PROTOCOL

Title:

FMRI neurofeedback treatment of self-blaming emotions in major depressive disorder – a pilot trial

Short Title:

NeuroMooD – Neurofeedback in Depression

Sponsor:

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Synopsis Study 1

Title of clinical trial	FMRI neurofeedback treatment of self-blaming emotions in major depressive disorder – a pilot trial
Protocol short title/Acronym	Neurofeedback in Depression / NeuroMooD
Sponsor name	Institute of Psychiatry, Psychology & Neuroscience, King's College London (KCL)
Chief investigator	Dr Roland Zahn
REC number	
Medical condition or disease under investigation	Partially remitted major depressive disorder (MDD)
Purpose of clinical trial	The overall purpose of this study is to investigate the feasibility and therapeutic potential of real-time functional MRI-based (fMRI) neurofeedback tackling self-blaming emotions in patients with major depression who have only had a partial response to standard treatments.
Primary objective	This study aims at testing clinical benefits and feasibility of a novel fMRI neurofeedback protocol aimed at self-blame-selective neural coupling abnormalities in major depressive disorder.
Secondary objective (s)	This study will further aim at investigating neurocognitive mechanisms underpinning the remission of depressive symptoms.
Trial design	Small randomised controlled clinical proof-of-concept trial.
Outcome measures	**Primary outcome measure:** 1) Reduction of depressive symptoms between Visit 1 and 5 as assessed by the Beck Depressive Inventory (BDI-II). (Reduction of depressive symptoms between Visit 1 and the last treatment session as assessed by the Beck Depressive Inventory (BDI-II) for those who do not complete the study.) **Secondary outcome measures:** 2) Reduction of depressive symptoms between Visit 1 and 5 as assessed by the Montgomery–Asberg Depression Rating Scale (MADRS) by a rater who is blinded to the treatment arm. 3) Reduction of self-rated depressive symptoms between Visit 1 and 5 as assessed by the Quick Inventory of Depressive Symptomatology (QIDS-SR 16). 4) Clinical Global Impression scale change between Visit 1 and 5 by a rater who is blinded to the treatment arm. 5) Withdrawal rates and adverse events after first treatment session. 6) Decrease in post vs. pre-training right ATL-SSCR correlation on fMRI (measured by regression coefficients for the time series as extracted by the FRIEND software for self-blame relative to blaming others (in neurofeedback arm). 7) Reductions in implicit self-blaming bias (self-contempt bias BIAT) between Visit 1 and 5. 8) Increase in Rosenberg Self Esteem Scale score between Visit 1 and Visit 5. 9) Positive Affect score increase and Negative Affect score decrease (PANAS scale) between Visit 1 and Visit 5. 10) Profile of Mood States (POMS) depression score change between Visit 1 and 5. 11) Self-blame ratings obtained prior to the first and after the last treatment session.

	12) Reductions in agency-incongruent self-blame on short version of the value-related moral sentiment task between Visit 1 and 5. 13) Dysfunctional Attitudes Scale (prior & post mood induction if time permits) between Visit 1 and 5. 14) Self- & observer rated clinical global impression on Visit 5 for change since Visit 1. (We may have to drop some of the secondary outcome measures depending on time constraints.)
Sample size	60 MDD patients completing the first treatment visit after being randomised to one of the two treatment arms (n=24 in each arm, plus an estimated 12 lost to follow-up))
Main eligibility criteria	**Main inclusion criteria**: DSM-V recurrent major depressive disorder MDD with at least one major depressive episode (MDE) of at least 2 months duration, insufficiently remitted from a major depressive episode (MDE) for at least 6 weeks, so that they display symptoms that are significantly bothering or impairing (Psychiatric Status Rating of 3 - 5 over the past 2 weeks on Longitudinal Interval Follow-up Interview [LIFE]). If treated with antidepressants, on stable dose for at least 6 weeks prior participation and planning to stay on this dose for the duration of the study. Patients have insufficiently responded to at least one course of cognitive behavioural therapy (CBT) or antidepressants or are not amenable to these standard treatments and are not currently undergoing psychotherapy. Age: 18 or older. Right-handedness in order to ensure homogenous response to our right hemisphere treatment target. Proficiency in English in order to ensure reliable responses on newly developed secondary outcome measures. **Main exclusion criteria**: greater than low suicide risk or risk of violence, other current or relevant past DSM-V axis-I psychiatric disorders. MRI exclusion criteria.

Synopsis Study 2

Trial Design: Case-control observational

In study 2 (case-control study): Panic disorder patients with insufficient remission (n = 30, including 5 dropouts). Healthy controls with no personal or family history of mood, anxiety disorders or schizophrenia (n=30, including 5 dropouts), melancholic MDD (n=30, including 5 dropouts), MDD with no specifiers (n=30, including 5 dropouts).

MDD participants will be either specifically recruited for this study or their data will derive from participation in study 1.

