

BMJ Open The NeMo real-time fMRI neurofeedback study: protocol of a randomised controlled clinical intervention trial in the neural foundations of mother–infant bonding

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ABSTRACT

Introduction Most mothers feel an immediate, strong emotional bond with their newborn. 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 MRI (fMRI)-based neurofeedback (NFB), we have designed and investigate fMRI-NFB 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 (rtfMRI), 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 NFB 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-intervention, post-intervention and at follow-up will serve as clinical outcome measures.

Ethics and dissemination Study procedures are in line with the recommendations of the World Medical Association (revised Declaration of Helsinki) and were approved by the Ethics Committee of the Medical Faculty, s-450/2017, Heidelberg University. All participants will provide written informed consent after receiving a detailed oral and written explanation of all procedures and can withdraw their consent at any time without negative consequence. Results will be internationally published and disseminated, to further the discussion on non-pharmacological treatment options in complex mental disorders.

Trial registration number DRKS00014570; Pre-results.

Strengths and limitations of this study

- The novelty of used methods allows the investigation of the effect of real-time functional MRI (rtfMRI) neurofeedback (NFB) on maternal bonding.
- The study investigates the ability of rtfMRI-NFB to upregulate brain activity in correlation with behavioural and biopsychological markers.
- The simultaneous investigation of two brain regions as well as the presence of a control group proposed in the methods of this protocol enables a comparative analysis of the benefits of the rtfMRI training, as well as increasing clarity regarding the role of differential brain regions in social reward.
- The proposed method, through its longitudinal design with follow-up measures, will help to evidence how NFB training brings about behavioural change, in turn allowing for better understanding of the potential applications, predictive neural signatures and participant criteria crucial for the success of rtfMRI.
- Due to the statistical co-occurrence of maternal bonding difficulties and postpartum depression and the similar pattern of muted reward responses in both instances, the explanatory power of the results of the rtfMRI-NFB intervention may be confounded.

INTRODUCTION

Neurobiological, emotional and behavioural aspects of maternal bonding

The parental bond is the first social bond that infants experience in life. Usually, it is the mother who serves as the infant's immediate and most central social interaction partner. Maternal bonding is reflective of the first emotional bond that a mother gradually develops with her infant, within the first weeks postpartum, and is characterised by positive feelings, emotional warmth and affection towards the infant.¹ In the eyes of some researchers, maternal bonding represents

one of the most important psychological processes that gradually unfold after birth² and is a significant and central aspect of the emerging relationship between mother and infant.³

The initial period after birth is also known as the 'Baby-Honeymoon', a state of euphoria and happiness fuelled by the desire to constantly be near and to 'fall in love' with the infant, which allows the mother to take on the challenges of the adaptation to parenthood. In this way, maternal bonding also fulfils a biological function by ensuring the care for and subsequent survival of the newborn.⁴ On the behavioural level, maternal bonding emerges through touch, eye-contact, use of 'motherese' and the smiling at or caressing of the infant.⁵ Maternal bonding can therefore be said to be expressed in the caregiving behaviours of the parent, in their focus on and high level of sensitivity to the needs of the infant.⁶ On the other hand, maternal bonding is also formed in the mother's emotions and thoughts about the infant and in the mental representations of motherhood that the mother holds.⁷

The strength of maternal bonding can also be demonstrated on a neurobiological level.⁸ Central structures such as the striatum, ventral tegmental area, amygdala, septum and hypothalamus are involved in affiliative behaviour, together with a combination of neurotransmitters and modulators such as dopamine and oxytocin.^{9 10} 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 contact¹¹ that underlie rewarding feelings of affiliation.

One finding of central relevance to maternal bonding in particular is that mothers who report a good emotional bonding to their infant show increased reward-related activation in dopaminergic brain regions (the nucleus accumbens in the ventral striatum) in response to infant stimuli.¹² These effects are particularly evident in the mother, in comparison to other caregivers, and have been assumed to be reinforced through the hormonal changes that accompany both birth and breastfeeding behaviours.^{13 14}

However, the bonding process is not always successful^{15 16} and impaired maternal bonding can lead to avoidance or ambivalent emotions or behaviour in the mother. Impaired bonding can result not only in a lack of affection but also, in extreme cases, in the immediate rejection or neglect of the infant, as well as the possible presence of hostility or aggressive impulses.^{2 7} Although postpartum bonding difficulties also occur in psychologically healthy mothers, they are observed particularly in the context of postpartum depression.^{17 18} In a representative German sample, 6.4% of psychologically healthy mothers reported difficulties in establishing emotional bonding with their infant. In depressed mothers, the rate of prevalence is significantly higher at 17%–29%.¹⁹ Furthermore, it has been shown that even subclinical depressive symptoms may negatively affect the developing bonding during the first months postpartum.⁶

