Final report

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The change of mental structure due to psychodynamic psychotherapy modulates brain activation in depression - the Zurich Depression Study

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Summary

While there is a large body of research demonstrating the efficacy of psychotherapy for the treatment of depression, we know little about the effects of psychotherapy on the brain. In the Zurich Depression Study, we explore changes in brain activation in depressed patients before and after six months of psychoanalytic psychotherapy. We link brain activation to relevant behavioural measures (e.g. the Operationalized Psychodynamic Diagnostics (OPD-2)).
In 2018, we were awarded an IPA research grant of 8000 USD. The grant was used to employ a part-time research assistant over several months who helped recruiting participants and assisted data acquisition, and to pay a compensation for study participants. Thanks to this support, we have well advanced in our research study during the past year. We now have acquired longitudinal neuroimaging data of 25 patients with depression who underwent psychoanalytic psychotherapy for six months and of a matched control group of 29 healthy subjects.
The next steps of this research project are the analyses of the acquired data and the publication of results.

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1 Original goals of the research study

The Zurich Depression Study explores changes in brain activation in depression before and after psychoanalytic psychotherapy. The aim of the study is to link changes in brain activation to behavioral measures which are psychoanalytically meaningful. More specifically, the original goal of this study was to include 60 psychotherapy patients with depression, treated by either psychodynamic psychotherapy or cognitive behavioural therapy, as well as 40 healthy controls. Functional magnetic resonance imaging (fMRI) is used to explore brain activation before psychotherapy, and after six and twelve months of treatment.
In a preparatory study, we had developed and validated a stimuli set (Interpersonal Relations Picture Set, IRPS, Fuchs et al., 2018), and an fMRI task (Wade-Bohleber et al., 2019) to use in the Zurich Depression Study. The fMRI task focuses on brain activation during the recall of a highly arousing and conflicting situation in a significant relationship. We assume that such conflicting experiences in relationships are highly meaningful to the pathogenesis of depression. Also, these experiences are the ones that are most often addressed and worked through early on in the psychotherapeutic process. We therefore hope that our fMRI task can capture brain activation that underpin early changes in the psychotherapeutic process. Changes in brain activation are linked to behavioural instruments measuring depressive symptoms (e.g. Beck Depression Inventory II, (BDI-II, Beck, Steer, & Brown, 1996), Hamilton Depression Scale, (HAMD, Hamilton, 1960)) but also psychoanalytically relevant constructs such as repetitive interpersonal behaviour patterns or aspects of psychic structure (as captured by the Operationalized Psychodynamic Diagnostics (OPD-2, Arbeitskreis OPD, 2006)).

2 Methods of the research study

We included patients with a primary DSM-IV diagnosis of depression. Comorbidities apart from addiction disorders and a psychotic disorder were allowed. In case of an antidepressant medication, it needed to be at a stable dosage four weeks prior to inclusion. Healthy controls needed to have no history of a depressive disorder as well as no current psychiatric disorder. Both groups needed sufficient German language skills and to fulfill none of the exclusion criteria necessary to undergo an MRI scan (e.g. metallic implants, pregnancy, claustrophobia, etc.).
Figure 1 illustrates the study design.

