PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	The NeMo Real-Time fMRI Neurofeedback Study: Protocol of a Randomised Controlled Clinical Intervention Trial in the Neural Foundations of Mother-Infant-Bonding
AUTHORS	Eckstein, Monika; Zietlow, Anna-Lena; Gerchen, Martin; Schmitgen, Mike; Ashcroft-Jones, Sarah; Kirsch, Peter; Ditzen, Beate

VERSION 1 – REVIEW

REVIEWER	Dr Konstantinos Kalafatakis University of Bristol (UK), University of Ioannina (Greece)
REVIEW RETURNED	12-Dec-2018

GENERAL COMMENTS	This is a presentation of the study protocol of a very interesting and ambitious randomised controlled fMRI-related clinical trial on the mother-infant bonding and whether neuro-feedback rtfMRI intevention could act as a meaningful therapeutic approach on cases of postpartum bonding difficulties. The manuscript is fine for publication, as it stands. Apart from saying good luck to the authors, I would like to just express some thoughts: 1) Since the handedness has been correlated with the neuroanatomical variations of the BOLD signal responses among individuals in the context of emotional processing [see for example (1)], it would be potentially useful for the authors to keep a record of the degree of handedness of the participants (to have the option of using this piece of information as a regressor for explaining possible variations in their task-based fMRI experiments). 2) Since this is not clearly explained in the text, I would like to make the following comment: ideally, blinding procedured should be planned not only for allocating subjects to the interventional groups but (equally important) when analysing the datasets. I appreciate that the state of absolute blinding is in some cases hard or impossible, but al least the different datasets (behavioural, fMRI, NFB rtfMRI) should be anonymised at an individual level for those team members performing preprocessing and cleaning steps of the data analysis, and at the group level for those team members performing group-level statistical comparisons. 3) I can confirm that sample size is most probably good to very good. Power calculations based on the data of my earlier fMRI studies on emotional processing for positive emotional stimuli in striatal regions using the methodology of Mumford JA et al (2, 3) for reaching a power of 80% and setting the type I error rate to 0.05, resulted in the estimation of a minimum group size to 25.

	4) Do the authors believe that the status of the mother-father relationship prior and during infancy could interfere with the process of the mother-infant bonding? If yes, are the authors controlling their study for this factor? 5) In page 15 Lines 26-27 the authoers state that "The women are instructed to try several strategies (of up-regulation) and use the one that works best. Afterwards, they are asked to report which strategy they used." It would be nice to further elaborate on this process to better understand what the authors aim at: why several strategies and not just one predefined? Won't this "liberal" approach create problems in modelling or interpreting the NFB rtfMRI data or the estimation of the effect size of the up-regulation strategies? 1. Royet JP, Plailly J, Delon-Martin C, Kareken DA, Segebarth C. fMRI of emotional responses to odors: influence of hedonic valence and judgment, handedness, and gender. Neuroimage. 2003;20(2):713-28. 2. Mumford JA, Nichols T. Power Calculation for Group fMRI Studies Accounting for Arbitrary Design and Temporal Autocorrelation. Neuroimage 2008; 39(1): 261-8. 3. Mumford JA. A power calculation guide for fMRI studies. Soc Cogn Affect Neurosci 2012; 7(6): 738-42.

REVIEWER	Dr Roland Zahn Institute of Psychiatry, Psychology & Neuroscience, King's College London, UK
REVIEW RETURNED	07-Jan-2019

GENERAL COMMENTS	Overall this is an interesting and innovative study, but the description is incomplete and I have some concerns about the control group decreasing the likelihood of group differences, but that may just be because the rationale is not described fully. Abstract and intro: -Although bonding and affiliative experiences are also associated with the striatal dopaimnergic system, this is not the only and arguably the least specific correlate in that oxytocin and opoids play a more specific role and the septohypothalamic area in particular (Moll et al J Nsci 2012, Moll and Shulkin, Depue et al Beh Br sciences) -What part of the anterior circulate? Dorsal anterior cingulate? - why was that chosen as a control region? -P4 again postpartum depression is not solely related to ventral striatal reward responses, best make clear that this is only one possible component. -Intro: cite Moll etal PLoS one Affilitative NFB study which addressed bonding directly Design -If the ACC control neurofeedback is hypothesised to show beneficial effects as well, how do the authors expect to show a difference between the intervention groups? -The randomisation method needs better explanation and also how blinding is ensured, the sequence of enrolment should not determine the randomisation but this is probably not what is meant here.