1. Background & Rationale

1.1. Need for research in this area

Depression is a leading cause of disability as measured by years lived with disability (World Health Organization, 2008). This is mainly because individuals with previous episodes of major depression, especially those with residual symptoms, have a greatly increased risk of developing further episodes (Eaton et al., 2008). Even optimal pharmacological and psychotherapeutic treatments fail to prevent recurrence in most patients with major depressive disorder (MDD): meta-analyses show that antidepressant medications (Viguera et al., 1998) and psychotherapy (Piet & Hougaard, 2011) are able to reduce recurrence rates by 50% in the short-term. However, after 5 years, over 60% of patients will have experienced recurrences despite continuing medication (Viguera et al., 1998) or psychotherapy (Bockting et al., 2009). Further, there is no evidence that combining medication and psychotherapy improves long-term outcomes (Lampe et al., 2013) and a high proportion of patients are not amenable to either treatment option (Prins et al., 2009). Therefore, there is an urgent need to develop novel treatments that improve the long-term outcomes of MDD.

1.2. Overall aim of this project

The overall purpose of this project is to test the therapeutic potential and feasibility of real-time functional MRI-based (fMRI) neurofeedback aimed at self-blaming emotional biases in MDD. Further, we aim at understanding the mechanisms by which self-blaming emotional biases affect treatment outcomes in major depressive disorder. Study 1 aims at testing the clinical benefits and general feasibility of a novel fMRI neurofeedback protocol to tackle self-blame-selective neural coupling abnormalities between the right superior anterior temporal lobe (ATL) and the septal/subgenual cingulate region (SSCR) in major depressive disorder. Study 2 aims at investigating neurocognitive mechanisms underpinning (the remission of) depressive symptoms.

1.3. Thematic background of the proposed work

In an fMRI study, we have identified the neural basis of self-blaming emotional bias in major depressive disorder, which persists after remission of symptoms (Green et al., 2012). More specifically, we detected neural coupling abnormalities between the right superior anterior temporal lobe (ATL) with the septal/subgenual cingulate cortex region (SSCR). Whilst decreased coupling was found in the anterior part of the SSCR during the experience of self-blame compared to other-blame, new data from a recently completed MRC-funded prospective study revealed that an increase in coupling in the posterior subgenual cingulate cortex when experiencing self-blaming emotions (e.g. guilt, self-disgust) predicted whether people with MDD whose symptoms had subsided will develop another episode over the next year. These results are in keeping with the importance of excessive self-blame in MDD and have revealed the first fMRI biomarker of recurrence risk in MDD. Self-blame-related fMRI coupling therefore represents an excellent target for interventions to reduce the largely increased risk of recurrent episodes in people who have had one major depressive episode but are currently remitted (Eaton et al 2008).

Jorge Moll, his team at the D'OR Institute for Research and Education in Rio de Janeiro (IDOR), in collaboration with Roland Zahn have provided the technical proof-of-concept that changes in self-blame-selective coupling on fMRI can be detected and fed back to the participants after a short temporal delay in a real-time fMRI setting (Moll et al., 2014). They have investigated whether coupling can be influenced through neurofeedback training (https://clinicaltrials.gov/ct2/show/NCT01920490?term=blame+rebalance&rank=1). This study was carried out at IDOR and is currently being prepared for publication (Principal Investigators: Jorge Moll and Roland Zahn). 24 patients with remitted MDD were double-blindly randomised to two different types of fMRI neurofeedback intervention delivered in

one session: one aimed at stabilising coupling between the anterior temporal lobe and the anterior subgenual cingulate region, the other aimed at increasing coupling between these regions. Both interventions were safe in that there was no increase in Beck Depression Inventory scores after neurofeedback. In fact, there was a trendwise decrease in BDI scores in the stabilisation group after a single session (t=-1.9, df=11, p=.08).
To our knowledge, there is no available neurofeedback intervention to reduce symptoms in patients with major depressive disorder (MDD) who have only insufficiently responded to standard treatment, one of the strongest clinical predictors of recurrence risk. Our novel approach of using fMRI neurofeedback aimed at brain connectivity whilst experiencing self-blaming feelings is highly promising, because it is aimed at the only functional anatomical change so far demonstrated to predict recurrence risk and residual symptoms in MDD. To date, there have been only two pilot studies using fMRI neurofeedback in MDD (n=8 vs. n=8 controls (1) and n=14 vs. n=7 controls (2)). These studies were promising in that patients' symptoms improved (1, 2). However, the studies were not randomised and investigated remission from the depressed state rather than early treatment resistance or recurrence risk. The clinical benefit of fMRI neurofeedback, however, is greater in those patients not sufficiently responding to standard treatment which is what the current study will investigate.