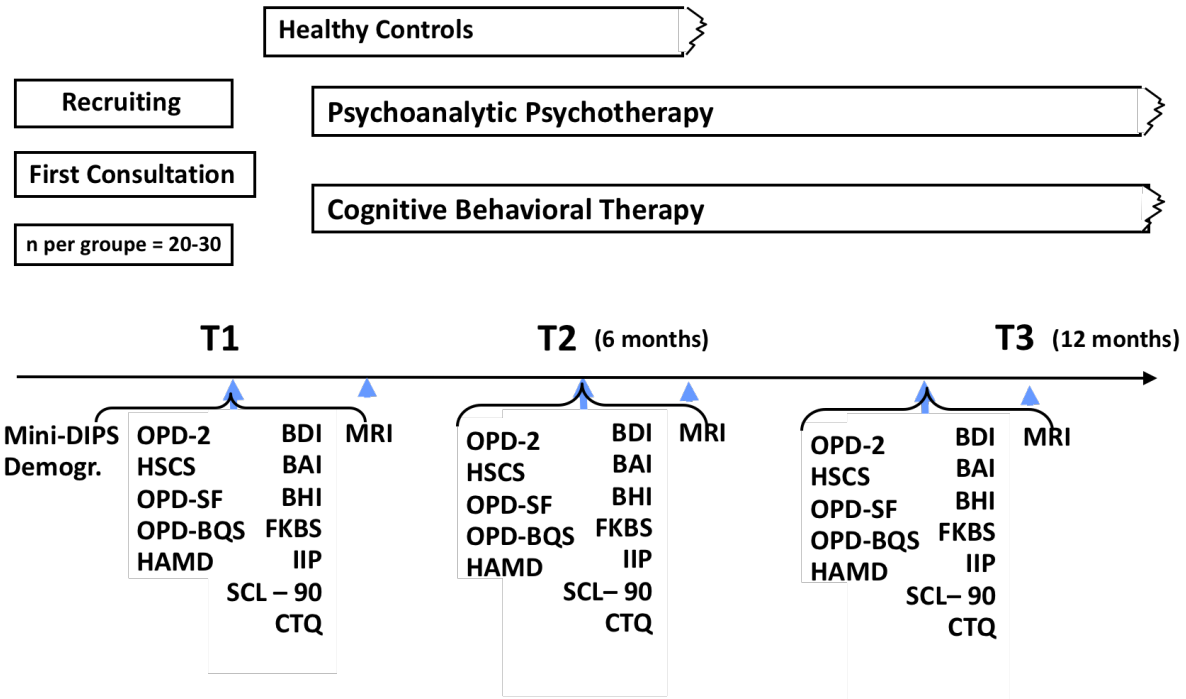

Figure 1. Schematic representation of the study design. Abbreviations: OPD-2 = Operationalized Psychodynamic Diagnostics, second version, HSCS = Heidelberg Structural Change Scale, OPD-SF = OPD Strukturfragebogen (OPD Structure Self-Questionnaire), OPD-BQS = OPD Beziehungsmuster-Q-Sort (OPD MIPQS = OPD Maladaptive Interpersonal Patterns Q-Sort), BDI = Beck Depression Inventory, BAI = Beck Anxiety Inventory, BHI = Beck Hopelesness Inventory, FKBS = Fragebogen zu Konfliktbewältigungsstrategien (Questionnaire on Conflict Resolutions Strategies), IIP = Inventory of Interpersonal Problems, CTQ = Childhood Trauma Questionnaire, SCL-90 = Symptom Checklist, MRI = magnetic resonance imaging.

Further methodological details of this study were outlined in our initial IPA grant application.

3 Progress achieved by the study

From June 2018 to September 2019, we recruited an additional three patients and twelve healthy controls. Moreover, we collected longitudinal data of 15 patients and 10 healthy controls after six months, and nine patients and eleven healthy controls after twelve months. So overall, we conducted 60 measurements.
We now have a sample of 25 depressed patients who underwent six months of psychoanalytic psychotherapy. Of 13 of these we have a measurement after twelve months of psychoanalytic psychotherapy. We also have data of a healthy control group, matched for age, gender, and education, with 29 subjects being measured after six months, and 14 after twelve months.
Currently, we are working on different projects of data analysis, exploring how depressed patients differ from healthy subjects on neural and behavioral dimensions before beginning their treatment. We will then investigate changes in these dimensions in the course of the psychoanalytic treatment

for the depressed patients and in the course of time for the healthy control subjects. We also plan a prediction analysis of the treatment outcome based on the pre-treatment fMRI measurements.
We had described first neuroimaging results comparing depressed patients to healthy controls in our initial IPA grant application.
These initial neuroimaging results were also presented in a research panel at the IPA congress in London during the month of July 2018.