	-Assessments: who is carrying these out? What training level, inter-rater reliability and blinding? -Sequence details for MRI sequences, which head coil?, Respiratory and cardiovascular parameters measured? -Which neurofeedback software is used?, referring to other paper is not sufficient, this information needs to be restated here. How are ROIs mapped into an individuals brain? How is movement and baseline activity considered? Data analysis plan: -This needs to describe the contrasts to be modelled in SPM and spell them out. -The primary and secondary outcome measures need to be described in a separate section or spelled out in the assessment section. Potential confounders to be considered such as movement parameters should be described. -Also, how are missing data going to be dealt with? -How is experience of success or relevance captured? A potential confounder. How is real neurofeedback success going to be accounted for? -Are there plans for treatment responder vs non-responder comparisons? -Are MDD patients subtypes recorded? Eg atypical, melancholic, anxious distress (DSM5)?

VERSION 1 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 1
Reviewer Name: Dr Konstantinos Kalafatakis Institution and Country: University of Bristol (UK) University of Ioannina (Greece) Please state any competing interests or state ‘None declared’: None declared

Please leave your comments for the authors below:
This is a presentation of the study protocol of a very interesting and ambitious randomised controlled fMRI-related clinical trial on the mother-infant bonding and whether neuro-feedback rtfMRI intervention could act as a meaningful therapeutic approach on cases of postpartum bonding difficulties. The manuscript is fine for publication, as it stands. Apart from saying good luck to the authors, I would like to just express some thoughts:

1) Since the handedness has been correlated with the neuroanatomical variations of the BOLD signal responses among individuals in the context of emotional processing [see for example (1)], it would be potentially useful for the authors to keep a record of the degree of handedness of the participants (to have the option of using this piece of information as a regressor for explaining possible variations in their task-based fMRI experiments).

We want to thank the reviewer for this helpful advice. We have included the Edinburgh Handedness Inventory (Oldfield, 1971) in our study, see Table 1.

2) Since this is not clearly explained in the text, I would like to make the following comment: ideally, blinding procedure should be planned not only for allocating subjects to the interventional groups but (equally important) when analysing the datasets. I appreciate that the state of absolute blinding is in some cases hard or impossible, but at least the different datasets (behavioural, fMRI, NFB rtfMRI) should be anonymised at an individual level for those team members performing preprocessing and cleaning steps of the data analysis, and at the group level for those team members performing group-level statistical comparisons.

We want to apologize for any missing details in the manuscript regarding blinding of the sample to the experimenter. The individual data is pseudonymized in all data sets. The behavioral data (video of interaction) will be coded by trained and reliable coders who are blind to the hypotheses of the study and group status of the dyad.

Blinding of the two treatment groups will be conducted using a hidden MatLab list that has been built by our co-worker, who is neither involved in data collection nor analyzing. He will reveal the group assignment only after main analyses on the group level have been conducted.

We have added this information in the manuscript on page 9:

This randomisation is based on the order of inclusion into the study and pre-assigned lists that are double-blind in nature using nonpublic lists made by a colleague not involved in assessments and analyses. During all three intervention sessions, participants will be trained to modulate activation of the same pre-defined brain region (right ventral striatum or right ACC) based on the functional tasks during T1. Blinding of the treatment group will be revealed after the analyses at group level.

3) I can confirm that sample size is most probably good to very good. Power calculations based on the data of my earlier fMRI studies on emotional processing for positive emotional stimuli in striatal regions using the methodology of Mumford JA et al (2, 3) for reaching a power of 80% and setting the type I error rate to 0.05, resulted in the estimation of a minimum group size to 25.

We are grateful for the reviewer’s confirmation of our power estimate and his on calculation. As this is our first study of the topic, we cannot use the fMRIpower toolbox that requires original SPM contrasts but will leave our behavior-based power calculation.