Depression during the postpartum period itself is generally characterised by loss of interest or joylessness, insomnia, feelings of guilt, difficulties concentrating and, in severe cases, suicidal tendencies. Intense feelings and self-blame about being a bad mother are also often reported.²⁰ On a neurobiological level, postpartum depression relates to a reduced level of reactivity in the striatal reward system, for example in the putamen,²¹ but also the amygdala network²² together with endocrine changes in the serotonin and steroid systems.²³ Studies show that in particular the mother–infant relationship,^{24 25} as well as the actual mother–infant interaction,²⁶ both short term and long term can be impaired by peripartum and postpartum depression.^{24 27} Results of a recent study suggest that the link between maternal depressive symptoms at 2 months postpartum and maternal report about interaction with the infant at 6 months was mediated by maternal feelings of attachment.²⁸ The present study focuses on bonding impairments, rather than postpartum depression, although there will be inevitable co-occurrence in the participant sample.

Research indicates that experiences and interaction in the 'sensitive' postpartum period have long-term consequences for the cognitive as well as socio-emotional development in children.^{24 29} Animal studies have also demonstrated that positive caring behaviours of the mother positively influence offspring brain development and long-term stress-coping behaviours even in the next generation via epigenetic changes.³⁰ Conversely, in humans, decreased maternal bonding can result in higher rates of self-directed affect regulation strategies and increased stress reactivity³¹ of the infant, as well as variable self-comfort behaviours, moderated by the infant's gender and age.³¹ Research also indicates that restrained (distant) maternal behaviour can have far-reaching negative consequences for self-regulation, social behaviour and stress management in the infant^{24 29} even into adulthood with potential influences on own parenting behaviour.³² Furthermore, the association between maternal depression, anxiety disorders and stress reactivity with changes in the hypothalamic–pituitary–adrenocortical axis (HPA axis) is well documented.³³ Indeed, recent studies indicate that infant exposure to maternal mental disorders can increase infant baseline cortisol levels, as the main outcome of the HPA axis, in case of maternal depression and increase infant cortisol reactivity in cases of maternal anxiety.³⁴ In a lower-income setting, exposure to variable intensities of maternal depression demonstrated a U-shaped response curve in infant cortisol reactivity levels in the context of immunisation. Those with exposure to moderate-maternal depression levels demonstrated the lowest cortisol reactivity during immunisation.³⁵ The importance of the influence of maternal interaction behaviours themselves is also clear. One particular study demonstrates, for example, that maternal sensitivity during the interaction with their infant has a moderating influence between maternal mental health during pregnancy and infant salivary cortisol levels.³⁶ Given data on

the transgenerational transmission of maternal care via epigenetics,³⁷ both in maternal bonding^{38–40} and caregiving behaviours,⁴¹ the importance of effective treatment and intervention plans is evident.

Current inpatient and outpatient mother–infant therapies, established in the context of postpartum mental disorders, focus not only on the disorder-specific treatment but also on specific elements for the promotion of the mother–infant relationship (eg, baby massage and video feedback methods). Video feedback interventions have been shown to have a positive influence on mother–infant interaction^{42–43} as well as the maternal self-efficacy in interacting and coping with the infant.^{44–45} To our knowledge, maternal bonding has thus far only been recorded as an outcome variable in one study using video feedback invention.⁴⁶ This intervention demonstrated improvements in maternal bonding; however, the participant pool only included mentally healthy women without postpartum bonding problems. Thus, interventions focussing on maternal bonding in women experiencing difficulties forming an emotional bond to their infant are urgently needed. Presently, such interventions or findings, directly relating maternal bonding difficulties and their effects on the infant's stress reactivity in either biological or behavioural domains, are still lacking and in particular non-pharmacological treatment concepts would substantially broaden the treatment options for affected mothers and their infants.