1.4. Background of methods used

1.4.1. Magnetic Resonance Imaging

Part of the participation in this study will involve a research scan with a 3T Magnetic Resonance Imaging (MRI) system, a common medical diagnostic tool that uses a strong magnetic field. Magnetic Resonance studies are accomplished by having the participant lie down on a bed that is slid into the 'bore' of the magnet. The 'bore' is a hollow cylinder that is 55-60 cm in diameter. A qualified person in an adjacent room performs the scan; audible communication is possible via intercom. In addition, the individual can be observed directly through a window between the two rooms. The individual can be removed immediately upon request or in case of emergency. MRI will be undertaken using modern scanners, which are less claustrophobic than older ones. During the scan, the participant will hear a thumping or buzzing sound. To reduce the level of noise and improve the comfort of the participants during the scanning, they will have ear plugs and ear padding to reduce the noise whilst also be positioned in the scanner as comfortable as possible. The duration of scanning varies from 45 minutes to 90 minutes and experience indicates that it is usually well tolerated by most participants.

1.4.2. Functional MRI

Functional Magnetic Resonance Imaging (fMRI) is used to monitor changes in signal intensity as a result of alteration of cerebral perfusion in response to cognitive stimulation. Significant technical advancements in the fast imaging techniques used in acquiring fMRI studies in the brain have been made allowing for the acquisition of multi-slice images for whole brain coverage in less than 2 seconds (Bandettini & Cox, 2000). Since neuronal activation (as compared to resting conditions) is accompanied by focal changes in cerebral blood flow, blood volume, blood oxygenation and metabolism, these changes can be measured and used to produce activation maps of cognitive, visual, motor and sensory tasks. Data will be analysed using the FRIEND neurofeedback software (primary outcome measure).

1.4.3. Real-time fMRI Neurofeedback

Technological advances in real-time functional MRI-based (fMRI) neurofeedback promise new treatment opportunities (Weiskopf, 2012; Sulzer et al., 2013). Using this technique, it has been demonstrated that people are quickly able to gain voluntary control over activity and

connectivity of specific brain regions (Weiskopf, 2012; Sulzer et al., 2013). Real-time fMRI neurofeedback is a training method in which real time information about changes in neural activity is provided to the individual in order to facilitate learned self-regulation and to produce changes in brain function, cognition, or behaviour (Stoeckel et al., 2014). Studies have demonstrated promise of real-time fMRI neurofeedback in the treatment of various clinical conditions including chronic pain (deCharms et al., 2005), tinnitus (Haller et al., 2010), stroke (Sitaram et al., 2012), schizophrenia (Ruiz et al., 2013) and also current depression (Linden et al., 2012). We will employ software (FRIEND: http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/OtherSoftware) specifically developed and validated for training brain coupling (Moll et al., 2014; Sato et al., 2013).

2. Methods

2.1. Study 1

2.1.1. Specific aim and hypothesis

To determine whether fMRI neurofeedback is effective in the reduction of self-blame and depressive symptoms in insufficiently remitted major depression through the normalisation of self-blame-related neural coupling between the right superior ATL and the posterior SSCR. We hypothesise that patients undergoing active neurofeedback (ATL-subgenual - correlation decrease) will show reduced depressive symptoms, decreased self-blame and increased self-worth.

2.1.2. Trial design

Single-blind, parallel group, controlled and randomised clinical trial comparing 2 arms comprising of 3 treatment visits by measuring change between pre-treatment (Visit 1) and post-treatment assessments (Visit 5) of clinical outcomes:

1) 3 sessions of anterior temporal lobe-posterior subgenual cingulate correlation fMRI neurofeedback + psychological self-guided intervention to reduce self-blame and increase self-worth
2) 3 sessions of a solely psychological intervention to reduce self-blame and increase self-worth

In all conditions (active fMRI neurofeedback vs. solely psychological intervention), patients are instructed to differentiate and reappraise self-blame-related autobiographical memories using techniques modified from cognitive therapy and related approaches. Further, a novel experimental task will be applied investigating whether changes in social agency inferences underpin self-blaming biases in MDD.

2.1.3. Participants

60 MDD patients (n=24 in each group, plus an estimated 12 lost to follow-up) with insufficient remission of symptoms, patients continue to experience significant symptoms which have not responded to adequate treatment or patients who have not been amenable to adequate treatment. Antidepressant medication is no exclusion criterion, but patients need to be on a stable dose for at least 6 weeks without improvement which they are able to remain on for the duration of the study.

2.1.4. Neurofeedback design

(n=24; 3 active neurofeedback sessions over 3 weeks)

Scanning will be carried out on a General Electric 3T MRI system using sequences optimised for ventral and anterior temporal lobe signal (Zahn et al., 2009). The neurofeedback software (functional real-time interactive endogenous neuromodulation and decoding: FRIEND; Sato et al., 2013) has been previously validated for correlation feedback in patients with MDD.