4) Do the authors believe that the status of the mother-father relationship prior and during infancy could interfere with the process of the mother-infant bonding? If yes, are the authors controlling their study for this factor?

Thank you for this helpful comment. Indeed, we are assessing several couple based characteristics such as the partnership questionnaire by Hahlweg and the dyadic coping questionnaire by Bodenmann, scores of which will be added as covariates in our analyses. A complete list of questionnaires in the table on page 11.

5) In page 15 Lines 26-27 the authors state that "The women are instructed to try several strategies (of up-regulation) and use the one that works best. Afterwards, they are asked to report which strategy they used." It would be nice to further elaborate on this process to better understand what the authors aim at: why several strategies and not just one predefined? Won't this "liberal" approach create problems in modelling or interpreting the NFB rtfMRI data or the estimation of the effect size of the up-regulation strategies?

We apologize for lack of clarity surrounding this point in the manuscript. We do not provide specific strategies to our participants because a predefined strategy that is guaranteed to work well in all participants cannot, if at all, be defined given the current state of the knowledge base. Instead, we instruct participants to explore different self-chosen strategies and find the best one that works for them personally. We have changed the description in the text to emphasize this point:

The women are instructed to try and explore different self-chosen strategies (of up-regulation) and find the one that works best for them. Afterwards, they are asked to report which strategy they used.

We also completely agree with the reviewer that the use of different strategies might add noise to the data. However, all strategies are applied with the goal to regulate the same brain signal, which should make their effects statistically comparable.

1. Royet JP, Plailly J, Delon-Martin C, Kareken DA, Segebarth C.
fMRI of emotional responses to odors: influence of hedonic valence and judgment, handedness, and gender. Neuroimage. 2003;20(2):713-28.
2. Mumford JA, Nichols T. Power Calculation for Group fMRI Studies Accounting for Arbitrary Design and Temporal Autocorrelation. Neuroimage 2008; 39(1): 261-8.
3. Mumford JA. A power calculation guide for fMRI studies. Soc Cogn Affect Neurosci 2012; 7(6): 738-42.

Reviewer: 2
Reviewer Name: Dr Roland Zahn
Institution and Country: Institute of Psychiatry, Psychology & Neuroscience, King's College London, UK Please state any competing interests or state ‘None declared’: Co-developer of FRIEND neurofeedback software, D'Or Institute for Research and Education, Rio de Janeiro, Brazil

Please leave your comments for the authors below:
Overall this is an interesting and innovative study, but the description is incomplete and I have some concerns about the control group decreasing the likelihood of group differences, but that may just be because the rationale is not described fully.

1.
Abstract and intro:
-Although bonding and affiliative experiences are also associated with the striatal dopaimnergic system, this is not the only and arguably the least specific correlate in that oxytocin and opoids play a more specific role and the septohypothalamic area in particular (Moll et al J Nsci 2012, Moll and Shulkin, Depue et al Beh Br sciences)

We agree with the reviewer that affiliation and bonding are complex processes involving multiple systems. In this proof-of-method-study, we focus on the dopaminergic striatal region as one of the most likely mediating areas in correlation with the endogenous oxytocin system. (Strathearn, Fonagy, Amico, & Montague, 2009; Strathearn, Li, Fonagy, & Montague, 2008). Indeed, future studies might expand the neurofeedback to other regions or even networks.

We have included further background discussion around this topic on page 4:

The strength of maternal bonding can also be demonstrated on a neurobiological level,[13]. Central structures such as the striatum, ventral tegmental area, amygdala, septum and hypothalamus are

involved in affiliative behaviour[14,15], together with a combination of neurotransmitters and modulators such as dopamine and oxytocin[14, 16]. For affiliative traits, it has been proposed that those are mediated by dopaminergic projections from the ventral tegmental area and endogenous opioids in the hypothalamus with projections to the septum, especially during physical contact [16], that underlie rewarding feelings of affiliation.

2.
-What part of the anterior circulate? Dorsal anterior cingulate? - why was that chosen as a control region?

