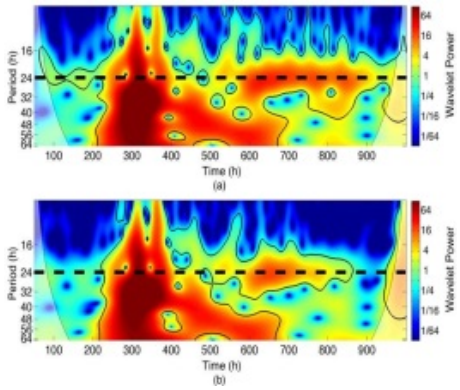
All patients will be assessed with the Hamilton Depression Scale, a mood rating scale (POMS), a cognitive test for slowing (CVST), a short memory test (Rey ALT) and a quality of life scale. The main outcome will be MRI parameters. A multimodal approach will be followed, using four lines:

- fMRI focused on temporal directed connectivity (Bernas et al., 2017)

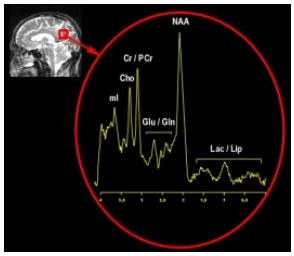


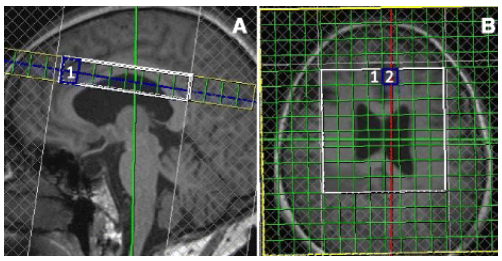


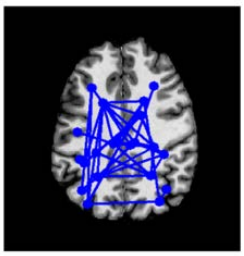
- fMRI focused on wavelet entropy (Bernas et al., 2018)



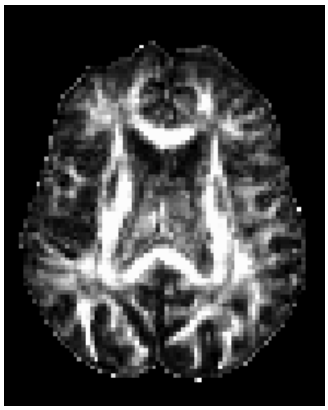
- Spectroscopy focused on whole brain neurotransmitter distribution networks (Van Veenendaal et al., 2016; 2018).

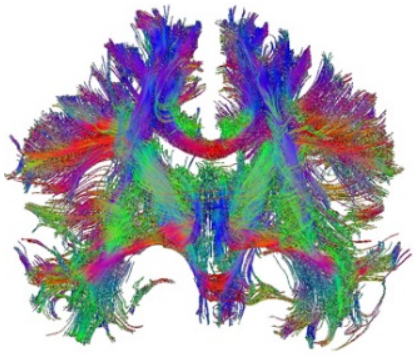






- DTI for analysis of anatomical connectivity.





Special attention will be paid to clean the fMRI data from confounding effects caused by, for example, breathing and cardiac cycle. For that purpose physiology data will be recorded during scanning and all fMRI data will be recorded with multiple echo's allowing for a more detailed analysis of the BOLD response (Kundu et al., 2012). This approach yields more reliable fMRI data allowing for improved analysis at the individual level.

There will be three work packages:

WP1. First year - preparation
- Clinically: patient selection and clinical investigations.
- Technical: preparing the exact sequences for multimodal MRI scanning.
Go/no go: sufficient patient inclusion

WP2. Second year - testing
- Scanning of the patients and controls.
Go/no go: drop-out rate < 10%

WP3. Third and fourth year – analysis and implementation
- Post-processing of MRI results and publications/PhD theses.
Go/no go: ---

Timing

The project start will start October 1, 2018. Starting dates of individual PhD projects are adapted to the availability of high-quality candidates. We currently anticipate that all positions will be filled within one year from the start of the project so that the projected end date is September 30, 2023. Project progress reviews occur twice a year, during the meetings of the steering committee.

3. Relation budget – project plan

As stated, two PhD students will be appointed in this project, one with a clinical background (psychiatry or clinical psychology) and one with a technical/engineering background. The two PhD students, the (scientific) support, facilities and supervision, the cost for patient inclusion, MRI scans and the necessary upgrade of the MR scanner, will be paid from the in-kind and in-cash contribution from the partners and the TKI support.