Reward learning in depression and its relation to maternal bonding difficulties

On a neural level, the dopamine-mediated reward system (specifically the ventral striatum and the nucleus accumbens) is crucial to the rewarding aspects of social interaction.^{47–48} The ventral striatum also appears to be specifically involved in learning rewarding stimuli, where high neural activation, correlated with the blood-oxygen-level-dependent '(BOLD) response' in the functional MRI (fMRI), is accompanied by an increased dopaminergic response.⁴⁷ As part of the learning process, this reward activation is first triggered by primary enhancers, such as glucose, and over the course of the learning process transfers to secondary enhancers, such as food or money. In humans, from early in life, repeated positive social experiences can be seen as very strong reward and provided the basis for the much discussed 'social brain hypothesis', in brain research.^{49–50}

Images of happy children are generally perceived as positive by healthy individuals and activate the striatal areas of the brain.⁵¹ Psychologically healthy mothers also show a differential neural activation response to visual stimuli of happy children, as compared with stimuli of more ambiguous facial expressions of children. Expressions of joy activated the right limbic and paralimbic areas, compared to ambiguous expressions that correlated to activity in the left higher cognitive and motor areas that are often linked to cognitive effort.⁵² Consequently, positively reinforcing activities that lead to such activation,

that is, positive social interaction, are likely to be subsequently performed more frequently. In the presence of depressive symptoms, however, such neural activation (ie, activation in striatal and limbic networks) seems to be diminished during positive social interactions, these activities are therefore perceived as less rewarding^{53–54} and diminish the motivation for social contact. Mothers with depressive symptoms demonstrated reduced activation in subcortical and cortical limbic regions (amygdala, cingulate) and cortical regions involved in emotion regulation (including the frontal cortex, insula, anterior cingulate), in line with symptomology of diminished capacities to experience joy and to downregulate anger, anxiety or worry.^{21–22–55} Notably, mothers with postpartum depression show a reduced activation in striatal reward areas in response to stimuli of their own children.^{21–22–55}

On a neuroendocrine level, basic research suggests that in rodents social-interaction-related reward is associated with receptor activation for the neuropeptide oxytocin in the nucleus accumbens.⁵⁶ Initial data in humans indicate that methylation of the oxytocin receptor gene is associated with attachment in different phases of the individual's lifespan⁵⁷ and higher methylation is associated with postpartum depression.⁵⁸ Antidepressant treatment, in turn, is assumed to lower methylation.⁵⁹ This may explain, on a neurobiological level, the correlation between postpartum depression and maternal bonding difficulties.⁶⁰ However, no contemporary intervention has yet focused on the perception of the mother–infant interaction in terms of reward and involved oxytocin-related outcomes as possible evaluation criteria.

rtfMRI-NFB as a treatment method

Neurofeedback (NFB) is a novel method which, through the visualisation 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 BOLD signal, 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/visualisation of the related brain activation patterns.⁶¹ Thus, volunteers can learn to regulate the activation of a previously defined brain region (see Sulzer *et al*⁶² for a review). NFB interventions have previously often used electroencephalography and other electrophysiological methods to visualise 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 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.⁶³ From a therapeutic point of view, the targeted modulation of specific brain areas and associated circuits via NFB should be associated with the improvement of mental symptoms.

In initial clinical pilot studies, for example, patients with borderline personality disorder, anxiety or obsessive-compulsive disorder have shown the ability to downregulate activation in the insula or the hyperactive amygdala in response to stress-related stimuli.^{64–66} Similarly, high-risk alcohol consumers learned to downregulate the reward-related activation of alcohol-related stimuli.⁶⁷ In patients with post-traumatic stress disorder, the changes in brain connectivity after fMRI-NFB correlate with the reduction of symptoms.⁶⁸ Based on the previously articulated and evidenced notion of the psychobiological mechanisms underlying attachment and bonding as goal oriented and reward drive,⁶⁹ the proposed study looks to investigate whether specific activation of the ventral striatum can be voluntarily increased through training in the context of maternal bonding. Indeed, in previous research, patients with major depressive disorder or schizophrenia were successfully trained to increase the activation of the hypoactive amygdala and the anterior cingulum in conjunction with positive stimuli.^{70–71} Therefore, in line with the current understanding and treatment of mental illnesses, rtfMRI-NFB represents a promising new intervention method for complex mental processes. Particularly important for understanding the potential of rtfMRI interventions is the transfer of the modulation of the BOLD signal towards behavioural changes⁶¹ which allows the value of this intervention form in a clinical setting to be distilled.

The planned trial

In the planned double-blind randomised intervention trial (the 'Neurofeedback for Mothers with Postpartum Bonding Difficulties Study', 'NeMo-Study'), three central points will be addressed.

1. Women with postpartum bonding difficulties (including women with postpartum depression) will be compared with healthy unaffected women in terms of reward-related brain activation to pictures showing their own infant and control stimuli. It is hypothesised that women with bonding difficulties show less brain response in the reward-related areas (ventral striatum) compared with the control group.
2. The clinical group will then undergo a regiment of NFB training. 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 hypothesised 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 interaction⁶¹ 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 for example, in cognitive reappraisal⁷² or response inhibition⁷³ may have gener-

al beneficial effects as shown in another NFB study⁷⁰ but also indirectly influence parental affect regulation. However, the more specific striatal feedback based on the rewarding aspects of the mother–child interaction are assumed to have stronger effects.