- Before undergoing their first MRI scan, patients will come in for a clinical assessment and neurocognitive testing. Prior to their first neurofeedback session, patients will receive training materials via email and we may discuss these over the phone. Participants will be told that an upward and downward moving thermometer scale will appear during the neurofeedback scan related to their brain connections.
- In each of the 3 fMRI neurofeedback visits, the following procedure applies: 1st fMRI data acquisition → 1st neurofeedback → 2nd neurofeedback → 2nd fMRI data acquisition (which may be modified slightly whilst keeping the overall scanning time)
- The baseline consists of counting backwards from an arbitrary new number for every baseline trial (113, 108, 110, etc.)
- Autobiographical events recorded prior to scanning are played back to participant by using a cue word defined before (2 or more scenarios/events for each condition). The self-blame-evoking scenarios must involve the participant being the main agent of the scenario. The other-blaming scenarios must involve another person acting. (Only for data acquisition not for feedback.) Ratings on these events are obtained prior and after the scan to see whether there is a change in attribution. In the scanner, after each run the participant is asked over the intercom to rate on a scale from 1 to 7 how much he/she felt self-blame or other-blaming emotions, as well as the level of concentration (from 1 to 7). Additionally, in the feedback runs, participants will be asked how easy it was to use the thermometer during the self-blame and other-blame conditions (from 1 to 7) and how successful they felt at influencing the thermometer scale.
- The following neurofeedback instructions will be given and may be modified or amended: 'On the screen you will see a bar filled with colour that can reach different levels. The levels are calculated from your brain activity patterns with a delay of 6 seconds. Whilst in the scanner, keep thinking about the situation related to the cue word that will be displayed. Try to bring down the level to which the bar is filled with color to the bottom. If you get to the bottom try to keep it there. If the level rises, try to bring it down again.'
- During the neurofeedback sessions, the correlation between the ATL seed and the other posterior septal/subgenual region ROIs is used for feedback.

2.1.5. Summary of neurofeedback design

(Durations and block lengths may be modified, but this will not affect the overall scan time of 60 minutes including structural scans or 90 minutes in case of technical difficulties.)

- The session will have 4 runs:
  - Run 1: functional localizer, consisting of self-blame blocks, other-blame blocks and subtraction blocks to assess relative correlations for self-blame and other-blaming emotions
  - Run 2: neurofeedback training
  - Run 3: same as run 2
  - Run 4: same as run 1 to assess training effects on correlations for self-blame and other-blame

- The first 5 volumes of each emotional block will be discarded due to high correlations guided by decrease in time series after subtraction conditions. The moving correlation sliding window will be 10 volumes.
- Thermometer displayed:
  - Maximum= average previous 10 volumes (sigmoid function) + 1 SD
  - Minimum= average previous 10 volumes (sigmoid function) – 1 SD

2.1.6. Trial flowchart

	Initial Patient Contact (email and phone)	Pre-Trial Assessment Visit 1 (day 0)	Treatment Session Visit 2 (1-13 days after Visit 1)	Treatment Session Visit 3 (7-13 days after Visit 2)	Treatment Session Visit 4 (7-13 days after Visit 3)	Post-Trial Assessment Visit 5 (7-13 days after last treatment visit)
Oral informed consent	X					
Introduction to the study	X					
Assessment of eligibility	X	X				
Written informed consent		X				
Clinical assessment & neuro-psychological tests		X				X
fMRI neurofeedback			X	X	X	
Psychological intervention only			X	X	X	
Mood assessment			X	X	X	

2.1.7. Outcome measures

Primary outcome measure:

1) Reduction of depressive symptoms between Visit 1 and 5 as assessed by the Beck Depressive Inventory (BDI-II). (Reduction of depressive symptoms between Visit 1 and the last treatment session as assessed by the Beck Depressive Inventory (BDI-II) for those who do not complete the study.)

Secondary outcome measures:

2) Reduction of depressive symptoms between Visit 1 and 5 as assessed by the Montgomery–Asberg Depression Rating Scale (MADRS) by a rater who is blinded to the treatment arm.
3) Reduction of self-rated depressive symptoms between Visit 1 and 5 as assessed by the Quick Inventory of Depressive Symptomatology (QIDS-SR 16).
4) Clinical Global Impression scale change between Visit 1 and 5 by a rater who is blinded to the treatment arm.
5) Withdrawal rates and adverse events after first treatment session.
6) Decrease in post vs. pre-training right ATL-SSCR correlation on fMRI (in neurofeedback arm).
7) Reductions in implicit self-blaming bias (self-contempt bias BIAT) between Visit 1 and 5.
8) Increase in Rosenberg Self Esteem Scale score between Visit 1 and Visit 5.

9) Positive Affect score increase and Negative Affect score decrease (PANAS scale) between Visit 1 and Visit 5.
10) Profile of Mood States (POMS) depression score change between Visit 1 and 5.
11) Self-blame ratings obtained prior to the first and after the last treatment session.
12) Reductions in agency-incongruent self-blame on short version of the value-related moral sentiment task between Visit 1 and 5.
13) Dysfunctional Attitudes Scale (prior & post mood induction if time permits) between Visit 1 and 5.
14) Self- & observer rated clinical global impression on Visit 5 for change since Visit 1.