The decision to choose the ACC as the control region was made for several reasons. Foremost, there is a large body of research on the subdivisions of the ACC. As the extensive review by (Etkin, Egner, & Kalisch, 2011) suggests, the anterior dorsal parts of the ACC (adACC) in particular are involved in the processing of emotional conflict. Wessa et al. (2007) similarly showed that emotionally instable patients involve the adACC in a very similar emotional go/nogo task. The individual 1st level analyses of our very first participants in the ongoing study, performed in order to build the ROIs, confirm that this area is also activated in our sample.

Furthermore, we have chosen to include the ACC an active control treatment group rather than a waiting group or joke feedback for ethical reasons. We assume that the ACC feedback will have beneficial effects for the mothers' well-being as it did for schizophrenic patients in a study by Cordes et al. (2015) via the rather unspecific properties of the dorsal and rostal ACC. In addition, the emotion regulation functions of the ACC have been discussion for their role in parenting (Feldman, 2015) and seem deficient in postpartum depression (Laurent & Ablow, 2013), therefore suggesting a strengthened ACC may indirectly support maternal behavior.

However, for the overall results, we expect the striatal feedback for have even better beneficial effects.

We have added the rational for the ACC on page 7:

Participants will learn to consciously increase the activation of reward-associated brain areas (specifically the ventral striatum), or a control region (anterior cingulate cortex, ACC), during the presentation of images of their own infant. For ethical reasons, an active control treatment was chosen rather than joke or non-feedback. The activation of the central nervous dopamine system via the striatum is hypothesized to improve bonding motivation and social interaction behaviour. The coupling of infant stimuli to the central nervous reward activation should make it easier for these women to feel more joy in the real interaction,[62] with their infant post-training and to be more attentive and more sensitive in their interactions. Training of the dorsal/rostral ACC with a rather unspecific role in emotion regulation, such as e.g. in cognitive reappraisal,[71] or response inhibition [72], may have general beneficial effects as shown in another NFB study [69] but also indirectly influence on parental affect regulation,[13]. However, the more specific striatal feedback based on the rewarding aspects of the mother-child interaction is assumed to have stronger effects.

3.
-P4 again postpartum depression is not solely related to ventral striatal reward responses, best make clear that this is only one possible component.

Thanks for this comment. In fact, our study does not focus on postpartum depression (PDD) but on postpartum bonding, although the prevalence of bonding disorders in patients with PDD is high. The target region in NFB is therefore chosen specifically for bonding not for PDD.
To be very clear, we had thought it best not to give too much emphasis on PDD in the introduction to prevent overlap of understanding in the readers between PDD and bonding disorders which, while often comorbid are not inseparable issues. However, we have expanded the background now.

Page 5:
On a neurobiological level, postpartum depression relates to a reduced level of reactivity in the striatal reward system, for example in the putamen,[26], but also the amygdala network [27] together with endocrine changes in the serotonin and steroid systems [28].

In addition, we plan to control for depressive symptoms in our analyses in order to partial out the specific effects of this region.

4.
-Intro: cite Moll et al PLoS one Affilitative NFB study which addressed bonding directly

We have included the NFB study in our introduction of NFB on page 6:

Neurofeedback (NFB) is a novel method which, through the visualization of real-time brain activation, allows an individual to consciously regulate one's own brain activation. While it is well-established that mental strategies modulate brain activation as measured by fMRI blood oxygen level dependent signal (BOLD), NFB asks participants to modulate activation in prescribed regions or even networks of their brain by their own volition and in response to the immediate feedback/ visualization of the related brain activation patterns,[65]. Thus, volunteers can learn to regulate the activation of a previously defined brain region (see,[66] for a review). NFB interventions have previously often used electroencephalography (EEG) and other electrophysiological methods to visualize and modulate activation in higher-cortical areas. However, smaller and deeper areas of the limbic and reward system can be imaged primarily with high-resolution magnetic resonance imaging (MRI). One previous study has proven that healthy volunteers can be trained to voluntarily increase their brain activation patterns that have been classified for affiliative emotions in the same individual subject using voxel pattern analyses [67]. From a therapeutic point of view, the targeted modulation of these specific brain areas and associated circuits via neurofeedback should be associated with the improvement of mental symptoms.