3. Effects of the NFB training will be related to the changes in behaviourally coded mother–infant interaction, maternal bonding quality and diagnostics, and epigenetic oxytocin receptor alterations, as assessed from peripheral blood. It is hypothesised that following the ventral striatum intervention, interaction, maternal bonding and epigenetic markers will approximate the values of the healthy control group.

Thus, the study will address reward-related processes in impaired maternal bonding, observable changes on a behavioural and neuroendocrine level post-training—important steps in illustrating the validity of rtfMRI-NFB as an intervention method.⁶¹ The proposed study is therefore well placed to produce a wealth of valuable and informative data, regarding the potential scope of rtfMRI as a non-pharmacological intervention to young mothers.

METHODS AND ANALYSIS

Design overview

To investigate points (1)–(3) (above), a controlled longitudinal study with randomised allocation of the two intervention groups to one of two anatomically defined regionally targeted areas in the NFB training will be employed. The two intervention groups will consist of mothers with identified maternal bonding difficulties, whereas the control group will consist of psychologically healthy mothers without bonding difficulties. The intervention groups will receive three NFB training sessions at intervals of approximately 14 days. Changes in maternal behaviours during mother–infant interaction, measured using standardised coding of behavioural observations, will be assessed as the primary outcome measure. Possible alterations in oxytocin receptor methylation and gene expression will serve as secondary outcome measures. See [figure 1](#) for overview of study design and timeline.

Participant eligibility and recruitment

Eligible participants

Intervention Group: Mothers, who report postpartum bonding difficulties, may present with a wide range of depressive symptoms.

Control Group: Psychologically healthy mothers with intact bonding to their infant.

Exclusion criteria for all groups

Mothers: acute suicidality, bipolar or schizophrenic disorders, diagnosed dementia or substance abuse or substance dependency. Necessarily fMRI exclusion criteria also apply.

Infants: multiple birth infants, preterm birth, confirmed physical or developmental disorders, which make participation impossible or unwise.

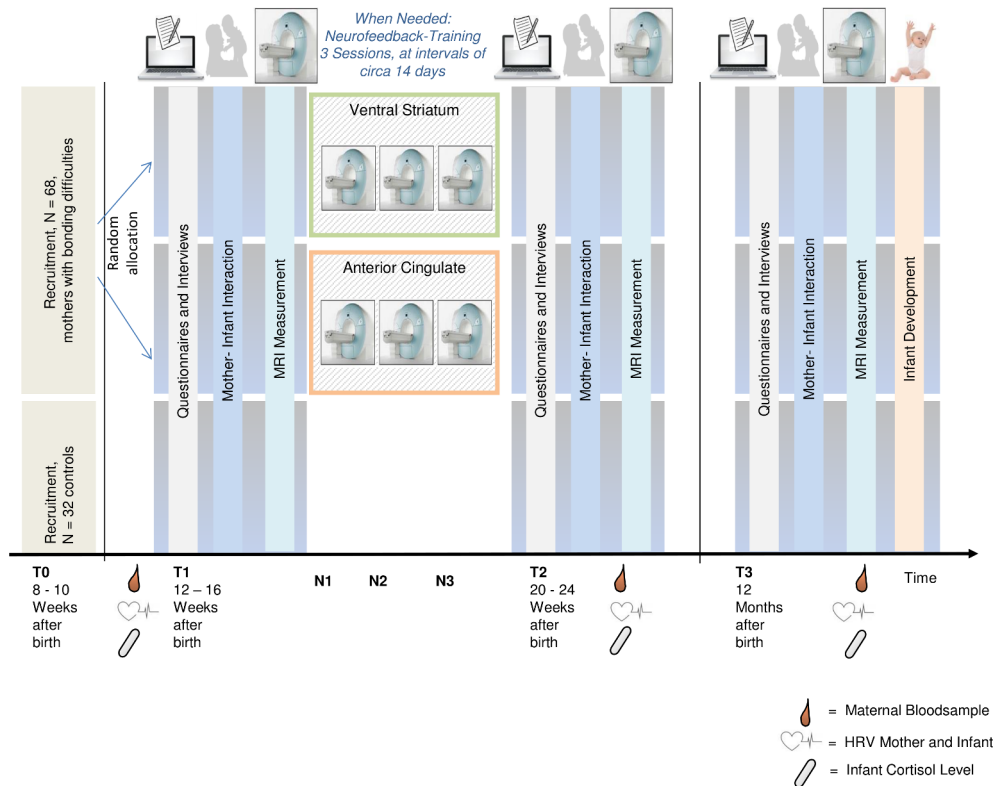


Figure 1 Overview of study design. HRV, heart rate variability.