We may have to drop some of the secondary outcome measures, depending on time constraints.

2.1.8. Statistical power

Sample sizes (n=24 in each group, plus an estimated 12 lost to follow-up) were calculated (G*POWER) to achieve 95% power at p=.05, 2-sided (t-test), based on a conservative estimate of an effect size (d=1.06) lower than that reported in a previous neurofeedback study of MDD.

Linden et al. (2012) reported a Cohen's d=1.5**,** with the neurofeedback group displaying a significant decrease (4.13 ± 2.75 from a mean of 14.38 to 10.25 on the Hamilton-17 Depression Rating Scale).

2.1.9. Strategy for addressing biases

The trial is fully randomised. Blinding will only be partly possible, but researchers assessing observer-rated outcomes will be blinded to group allocation. Reporting bias will be avoided by a priori definition of design and analyses in a public trial register. We will analyse all collected data of patients lost to follow-up to estimate attrition bias. Partial outcome data for patients lost to follow up will be included in analyses.

2.2. Study 2

2.2.1. Specific aim and hypothesis

Case-control study to investigate neurocognitive mechanisms underpinning self-blame bias in major depressive disorder compared with panic disorder and healthy control participants. This study will gather the first evidence how specific self-blaming biases previously demonstrated in MDD (Green et al., 2013) are when compared with another mental health disorder. Further, a novel experimental task will be applied investigating whether changes in social agency inferences underpin self-blaming biases in MDD. We hypothesise that patients with MDD show self-blaming emotional biases and overgeneralisation of self-agency for failure when compared with panic disorder and healthy control participants. In case participants perceive the implied neurocognitive testing as emotionally distressing, they are offered consultation by a psychiatrist.

2.2.2. Participants

Two control groups: Panic disorder patients (n=30, including 5 dropouts) with insufficient remission, with no history of MDD. Antidepressant medication will be allowed to be comparable with the MDD group. Healthy control participants with no personal or family history of mood, anxiety disorders or schizophrenia: (n=30, including 5 dropouts), melancholic MDD (n=30, including 5 dropouts), MDD with no specifiers (n=30, including 5 dropouts). MDD participants will be either specifically recruited for this study or their data will derive from participation in study 1.

3. General Experimental Procedures

Patients insufficiently remitted from MDD for at least six weeks, healthy volunteers and subjects with insufficient remission of panic disorder will be recruited through radio and newspaper adverts, internet adverts, flyers posted to university bulletin boards and e-mail advertisements as well as sent to self-help groups. We will also send out flyers to general practitioners and specialists and recruit through GP practices after obtaining primary care R&D approval.

- Patients referred from doctors will be evaluated clinically or by phone to screen for inclusion and exclusion criteria. Participants responding to adverts will be pre-screened for inclusion and exclusion criteria by a phone interview, they will be asked for permission for conducting the phone interview at the beginning of the conversation by reading the following statement to them: 'I would like to do a short phone interview with you, which will take around 15 minutes. This is necessary to see whether some conditions rule out that we can include you into the study. You will be asked questions about psychiatric, neurological and medical symptoms, treatments, learning problems and whether such symptoms occurred in your family. I will also ask about substance or alcohol abuse. Things which are an obstacle to participate in MRI studies such as possible pregnancy or metallic objects will also be asked. Results of these questions will not be stored, but we ask your permission to store your contact information and whether you passed the screening for the study group in an electronic database which is protected by a password and can only be accessed by the investigators.'
- For the case-control study (study 2) we may offer participants to complete electronic questionnaires by e-mail. Consent forms will be sent to them for printing out and participants are asked to sign them and send a scanned copy back to us as an e-mail attachment, a fax or by regular mail. They will send completed electronic questionnaires by e-mail. Those questionnaires will contain no personally identifiable information.
- During the first session scheduled after screening for inclusion and exclusion criteria, standardised psychiatric assessments as well as self- and observer-report scales will be used to assess neuropsychiatric symptoms and to verify the clinical diagnosis. Clinical evaluation may take up to 2 hours and follows standard practice. Diagnostic interviews and scales will be limited to a maximum of 3 hours.
- In the fMRI neurofeedback condition, a separate session in a mock scanner may be arranged for people with no experience in MRI scanning to get familiar with the environment.
- At each visit, before and after the treatment session, patients will receive standardised scales to assess measures of individual differences on mood, cognition and personality. The researcher will alert the psychiatrist if the BDI-II suicidality item is rated above 0 and the subsequent Mini International Psychiatric Interview suicidality module results in a score indicating more than a low risk. The psychiatrist will then offer a consultation and decide with the patient whether to continue with the study.
- Participants will perform practice tasks prior to the MRI. This preparation may take up to 45 minutes. Scanning, including clinical, structural and functional scans will take 1 hour but may exceed that time in case of technical difficulties and if the patient/subject is willing to continue for up to 90 minutes, in very rare occasions 120 minutes. After the scanning participants perform computerised tests to correlate performance during the MRI scanning with performance outside of the scanner. This testing may take up to 1 hour.
- On two separately scheduled testing days (pre- and post-trial assessment, Visits 1 & 5), patients will perform neuropsychological tasks or give computerised self-report