5.
Design
-If the ACC control neurofeedback is hypothesised to show beneficial effects as well, how do the authors expect to show a difference between the intervention groups?

Indeed, we predict that the ACC feedback will have beneficial effects for the mothers' well-being as it did for schizophrenic patients in a study by Cordes et al. (2015) via the rather unspecific properties of both the dorsal and rostal ACC. In addition, the emotion regulation based functions of the ACC have been discussed for their role in parenting. As the ACC is included in the empathy network (Feldman, 2015) a strengthened ACC may indirectly support maternal behavior.

Nevertheless, we assume that upregulating the ventral striatum will show greater effects on the quality of mother-infant interaction based on the finding that mothers who report a good emotional bond with their infant show increased reward-related activation specifically in dopaminergic brain

regions (the nucleus accumbens in the ventral striatum) in response to infant stimuli (Strathearn et al., 2008). However, future studies might use the whole network as a basis for connectivity feedback.

-The randomisation method needs better explanation and also how blinding is ensured, the sequence of enrolment should not determine the randomisation but this is probably not what is meant here.

We want to apologize for any missing details in the manuscript, this was also noted by reviewer 1. (See comment 3 above for reviewer 1).

Blinding of the two treatment groups is conducted using a hidden MatLab list, that assigns the ROI for the feedback to the participant number, whereas the participant number is given to the participants based on the order in which they are included in the study. The list has been built by our co-worker, who is not involved in data collection nor analyzing. The group assignment will be revealed only after main analyses on the group level.

We have added this information in the manuscript on page 9:

This randomisation is based on the order of inclusion into the study and pre-assigned lists that are double-blind in nature using nonpublic lists made by a colleague not involved in assessments and analyses. During all three intervention sessions, participants will be trained to modulate activation of the same pre-defined brain region (right ventral striatum or right ACC) based on the functional tasks during T1. Blinding of the treatment group will be revealed after the analyses at group level.

6.
-Assessments: who is carrying these out? What training level, inter-rater reliability and blinding?

Assessments of maternal psychiatric status as well as maternal bonding difficulties are carried out by clinical psychologists and medical staff who are all trained in diagnostic interviews. To guarantee inter-rater reliability, the clinical interviews to assess maternal psychiatric status are recorded and 10-20% will be double coded by other clinical psychologists to ensure inter-rater reliability. Regarding the mother-infant interaction, all Face-to-Face Still Face paradigms as well as the free play and limit setting situations are videotaped and coded by blind and reliable coders who are independent of the current study, 10-20% of the videos will be double coded for inter-rater reliability.

7.
-Sequence details for MRI sequences, which head coil?, Respiratory and cardiovascular parameters measured?

We have included details on the fMRI sequence on page 15:

Functional images are acquired with a Siemens Tim Trio using a T2*weighted echoplanar sequence (TR = 1.64s, TE = 30ms, 30 slices, 3mm slice thickness, FoV = 192mm, flip angle 73°, voxel size 3x3x3 mm, 343 volumes per trainings run, distance factor of 33% and GRAPPA with iPat = 2) and a 32 channel head coil. Control for cardiovascular parameters is conducted using the built-in pulse clip.

8.
-Which neurofeedback software is used?, referring to other paper is not sufficient, this information needs to be restated here.

We do not use a special software for neurofeedback but in-house Matlab software based on SPM12 functions to conduct rtfMRI NFB. We have added details on page 14:

In-house Matlab software based on SPM12 functions is used to conduct the rtfMRI NFB and Presentation software (Neurobehavioral Systems, Inc., Albany, CA, USA) is used to present pictures and the feedback signal image. At the beginning of each NFB training session, the anatomical image is segmented and normalized to MNI standard space. The inverse deformations of the normalization are then applied to warp the masks of the target regions into subject space.
To correct for movement, each acquired volume is realigned to the first image of the run. Then, volumes with more than 0.5 mm scan-to-scan movements are identified and marked in dummy regressors. Afterwards, the average intensity values from the target region and a cerebrospinal fluid (CSF) mask are extracted and the signal of the target region is corrected for the estimated motion parameters, high-motion dummy regressors, and the CSF signal. For calculation of the feedback signal the ROI intensity value of the last 3 volumes is averaged and compared to the average intensity of the baseline condition.