Participant recruitment

Participants will be recruited both online and by flyers disseminated through midwives, gynaecologists, paediatricians, in pharmacies and in maternity hospitals as well as mothering forums or self-help groups (eg, 'Shadow and Light') and registration offices. They receive thorough information about the study procedures both orally and in written form. The volunteer recruitment structure of the study makes it possible that given the intense feelings of self-blame symptomatology of the often co-occurring postpartum depression,¹⁸ those most severely affected may not volunteer for the study. This limitation will be addressed via carefully worded and emphatic recruitment materials and processes.

Patient and public involvement

Patients and the general public were not involved in the design or implementation of this study. However, the participants are asked to report on the cognitive strategies they adopted during their rtfMRI-NFB sessions and their subjective success with those strategies. These findings may inform future formulations of patient based NFB interventions.

The results of this study will not be disseminated to the participants directly but will be openly accessible online.

Screening assessment and group allocation

Screening assessment

For inclusion in the study, all potential participants will be screened (T0) prior to inclusion.

Random group assignment procedure

True random assignment to the two clinical intervention groups or the control group cannot occur due to the quasi-experimental nature of the design: The mothers are assigned to being clinical or control based on the quality of their postpartum bonding to their infant. Inclusion as part of the clinical intervention group is based on the categorical assessment of impaired maternal bonding using an in-depth interview based on the proposed criteria by Brockington *et al*¹⁹ and asked during the clinical interview. Bonding assessment is further elaborated by the use of additional questionnaires exploring bonding impairment, such as the Postpartum Bonding Questionnaire¹⁶, which holds an internal consistency of Cronbach's $\alpha=0.085$.⁵ This approach additionally allows for the dimensional assessment of maternal bonding impairments.

Within the intervention group, participants will be completely randomly and automatically assigned to one of the following two conditions: NFB of the right ventral striatum (clinical intervention group I) or NFB of the right ACC (clinical intervention group II). This randomisation is based on the order of inclusion into the study and pre-assigned lists that are double-blind in nature using non-public 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.

Power analysis and size estimation

The programme G-Power V.3.1.9.2⁷⁴ was used, in order to calculate the required sample size. To test the hypotheses mentioned above, a total of approximately $n=100$ cases is estimated.

To perform a simple group comparison of maternal sensitivity between two treatment groups with a middle to large effect size ($d=0.78$)⁴³ with a power of 90% and an alpha-error threshold of $p=0.05$, a minimum group size of $n=30$ for each clinical intervention group is required (I, NFB of the ventral striatum, II, NFB of the ACC). Assuming a drop-out rate of approximately 10%, an experimental sample of $n=100$ will be aimed for in the projected study. With a repeated measures analyses and the T3 (follow-up) measurement, the power is improved, which makes it possible to observe even medium effects with this planned sample.

$n=68$ mothers with postpartum bonding difficulties will be included in the intervention ($n=34$ to NFB region I ventral striatum, $n=34$ to NFB region II ACC). Mental disorders, and especially postpartum depressive symptomatology, are measured in a multi-dimensional fashion through a structured clinical interview and a validated peripartum period questionnaire. Variability in depressive symptoms, ranging from none to moderate symptom load is sought, thus allowing for appropriate and adequate statistical analysis of this covariate factor. As a control group, $n=32$ psychologically healthy women with a good bond with their infant will be recruited.

Pre-intervention, post-intervention and follow-up assessments (T1, T2 and T3)

Before (T1) and after the training (T2), participants will perform an extensive battery of diagnostic assessments characterising the clinical aspects of bonding, including the instructed mother–infant–interaction in the Face-To-Face-Still-Face (FFSF) Paradigm.^{75 76} A baseline fMRI session will assess the sensitivity of both the reward system and the limbic system using established fMRI tasks and blood samples will be collected for analysing hormonal and (epi-)genetic markers. After the end of the last NFB training a post-intervention measurement (T2) and a 12 months a follow-up (T3) will be performed using the same methods as at T1. At T3, mothers and infants will be instructed to freely play⁷⁷ and videotaped. Age-specific markers of the infant's development will be coded using a standardised developmental test.⁷⁸ (Refer to figure 1 for timeline clarification.)

This combination of assessments allows for a comprehensive understanding of maternal bonding and behaviour on a neural, neuroendocrine, epigenetic and behavioural level.

The primary behavioural outcome measures include the quality of maternal–infant interaction behaviour (composite scores of maternal and dyadic behaviour) while 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.