ratings on mood, cognition and personality as well as on the stimuli delivered during MRI. These ratings may also be sent out as files to be completed by e-mail and returned by e-mail. Personally identifiable information will not be contained in the files exchanged by e-mail. Testing will be limited to 3 hours per day for patients and up to 4 hours per day for normal subjects, breaks will be planned depending on the needs of the participant.

- Following the post-trial assessment at Visit 5, the participant's GP will be notified about the results of relevant clinical measures.
- All patients and healthy subjects will be asked to give consent for being recontacted by mail, e-mail or phone to take part in additional longitudinal follow-up evaluations including further imaging and/or neuropsychological evaluation. Longitudinal follow-up studies allow us to study the predictive value of our neuropsychological and imaging measures to predict later clinical outcome and to test the re-test reliability of the employed measures. The realisation of longitudinal follow-up studies will depend on the success of further grant applications.
- Participants will receive reimbursement for time and travel expenses after their final participation day in the study. Participants are compensated in form of High Street gift vouchers or Shopping vouchers: £10 for pre-trial assessment session (Visit 1), £20 per treatment session (3x£20 = £60 for Visit 2, Visit 3, Visit 4), £30 for final follow-up session (Visit 5).
- If requested, participants will be informed of the final results after completion of the study.

These methodological details apply to all of the experiments proposed below, except where otherwise stated.

4. Diagnostic, Behavioural & Neuropsychological measures

From the following study measures we will select tests and measures which can be feasibly run within the stated time limits. We will therefore test the feasibility in a small group of patients to get a realistic time estimate and insure that patients and healthy controls are not overloaded with testing. All groups will have a baseline assessment of depressive symptoms (BDI-II, MADRS and QID-SR16) and experimental cognitive and emotional tests initially and as part of the post-trial assessment at Visit 5 (see outcome measures). Self-report scales (BDI-II and PANAS) will be carried out after each treatment session.

Clinical evaluation:

- Phone screening for exclusion and inclusion criteria of 15 to 20 minutes, major medical illnesses, substance abuse, axis-I disorders, pregnancy and MRI exclusion criteria, history of psychiatric and neurological treatments
- Non-structured clinical interview (all except healthy volunteers)
- Medical history including GP records if necessary (all)
- Day of menstrual cycle in women to use this as a covariate in the imaging analysis (in the high estrogen phase of the cycle brain activity is largely enhanced which adds variability to the data if not controlled for)
- Age at onset, episode duration, total illness duration
- MDD course: number of episodes, chronic, phasic, medication
- Beck Depression Inventory II (BDI-II; Beck & Brown, 1996)
- Montgomery-Asberg Depression Rating Scale (MADRS; Montgomery & Asberg, 1979)
- Global Social Functioning (GAF) Score (First et al., 2002)

- Psychiatric Family History Screen (Andreasen et al., 1977)
- AMDP Psychopathology Interview questions of depression items (translated from German; Faehndrich & Stieglitz, 1997; 2007)
- Mini International Neuropsychiatric Interview (MINI) suicidality Screen (Sheehan et al., 1998)
- Structured Clinical Diagnostic Interview (SCID)-I. Research Edition (First et al., 2002)
- Life Events Questionnaire (32 items). The scale aims to look at negative and positive life events, those occurring in the past and whether the respondent thinks they have a continuing influence and indicate whether the event was considered 'good', 'neutral' or 'bad'. Adapted from the List of Life Threatening Experiences (LTE; Brugha et al, 1985)
- Clinical Global Impression Scale (Busner & Targum, 2007)
- [LIFE] Longitudinal Interval Follow-up Interview (Keller et al., 1987)
- Maudsley modified PHQ-9 (for validation, based on modification of the standard PHQ-9 as used in primary care).