9.
How are ROIs mapped into an individual brain?

We are sorry for insufficient description of the ROI procedure. The individual masks for extraction of the neurofeedback value are built after the 1st level analyses of the reward task and the emotional go/nogo task. The peak voxel coordinates in the right ventral striatum based on the contrast [reward > baseline] from the reward task are used to build a 12mm-sphere for the striatum ROI using the marsbar toolbox (Brett et al, 2002). The same procedure is done for the ACC ROI with the contrast [faces nogo > faces go] from the emotional go/nogo task.

We have added these details to the methods section on page 14:

The individual masks for extraction of the neurofeedback value are constructed after the 1st level analyses of the reward task and the emotional go/nogo task submitting the peak voxel coordinates in the right ventral striatum and ACC based on the contrasts [reward > baseline] and [faces nogo > faces go] to build a 12mm-sphere for the striatum ROI and ACC using the marsbar toolbox, [122].

10.
How is movement and baseline activity considered?

We have added information on movement during NFB scanning to page 14:

To correct for movement, each acquired volume is realigned to the first image of the run. Then, volumes with more than 0.5 mm scan-to-scan movements are identified and marked in dummy regressors. Afterwards, the average intensity values from the target region and a cerebrospinal fluid (CSF) mask are extracted and the signal of the target region is corrected for the estimated motion parameters, high-motion dummy regressors, and the CSF signal. For calculation of the feedback signal the ROI intensity value of the last 3 volumes is averaged and compared to the average intensity of the baseline condition.

11.
Data analysis plan:

-This needs to describe the contrasts to be modelled in SPM and spell them out.

We want to apologize for any missing details. We have added information on the contrasts on page 16:

For all MRI tasks, all events of the paradigms are modelled by means of general linear model. The relevant contrasts for the go/nogo task are [faces nogo > faces go],[child faces nogo > adult faces nogo] and [negative faces nogo > positive faces nogo]. The relevant contrasts for the reward task are [reward high > reward low], [reward high cognitive load > reward low cognitive load] and [anticipation of reward > baseline]. The relevant contrasts for the passive viewing task are [own infant > unfamiliar child], [positive infant > negative infant], [own partner > unfamiliar man] and [own infant > own partner].

12.
-The primary and secondary outcome measures need to be described in a separate section or spelled out in the assessment section. Potential confounders to be considered such as movement parameters should be described.

The outcomes are assessed on behavioral as well as neuronal levels:

The primary behavioural outcome measure includes the quality of maternal-infant interaction behavior (composite scores of maternal and dyadic behavior).
On the neuronal level, we assess the BOLD response to positive stimuli of the child as primary outcome measure. Psychophysiological, endocrine and genetic markers serve as secondary outcomes.

We have included this information on page 10:

The primary behavioural outcome measures includes the quality of maternal-infant interaction behavior (composite scores of maternal and dyadic behavior) while on the on the neuronal level, we assess the BOLD response to positive stimuli of the child as primary outcome measure. Physiological, endocrine and genetic markers serve as secondary outcomes.

For discussion of movement confounds please see the adjustments on page 16 of the manuscript made in response to point 10 above.

13.
-Also, how are missing data going to be dealt with?
First of all, we will make every effort to reduce the amount of missing data. Second, before carrying out our analyses we will test if missing data is completely at random (MCAR). If the Little`s MCAR-test is non-significant, it is unlikely that excluded cases and the final sample differ regarding considered variables and will be treated with multiple imputation. Therefore, we will consider socio-demographic data (e.g. age), birth data (e.g. gestation age), self-report data (e.g. maternal bonding), cortisol data and mother- infant-interaction data at the last measurement point for this procedure. Moreover, child and gestation age, APGAR values, child gender, maternal age and education as well as marital status will be checked for differences between the control and the clinical group via t-tests, U-tests and χ^2-tests to ensure their comparability. Third, if appropriate, we will perform sensitivity analyses. Fourth, we will discuss the potential impact of missing data on the findings in the respective discussion sections.

14.
-How is experience of success or relevance captured? A potential confounder. How is real neurofeedback success going to be accounted for?