See table 1 for further details on the assessments and scheduling of measure collection.

Survey instruments and coding systems used in the study

Detailed description of measures, methods and instruments used

Initial assessments

Baseline assessment

For the baseline testing period (T1), the mothers will be invited to our video laboratory together with their infants. A structured clinical interview according to Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition as well as an interview regarding postpartum bonding difficulties will be carried out. Subsequently, mother–infant interaction will be assessed and videotaped during the FFSF paradigm, a widely used paradigm for evaluating the quality of early parent–infant interaction.⁷⁵ To determine infant stress reactivity, cortisol and alpha-amylase will be extracted from infant saliva according to standard protocols,⁷⁹ which is collected before (C1), immediately after (C2), 20 min (C3) and 30 min after the FFSF (C4).

Instructed mother–infant interaction

Mother–infant interaction pre–post-intervention (T1 and T3): The standardised mother–infant interaction before and after the intervention follows the established FFSF paradigm.^{75 76} It consists of three consecutive instructed 2 min episodes in which the mother, with the infant seated in the baby chair, interacts in accordance with a fixed pattern: First, an initial face-to-face interaction in which the mother is instructed to play with her infant as usual (without the aid of toys and pacifiers). Next, the still-face episode in which the mother has to turn her head aside while silently counting to 10 and then turn back to the infant but not engage in any gestures, facial expressions or vocalisations. Finally, the procedure ends with the reunion episode in which the mother is required to resume face-to-face play with her infant.

Mother–infant interaction follow-up (T4): As the Still-face paradigm can be conducted up to the age of 9 months, mother–infant interaction will be assessed at T4 during a 15 min free-play situation and a subsequent limit setting task. All interaction episodes will be videotaped and coded according to the Coding Interactive Behaviour (CIB) Scales.⁷⁷ The CIB scales assess parental sensitivity and responsiveness as well as intrusiveness and withdrawal via composite scores.⁸⁰

Psychobiological measurements

Epigenetic information on the oxytocin system and cortisol/alpha-amylase in saliva

Maternal blood samples are taken to examine the endogenous oxytocin level, gonadal hormones and epigenetic parameters of the oxytocin gene and oxytocin receptor gene. For the endocrine investigation of the stress hormone cortisol, painless saliva samples are taken from the infants directly before, immediately after, 20 and 30 min after the mother–infant interaction using a saliva

Table 1 Schedule of measures used the in study

Measure	Citation	M.	F.	I.	T0	T1	N	T2	T3
Mother and infant:									
Mother–infant interaction (FFSF)	75 76	X		X		X		X	
Free-play situation and limit setting	77	X		X					X
Interviews:									
Diagnostic interview for mental disorders	92	X				X		X	X
Interview for postpartum bonding difficulties		X				X		X	X
Attachment style interview	93	X	X			X			
Questionnaires:									
Postpartum Bonding Questionnaire 16 R	5	X	X			X		X	X
Edinburgh Postnatal Depression Scale	94	X	X			X		X	X
Agoraphobic Cognitions Questionnaire, Body Sensations Questionnaire, and Mobility Inventory	95	X	X			X		X	X
Maternal Self-Confidence Scale	96	X	X			X		X	X
Prenatal Emotional Stress Index	17	X	X			X			
Parental Bonding Instrument	97	X	X			X			
German version of the EMBU questionnaire regarding remembered parenting behaviour	98	X	X			X			
Experiences in Close Relationships-Revised	99	X	X			X			
Social Support Questionnaire	100	X	X			X		X	X
Personality Inventory-DSM 5 Short Form	101	X	X			X			
Childhood Trauma Questionnaire	102	X	X			X			
Partnership Questionnaire	103	X	X			X		X	X
Dyadic Coping Inventory	104	X	X			X		X	X
Parenting Stress Inventory	105	X	X			X		X	X
Vulnerable Attachment Style Questionnaire	106	X	X			X			
Edinburgh Handedness Questionnaire	107	X				X			
Infant:									
Infant Behaviour Questionnaire	108	X	X			X			X
Development Assessment: Infant									
Bayley's Infant Development Scale III	78			X					X
Physiological measures									
Infant saliva sample				X		X		X	X
Mother blood sample		X				X		X	X
Neurofeedback training		X					X		X

Continued

Table 1 Continued	Citation	M.	F.	I.	T0	T1	N	T2	T3
Measure									
Reward task	83	X				X		X	X
Emotional go-no-go	73	X				X		X	X
Passive viewing task	84	X				X		X	X