Appendix A: Scientific project description

PhD1 (technical PhD)

Abstract and objectives

The goal of the overall project is to further develop and validate MRI-based biomarkers for diagnosis and treatment stratification of (major) depression. The specific task of the technical PhD student is to establish a 3T MR data acquisition and data processing pipeline that can be used in a clinical setting. In particular, for the validation of the imaging biomarkers, it is key to minimize the effect of confounding variables in the measurement. For example, from several fMRI studies it is known that these confounders may contribute to signal changes, that can be mistaken as a BOLD effect. Acquiring physiology data simultaneously and using multi echo techniques can significantly reduce the confounders and improve the reliability of the signal and the analysis.

Justification

Current diagnostic tests in psychiatry are subjective and inaccurate. The diagnosis is based on the person's reported experiences and a mental status examination. There is no laboratory test for major depression. Objective and accurate biomarkers are therefore urgently needed to improve treatment at lower costs (Swedish council of HTA, 2004).

State of the art

Although many years of research has yielded several “candidate” imaging biomarkers for major depression, none of these biomarkers have been clinically validated. Furthermore, most of these biomarkers were “only” able to e.g. separate responders from non-responders (for a specific treatment) at the group level. In order to be clinically relevant, a biomarker needs to have a high specificity and sensitivity at the level of the individual patient.

Impact

Having MRI-based biomarkers for diagnosis and treatment stratification of (major) depression will have a strong positive impact on the patient value of patients with major depression and can significantly reduce costs and improve efficiency. In particular, to establish this, it is key to develop a .3T MR data acquisition and data processing pipeline that can be used in a clinical setting.

PhD2 (clinical PhD)

Abstract and objectives

The goal of the overall project is to further develop and validate MRI-based biomarkers for diagnosis and treatment stratification of (major) depression. The specific task of the clinical PhD student is to keep the project clinical driven. Focus is on patient selection, validation of the correct diagnosis and assessment of the patients (the non MRI measurements). During the phase of publication this PhD student focuses on the clinical implication and 'the return to clinical practice'.

Justification

The value of biomarkers is not only its identification but also the association with clinical interpretation. This requires correlation with questionnaires but also with diagnostic categories (e.g. DSM-5).

State of the art

See description of the technical PhD-student.

Impact

The impact of markers that can serve as treatment navigator can potentially transform the treatment and the follow-up of this disorder. Potentially it can identify patients that need other forms of treatment (e.g. neurostimulation/ECT) at a much earlier stage.

Openbare samenvatting samenwerkingsproject (projecttoeslag)

Projectgegevens

TKI('s):	HTSM
Deelnemers:	TU Eindhoven, Philips Research, Hobo Heeze, GGZ Eindhoven
Projecttitel:	NEUROTREND
Startdatum project:	01-10-2018 Einddatum project: 30-09-2023

Samenvatting project

Major depressive disorder (**MDD**), is a mental disorder characterized by at least two weeks of low mood that is present across most situations. Depression is the most prevalent neuropsychiatric disorder, and in 15-20% of cases becomes chronic. The costs of depression (directly and indirectly) amount to 3 billion euros in the Netherlands, with high costs and large impact on quality of life. Most of the costs are generated in the group of patients with chronic depression (about 30% of the patients). Furthermore, in that patient group the highest impact on quality of life is found. Current diagnostic tests are subjective and inaccurate. The diagnosis is based on the person's reported experiences and a mental status examination. There is no laboratory test for major depression. Objective and accurate biomarkers are therefore urgently needed to improve treatment at lower costs.
Research during the last decade identified MR-outcomes as potential powerful biomarkers (i.e. the connectome signatures in fMRI Lui et al., 2011). In our own work, connectivity changed as a consequence of neurostimulation (repetitive TMS) showing a functional reorganisation from a high clustered (dense connected) default mode brain network to a more steady state after neurostimulation only in responders.
The goal of our project is to further develop and validate MRI-based biomarkers for diagnosis and treatment stratification of depression. The project will be embedded in a close collaboration and colocation of researchers, and can leverage strongly on ongoing and future e/MTIC projects (such as the Medicaid project presented to the TKI HTSM). The focus of the project is on patient value and industrial valorization, and scientific excellence as well as industrial relevance are both guaranteed through the TU/e-Philips unique way of cooperating in which all project are jointly supervised by the university, the hospitals and industry.
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