Standard scales:

- Positive and Negative Affect Scale (PANAS; Watson et al., 1988)
- Rosenberg Self Esteem Scale (Rosenberg, 1965)
- Profile of Mood States (POMS) Scale (McNair et al., 1971)
- Altman Self-Rating Mania Scale (Altman et al., 1997)
- Quick Inventory of Depressive Symptomatology (QIDS-SR 16; Rush et al., 2003)
- Brief Implicit Association Test (BIAT; Greenwald et al., 1998)
- Dysfunctional Attitudes Scale (Weissman & Beck, 1978)
- Childhood Trauma Questionnaire (CTQ; Bernstein & Fink, 1998)
- Hypomania Check List (Angst et al., 2005)

Standard neuropsychological tests:

- Standard neuropsychological tests of language, emotional and social cognition, memory, praxis and attention in patients with suspicion of cognitive impairments (Addenbrooke's Cognitive Examination-III; Hsieh et al., 2013)

Experimental neuropsychological tests/scales:

- Short version of the value-related moral sentiment task
- Additional ratings of autobiographical memories associated with self-blame and other-blame
- Causal social agency inference and evaluation task

5. Inclusion/Exclusion Criteria

All participants are screened over the phone for inclusion and exclusion criteria after being informed and asked for oral consent before formal evaluation.

Psychiatric diagnoses after the screening are established using an unstructured clinical interview by a psychiatrist and via a structured interview using the Structured Clinical Interview (SCID-I) for the Diagnostic and Statistical Manual of Mental Disorders **(**DSM). The clinical evaluation also includes a physical examination & history taking and a brief psychiatric family history screening questionnaire. Participants can take part in all studies if they fulfil the inclusion and exclusion criteria. Informed consent is obtained separately for each study and session to monitor continued consent.

5.1. Inclusion criteria

Participants meeting the following criteria will be considered for inclusion into the studies:

MDD Patients

- Recurrent major depressive disorder (MDD) according to DSM-V with at least one major depressive episode (MDE) of at least 2 months duration, insufficiently remitted for at least 6 weeks, so that they display symptoms that are significantly bothering or impairing (Psychiatric Status Rating of 3-5 over the past 2 weeks on Longitudinal Interval Follow-up Interview (Keller et al., 1987)
- If treated with antidepressants, on stable dose for at least 6 weeks prior participation and planning to stay on this dose for the duration of the study
- Patients have insufficiently responded to at least one course of cognitive behavioural therapy (CBT) or antidepressants or are not amenable to these standard treatments and are not currently undergoing psychotherapy.
- Age range: 18 or older
- Right-handedness in order to ensure homogenous response to our right hemisphere treatment target.
- Proficieny in English in order to ensure reliable responses on newly developed secondary outcome measures

Control Groups:

- Age-matched and education matched to respective study population
- Proficient in English
- Right-handedness
- Panic Disorder patients: Diagnosis obtained according to the DSM; insufficient remission of symptoms for at least 6 weeks, no other relevant psychiatric or neurological disorders in history or currently
- Healthy volunteers: No psychiatric or neurological disorders in history or currently

5.2. Exclusion criteria

A participant will not be eligible for inclusion if any of the following criteria applies:

- Standard MRI contraindications such as exclusion of participants with any kind of non-removable ferromagnetic devices or implants due to possible dangerous effects of the MRI magnet upon metal objects in the body
- History of learning disabilities or developmental disorders
- Impairments of vision or hearing which cannot be corrected during the experiment
- History of manic or hypomanic episodes, of schizophreniform symptoms or schizophrenia, of substance abuse, neurological disorders such as seizures, loss of consciousness following brain injury or medical disorders affecting brain function, blood flow or metabolism
- Current intake of benzodiazepines, GABAergic or benzodiazepine receptor agonists
- Current recreational drug use
- Pregnancy

MDD Patients

- Greater than low risk of suicidality or violence
- Current MDE with a duration of more than one year
- Prior specialist diagnosis of ADHD, antisocial or borderline personality disorder
- Significant impairment of psychosocial functioning (at least moderate impairment in interpersonal, work or leisure domains on the Longitudinal Interval Follow-up Interview [LIFE]) in the year prior to the last MDE as a sign of a possible co-morbid personality disorder

- Current self-harming behaviours

Control Groups:

- Panic Disorder patients: history of MDD or other relevant psychiatric or neurological disorders
- Healthy volunteers: history of axis-I disorder in family; history of psychiatric disorders or psychotropic medications

6. Protocol Consent Process and Documents

Each participant will receive an oral and written explanation of the purposes, procedures, and risks of this study in language appropriate for the individual's level of understanding. Written consent will be obtained after explaining the goals, procedures, risks (and discomforts), benefits, and nature of the studies to patients and control groups. Only adult healthy volunteers and patients who are capable of understanding the fMRI neurofeedback study procedures will be allowed to sign the consent forms.

7. Withdrawal of Subjects and Risk Management

A subject can decide to withdraw from the trial at any time and this will be made clear to the participants in the information sheets and consent forms. In this case, the subject must contact the Investigator and state that he/she is leaving the trial. The reason for withdrawal does not need to be stated; however the subject should feel free to do so.

The Investigator has to withdraw a subject from the study in the case of occurrence of a significant adverse event or any other condition, which in the opinion of the Investigator does not justify a safe continuation of the study. In the case of withdrawal, the subject's GP will be notified. Patients who experience adverse events will be offered advice by the consultant psychiatrist and Chief Investigator.