M., mother response; F., father response; I., infant response; T0, screening assessment; T1, baseline assessment; N, neurofeedback sessions; T2, post-assessment; T3, follow-up. DSM-5, Diagnostic and Statistical Manual of Mental Disorders, EMBU, Egna Minnen Beträffande Uppfostran (Own Memories of Child Rearing Experiences); Fifth Edition; FFSF, Face-to-Face-Still-Face.

probe. An elevation of infant stress reactivity is expected during the interaction, from these elevations the Peak and Recovery will be ascertained. The area under the curve is therefore analysed as a reactivity index⁸¹ as is standard practice.⁸²

MRI tasks

Reward task

The task (adapted from Martin-Soelch *et al*⁸³) requires participants to perform a spatial working memory task with two levels of cognitive load, differentiated by the number of circles to be remembered. Subjects first see a cue informing them about the potential monetary reward value—high or low. After presentation of the fixation cross, an array of yellow circles (three or seven circles) is displayed followed by the target, a green circle, that is then presented at any position on the screen. The participants must decide whether this circle is in the same position as one of the circles presented previously. In the rewarded condition, a feedback about the win followed by the cumulated amount of earned money appears. Correct responses are reinforced by two different amounts of monetary reward that are counterbalanced with the levels of cognitive load. Incorrect responses on rewarded trials result in no monetary gain. While performing the task, participants rate their mood and stress levels a quarter of the trials.

Emotional go/nogo

The participants are presented with positive and negative expressions of unknown babies, unknown adults as well as un-social control stimuli (geometric figures; a circle, a cross, a diamond and a triangle) over three presentation blocks.

The following factors are systematically manipulated: child versus adult and emotionality of facial expression (positive vs negative). In two blocks, the participants receive instructions to respond by pressing a button as fast as possible to all facial expression except the negative (one block babies, one block adults). In two other blocks, they are instructed to respond as fast as possible to all except the positive (one block babies, one block adults). In the two non-social blocks, the participants should react as fast as possible to all shapes but not to a circle or a diamond.⁷³

Passive viewing task

The participants view previously collected neutral-positive images of partners and their babies in positive and negative affect, with instructions to observe carefully. Unfamiliar men and babies will serve as control stimuli. Viewing images of partners and children leads to the activation of a broad socio-emotional neural network, that is involved with empathy and socio-emotional cognition.^{21 84}

Coding systems used in the study

Coding interactive behaviour

For the evaluation of the mother-infant– interaction over all measurement points, the Coding Interactive Behaviour

(CIB) System will be used⁷⁷. The CIB is a widely used, global rating system for analysing mother–infant interaction. The system uses multiple codes for the infants, parents and dyadic codes that aggregate into meaningful theoretically based constructs (eg, sensitivity, intrusiveness, reciprocity, social engagement, withdrawal). The psychometric characteristics are all well described.⁸⁵ The mother–infant interaction will be 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.

Infant development diagnostics used in the study

Bayley Scales of Infant and Toddler Development-III

The Bayley Scales of Infant and Toddler Development-III (Bayley-III^{86 87}) assess the development of infants and toddlers between 1 and 42 months of age. The test battery covers the domains of cognition, language, motor, social-emotional and adaptive development using IQ-scaled composite scores. Whereas the first three aspects are assessed by behavioural observation, the latter two utilise questionnaires, with duration ranging between 50 and 90 min.⁸⁸ The Cognitive Scale assesses sensorimotor development, exploration and manipulation, object relatedness, concept formation and memory. The Language Scale is composed of the two subscales (receptive and expressive communication), testing pre-verbal behaviour, vocabulary development, understanding of morphological markers, social referencing and verbal comprehension and pre-verbal communication, vocabulary development and morpho-syntactic development, respectively. In addition, the Bayley Scales include a Gross- and Fine-Motor Scale, a Social-Emotional Scale and an Adaptive Behaviour Scale. This study focuses on the language and cognitive composite scores due to the rather small proposed sample size.

The Bayley-III indices and subscales demonstrate good internal consistency and good split-half-consistency according to the Spearman-Brown formula.⁸⁸ Regarding construct validity, a confirmatory factor analysis of the subtests of the Cognitive, Language and Motor Scales supported a three-factor model across all ages. The Bayley-III scales have been normed for German infants and children.⁸⁹ This method is taken standard internationally, particularly in terms of reviewing developmental

delays and planning targeted early interventions. The order of the subtests can be adapted to the needs of the child.

NFB setup

The mothers with bonding difficulties will be randomised to receive one of the two following interventions: (I) NFB for activation of the ventral striatum or (II) NFB for activation of the ACC.