We are sorry for any missing information in the manuscript. Indeed, we assess the subjective success experience asking the participants after each NFB session.
Objective success is assessed with the levels of the thermometer.

Page 14:
Afterwards, they are asked to report which strategy they used and about their subjective success experience.

15.
-Are there plans for treatment responder vs non-responder comparisons?

Thanks for this extremely helpful comment. Indeed, comparisons would be highly interesting and relevant.
As this is the very first proof of method study, we do not yet know how many participants will not respond. Depending on the distribution of responders and non-responders allows, we will perform the relevant comparisons.

16.
-Are MDD patients subtypes recorded? Eg atypical, melancholic, anxious distress (DSM5)?

The maternal psychiatric status is assessed via a structured clinical interview according to DSM-5 (DIPS; Margraf, Cwik, Suppiger, & Schneider, 2017). It assesses the following depressive disorders: Persistent Depressive Disorder (Dysthymia), Major Depressive Disorder (mild, moderate, or severe, with/without psychotic symptoms, in full or partial remission), and Unspecified Depressive Disorder. Additionally, we assess psychiatric symptoms or diagnoses separately for every pregnancy trimester and for the postpartum period.

VERSION 2 – REVIEW

REVIEWER	Konstantinos Kalafatakis University General Hospital of Heraklion, Greece, University of Ioannina, Greece, University of Bristol, UK
REVIEW RETURNED	12-Mar-2019

GENERAL COMMENTS	The paper is ready for publication. I wish the authors good luck with this research project!

REVIEWER	Roland Zahn King's College London, UK
REVIEW RETURNED	14-Mar-2019

GENERAL COMMENTS	The authors have addressed my concerns apart from the abstract which needs some rewording/clarification:

	I suggest: -to replace ”brain's reward system" with "brain reward systems" to reflect the fact that there is an affiliation reward system which dissociated from the dopaminergic. -to replace"specifically the striatal dopaminergic region" with "including the striatum" as the striatum is modulated by a multitude of neurotransmitters and dopamine is not measured here and because the striatum is unlikely to be the only relevant region for rewarding responses to infant. -to replace "we conceptualised and offer" with "designed and investigated"

VERSION 2 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 1

The paper is ready for publication. I wish the authors good luck with this research project!

OUR RESPONSE: We thank the reviewer for his positive evaluation of our project and helpful advice.

Reviewer: 2

The authors have addressed my concerns apart from the abstract which needs some rewording/clarification:

I suggest:

-to replace ”brain's reward system" with "brain reward systems" to reflect the fact that there is an affiliation reward system which dissociated from the dopaminergic.

-to replace"specifically the striatal dopaminergic region" with "including the striatum" as the striatum is modulated by a multitude of neurotransmitters and dopamine is not measured here and because the striatum is unlikely to be the only relevant region for rewarding responses to infant.

-to replace "we conceptualised and offer" with "designed and investigated"

OUR RESPONSE: We thank the reviewer for his helpful advice. We have rephrased the abstract as follows.

“Introduction:

Most mothers feel an immediate, strong emotional bond with their new-born. On a neurobiological level, this is accompanied with the activation of the brain reward systems, including the striatum. However, approximately 10% of all mothers report difficulties to bond emotionally with their infant and display impaired reward responses to the interaction with their infant which might have long-term negative effects for the child’s development.

As previous studies suggest that activation of the striatal reward system can be regulated through Functional Magnetic Resonance Imaging (fMRI) based Neurofeedback (NFB), we have designed and investigate fMRI-NBF training to treat maternal bonding difficulties.

Methods and analysis:

In the planned trial, mothers will be presented pictures of their infant and real-time fMRI, peripheral measures, neural, endocrine, psychophysiological and behavioural measures will be assessed. Mothers with bonding difficulties (N= 68) will be randomised to one of two double blind intervention groups at 4-6 months postpartum. They will participate in three repeated neurofeedback training sessions with rtfMRI NFB training to increase activation of a) the ventral striatum or b) the anterior cingulate. Interview data and real-time mother-infant interaction behaviour pre-, post-intervention and at follow-up will serve as clinical outcome measures.”