8. Evaluation of Benefits and Risks

8.1. Evaluation of benefits

There is a slight possibility that an individual participant might benefit from the earlier detection of occult neuropathology previously unrecognised when participating in the MRI arm of the study (e.g. tumors, strokes, arteriovenous malformations, etc.). There are no documented benefits to subjects participating at this point. However, this study aims at investigating the potential benefits of fMRI neurofeedback on self-blaming emotional bias in remitted depression. Even if such benefits will not be shown, the results of this study may be used to improve our design of tests that are sensitive to brain dysfunction, provide better outcome measures in clinical trials, and teach us about the neural and cognitive mechanisms of neuropsychiatric disorders which aid in the diagnosis and treatment of these disorders.

8.2. Evaluation of risks

Risks from psychiatric assessments are minimal or non-existent. Some participants may find the interviews and tests tiring. To reduce this burden we have kept the number of clinical assessments to a minimum by using only relevant, widely used and validated assessment. MRI is safe when used on participants that are appropriately screened for the procedure (Shellock & Bierman, 1989). It is deemed that the risks to the participants in performing the neuropsychological, fMRI neurofeedback assessments in this protocol are minimal. Neurofeedback is reported to be a safe treatment, with only occasional reports of the

occurrence of a possible side effect such as fatigue, headache, anxiety and difficulty falling asleep.

9. Assessment of Safety

9.1. Procedures for recording and reporting adverse events

An adverse event (AE) is any untoward medical occurrence in a patient or healthy volunteer, which does not necessarily have a causal relationship with the study procedures (i.e., neuropsychological, neuroimaging assessments, or neurofeedback training). The period of recording of AEs will last from the time that the subject signs the informed consent form to the last trial day according to the clinical trial protocol.

9.1.1. Adverse event recording

Each AE occurring to a subject either spontaneously revealed by the subject or observed by the Investigator, whether believed by the Investigator to be related or unrelated to assessment, will be recorded in the subject's source data.
The following aspects of AEs will be documented by the Investigator and the present medical support in the source data: each single symptom, if required possible diagnosis or syndrome, date and time of onset and end of AE, causal relationship with investigation (definite / probable / possible / unlikely / not related), outcome (resolved / resolving / not resolved / resolved with sequelae / fatal / unknown), treatment of event, if applicable (e.g. any medication as well as any other medical measures), actions taken regarding assessment.

9.1.2. Adverse event reporting

The Investigator will report to the Chief Investigator all AEs, which occur during the trial, regardless of their relationship to the assessments by documentation in the case report form. In cases of medical emergencies the research team will adhere to the guidelines of the institute. In the case of patients and healthy controls, their GPs will be notified in writing of any significant adverse events.

9.2. Termination criteria for participation

At each visit, patients will receive standard depression scales to assess changes in mood. The researcher will alert the study psychiatrist if the BDI-II suicidality item is rated above 0 and the subsequent MINI suicidality module results in a score indicating more than low risk. The psychiatrist will then offer a consultation and decide with the patient whether to continue with the study.
If the patient shows an increase of more than 10 points on the BDI-II during the course of the study, the patient will terminate the study and a consultation with the study psychiatrist will be offered. The GP will be informed.

10. Data Management, Documentation and Curation

10.1. Managing, storing and curating data

Data are stored on a shared King's College London (KCL) drive which is only accessible to the investigators of the study. Data are transferred via encrypted hard drives as master copies to the Chief Investigator Dr Roland Zahn. All anonymised data are backed up on raid drives and anonymised imaging data also on external hard drives. All personally identifiable data are in encrypted .xlxs files and are backed up on encrypted hard drives.

10.2. Metadata standards and data documentation

All variables are labelled clearly and referred to in our experimental protocol.

10.3 Data preservation strategy and standards

The Chief Investigator Dr Zahn will store, own, and be responsible for personally identifiable data and consent forms for 5 years after publication in case data needs to be checked for accuracy on password protected encrypted hard drives and computers in locked rooms and/or cabinets at King's College London. Data containing no personally identifiable data may be kept indefinitely in electronic form for comparison with future cohorts. KCL copies will be regarded as master copies on transfer.

11. Data Security and Confidentiality

See above.

11.1. Formal information/data security standards

Our information and data security standards will comply with King's College London policies.

11.2. Main risks to data security

Personally identifiable information is only accessible to the investigators of the study and protected by password, file encryption and encryption of portable drives if they are used for transfer of data. Hardcopies of consent forms are in a locked file cabinet in a locked room at King's College London and will stored in the same on completion of the study.

12. Direct Access to Source Data and Documents

The Chief Investigator Dr Zahn will permit direct access to source data/documents for study-related monitoring, audits, and regulatory inspections.

13. Publication of Results

Upon completion of the analyses, the study data will be presented on scientific conferences, published in scientific journals and published as part of a PhD dissertation.

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