The individual masks for extraction of the NFB value are built after the first 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 12 mm sphere region of Interests (ROIs) for the striatum and ACC using the marsbar toolbox.⁹⁰

Participants will partake in NFB training over three sessions at intervals of approximately 14 days (refer to [figure 1](#)). At baseline, a high-resolution structural MRI scan and the activation pattern based on the infant-like stimuli will be recorded (using a Tim Trio 3T MRI scanner, Siemens, Erlangen, Germany).

Each intervention session will last approximately 60 min and will begin with a 10 min preparatory structural MRI scan. A 6 min resting state fMRI scan is then conducted to allow a resting baseline to be established and to prepare the NFB setup. Afterwards, three rtfMRI-NFB runs of 9:29 min are conducted. During NFB training, positive and neutral pictures of the participants' own infant taken from the recorded mother–infant interaction session will be presented together with an on-screen 'thermometer' which represents the current intensity of activation in the striatum or ACC and must be upregulated. In each run, six alternating phases of upregulation (~41 s, including a ~10 s initial period without thermometer display) and of rest (observation of a fixation cross, ~41 s) will be performed (see [figure 2](#) for details). The women are instructed to try and explore different self-chosen strategies (of upregulation) and find the one that works best for them. Afterwards, they are asked to report which strategy they used and about their subjective success experience. The third and last run of each session is implemented as a 'transfer' block without the visible 'thermometer' display.^{65 67 71}

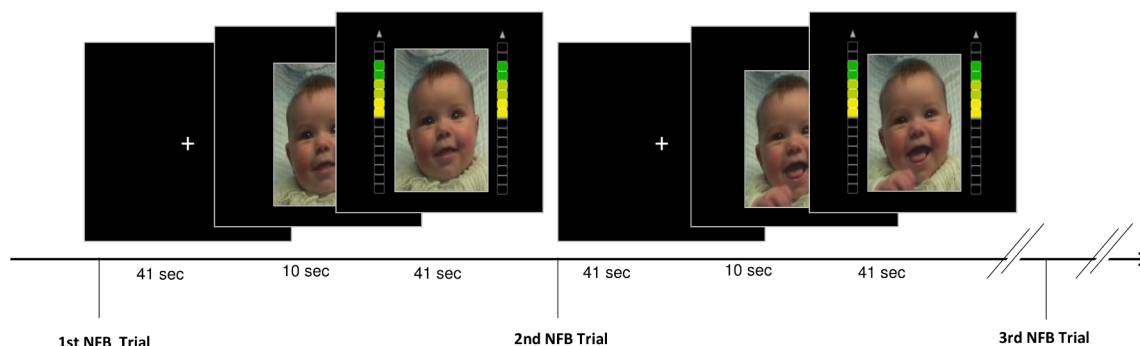


Figure 2 Two trials of the NFB intervention within a run. NFB, neurofeedback.

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 3×3×3mm, 343 volumes per trainings run, distance factor of 33% and GeneRalized Auto-calibrating Partial Parallel Acquisition (GRAPPA) with iPat=2) and a 32 channel head coil. Control for cardiovascular parameters is conducted using the built-in pulse clip. In-house Matlab software based on statistical parametric mapping 12 (SPM12) functions is used to conduct rtfMRI-NFB and Presentation software (Neurobehavioral Systems, Albany, CA, USA) is used to present pictures and the feedback signal. At the beginning of each NFB training session, the anatomical image is segmented and normalised to Montreal Neurological Institute (MNI) standard space. The inverse deformations of the normalisation 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 0.5mm 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 three volumes is averaged and compared with the average intensity of the baseline condition. For further technical details regarding the NFB setup, please refer to Gerchen *et al.*⁹¹ which uses an identical NFB procedure in the context of alcohol addiction.

Data analysis plan

Statistical analyses, namely the main comparison of the two groups (mothers with bonding difficulties vs the control group) and the longitudinal analysis of positive relationships changes after the NFB intervention (interaction behaviour, attachment data, as well as psychophysiological, neuroendocrine and epigenetic markers (see table 1) will be done using IBM SPSS Statics and R (r-project.org). The MRI data will be analysed with general linear models using statistical parametric mapping with SPM (<https://www.fil.ion.ucl.ac.uk/spm/software/spm12/>) implemented (Wellcome Department of Cognitive Neurology, London, UK) in MATLAB (MathWorks, Natick, MA).

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), (infant 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 infant), (positive infant >negative infant), (own partner >unfamiliar man) and (own infant >own partner).

To calculate pre-intervention, post-intervention and follow-up group differences between the intervention and control groups, repeated measures analyses of variance will be calculated while multi-level models will be used to model changes over the time course.

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