4 Challenges encountered

In spite of intense efforts by our research team, we were not able to recruit a significant number of depressed patients undergoing CBT. We had established a cooperation with different institutions that treat depressed patients with CBT in Zurich, such as the training and research institute at the University of Zurich and a large outpatient clinic specialized in the treatment of depression. Yet, we did not get a significant number of referrals during the past three years. Even the intensified recruitment efforts undertaken by our research assistant (regular phone calls, and personal visits) did not change this. We therefore had to take the decision to not pursue recruiting in this treatment arm and instead focused on those patients treated with psychoanalytic psychotherapy.
Also, we were confronted with a significant number of dropouts, especially in the period from six to twelve months of treatment. However, as the financial and personal resources of this research study are limited, we decided to now terminate recruitment and work with the data that we were able to collect to this point.

5 List of future plans

We have now terminated the data collection for our study. The next steps of our research study focus on data analyses and the publication of results.

- **Project 1:** We will explore differences in brain activation in depressed patients and healthy controls in our fMRI task at T1 (before the beginning of treatment). Such differences will be linked to relevant behavioural measures such as the OPD-2. This set of analyses will be complemented by exploring functional connectivity during the task. We will also investigate if we can differentiate depressed from healthy participants by using a classifier in a multivoxel pattern analysis (Mahmoudi, Takerkart, Regragui, Boussaoud, & Brovelli, 2012). For project 1, we can use a larger sample of participants as we can include patients also from the CBT treatment arm as well as patients who dropped out of the study after the first measurement.
- **Project 2:** We will investigate changes of brain activation in depressed patients after six and twelve months of treatment with reference to the healthy controls. These changes will be linked to **a.** changes in depressive symptoms such as captured by the BDI and HAMD, and **b.** to changes in aspects of psychic structure as captured by the OPD-2 (more specifically dimensions related to reflective functioning or mentalizing such as “empathy”, “use of phantasies”, “experiencing affects”).
- **Project 3:** We will perform an fMRI prediction analysis, although this is limited by our small sample size. We will explore if the functional connectivity of certain regions of interest in our

fMRI task predict treatment outcome. Our hypothesis is that patients with a higher functional connectivity between the regions of interest are those who score higher on certain dimensions of psychic structure relating to reflective functioning or mentalizing. We expect that these patients will benefit more from the psychanalytic psychotherapy (cf. e.g. Ekeblad, Falkenström, & Holmqvist, 2016).

At the moment, we are in the search of funding to support these projects of data analysis.
Once funding is acquired and the data analyses achieved, results of project 1, 2, and 3 will be published in the form of scientific articles. We plan to submit two articles resulting from project 1 at *NeuroImage* and/or *Scan* and/or *Frontiers in Psychology (section Psychoanalysis and Neuropsychoanalysis),* the article resulting from project 2 to the *Journal of Affective Disorders,* and the article from project 3 to *Psychological Medicine* or *Neuropsychoanalysis*.

6 Finances: use of the grant

The amount of 8000 USD that the IPA grant accorded us corresponded to 7725.6 Swiss Francs (CHF). A research assistant, MSc. Eleonora Fadel, was employed from 01.12.2018 to 31.05.2019 at 10%. The costs for her salary were 5079.6 CHF. The compensation for participants over 150CHF for 18 measurements added up to a cost of 2700 CHF. The total amount of the IPA grant was thus spent for our study during the last year.

	CHF
Research assistant 10% for 6 months	5079.6
Compensation for 18 measurements (150CHF)	2700
Total	**7779.6**

7 Acknowledgment

We would like to express our gratitude to the IPA for according us this grant. This grant was crucial for the continuation of our research study during the past year. It enabled us to arrive to a point where we can now terminate the recruiting process and start the data analysis. So far, there are only a handful of neuroimaging studies exploring the effects of psychoanalytic psychotherapy on brain activation. Findings from our study will provide insights on these effects in depression, and, hopefully, serve as a stepping stone for an interdisciplinary dialogue on neurobiological and psychodynamic mechanisms underlying the treatment of this disorder.

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