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Vocal Brain Development in Infants of Mothers with Serious Mental Illness (CAPRI-Voc) - study protocol

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ABSTRACT

Introduction

Improving the lives of children and adolescents with parental mental illness (CAPRI) remains an urgent political and public health concern for the United Kingdom (UK) and European Union (EU). Recurrent parental mental illness is believed to lead to fractures in the family, academic and social lives of these children yet interventions are poorly targeted and non-specific. Part of an interdisciplinary programme of work (the CAPRI Programme[1]. Grant number: 682741), CAPRI-Voc aims to achieve two goals: First, to test the feasibility of our longitudinal imaging paradigm in mother-infant pairs where the mother has a diagnosis of severe mental illness. Second, to compare development of vocal processing in these infants with infants in the general population.

Methods and Analysis

We aim to recruit 100 infants of mothers with mental illness, alongside 50 infants of healthy mothers. Both cohorts of infants will undergo functional near infrared spectroscopy (fNIRS) brain imaging at three time points: 9, 12 and 18 months to explore differences between cohorts in their neural responses to vocal stimuli in our language paradigm. Mothers will complete an interview and psychological questionnaires. We shall also complete an infant developmental battery and mother-child interaction play session. Data on recruitment, retention and dropout will be recorded.

Ethics and Dissemination

It will be made clear that fNIRS is a safe, non-invasive technology widely used in infant clinical and psychological research. We shall reassure mothers that no definitive causal link exists between maternal mental illness and language development in infants, and that individual data will only exist as part of the wider dataset. As the study includes both children and vulnerable adults, all research staff will complete NHS Safeguarding level 3 training. Dissemination will be via direct feedback to stakeholders, patient and advisory groups, and through presentations at conferences, journal publications and University/NHS trust communications.

Strengths and Limitations of this study

- Potential to deliver ROAMER priority 1[2] and the Child and Adolescent Mental Health in Enlarged European Union (CAMHEE) objectives[3] to acknowledge the needs of children in families with parental mental illness
- Uncovering a biomarker of early abnormal development will allow targeting of interventions to those most at risk within a risk subset

- This new approach could be used in future to assess early resilience and risk of atypical speech and language development in very young children (alongside its links to other poor outcomes for CAPRI), within routine clinical settings in the absence of parental mental illness
- The group we wish to recruit raises challenges, including recruitment and attrition
- This fNIRS imaging protocol is untested within the ecologically valid setting of the home which may affect data analysis and thus inference to the wider population

Key Words: CAPRI, infant, parental mental illness, resilience, risk, language development, fNIRS

INTRODUCTION

The numbers of children living with parental mental illness (CAPRI) are increasing[4]. Numerous studies illustrate the risk of CAPRI developing their own mental illness[5–10]. However, risk of mental illness is likely to be relatively rare compared to other more common outcomes including behavioural, educational, social and other difficulties [8,11–18]. Some evidence suggests that paternal and maternal depression is associated with atypical cognitive development in CAPRI, with significantly delayed expressive language and lower IQ [13,14,19], particularly in exposed boys [15].

In spite of this, most CAPRI will remain resilient. Social support and education about mental illness may improve resilience [20–24], but little reliable information exists to help parents and clinicians understand better which children in the risk-set are likely to be at greatest risk and which may be resilient; this lack of understanding creates a challenge for services with limited resources. This is important not only for economic reasons, but also because those at greatest risk are also those likely to be most sensitive to intervention[25]. Identifying a biomarker in infants for greatest risk of later cognitive deficits might allow early intervention or even prevention and improve the quality of life for a growing number of vulnerable children.

fNIRS and CAPRI-Voc

fNIRS is a relatively new functional imaging technique, particularly suited for use in infants, due to safety (emission of visible light) and the smaller surface area of infant heads. It is based on the principle that many biological tissues are relatively transparent to light in the near and infrared ranges between 700-1150nm. Chromophores, tissues that absorb light, such as oxygenated (HbO) and deoxygenated haemoglobin (HHb) absorb specific wavelengths in this range offering an 'optical window' for non-invasive assessment of these compounds in the brain. Attenuation of specific wavelengths of near infrared light transmitted through the tissue of interest allows calculation of changes in the concentration of HbO and HHb (in m-molar units) by applying the modified Beer Lambert law. Using

multiple light emitting sources and detectors allows for topographic maps of changes in HbO and HHb to be generated across the illuminated region. Analogous to functional magnetic resonance imaging (fMRI), using blood oxygen level dependent (BOLD) changes, fNIRS provides an index of functional brain activity via downstream cortical blood flow and neuronal activity. Burgeoning evidence supports reasonable concordance between fMRI and fNIRS measures, although they are best viewed as complementary methodologies[26]. fNIRS lacks the spatial resolution of fMRI and, in particular, is limited to measuring superficial cortical areas close to the scalp with the depth determined by the separation between transmitter and detector. It is, however, a low cost, portable, safe, quick and extremely well tolerated 'bedside' technology that allows neuroimaging to be carried out when fMRI scanning is difficult or contraindicated. fNIRS provides greater temporal resolution than fMRI (data acquisition typically in the order of 10Hz) allowing for detailed analysis of the haemodynamic response function of oxyhaemoglobin but also deoxyhaemoglobin associated with neural activity, e.g. latency effects.

This study will utilise a bespoke fNIRS imaging paradigm and array design which has been piloted already in young infants of 40 healthy mothers to assess early language development[27,28]. fNIRS is particularly suited to infants as it does not require the infrastructure, cost or tolerance of MRI or the addition of conductive gels (e.g. EEG) in order to acquire data. The fNIRS system (mini-NTS, Gower labs, UCL, UK) is a bedside, portable imaging system that can be operated in participants' homes or at a familiar clinical setting such as a GP surgery or health centre, allowing the research team greater scope to recruit new mothers and infants and perform those assessments in familiar environments. The fNIRS system provides a 48-channel array for topographical coverage of bilateral superior temporal cortices.

Several brain imaging studies agree that healthy infants can discriminate speech/vocalisations from other sounds by around 6 months old, through differential responses viewed within the frontal, temporal and parietal cortices[29–31]. By recruiting infants aged between 9-18months (+/- 1 month), we aim to capture vocal developmental changes, not only between healthy and at-risk infants, but also in within-subject longitudinal data. Voice recognition is a precursor of early language acquisition[32] which, in turn, is a key predictor of a range of subsequent life outcomes. Previous 'high risk' studies[33,34] in older children have reported abnormalities in speech and language using observer-rated measures. Similar behavioural assessments cannot distinguish infants at low and high-risk of autism, whereas fNIRS studies were able to reliably identify differences in brain function of very young infants, and assign them to low and high autism risk [35,36]. Work packages 1 & 2 are exploring epidemiological data that will allow work package 3 (CAPRI-Voc) to stratify infants into higher and

lower risk sets for atypical neurocognitive outcomes. We shall validate this grouping by examining differences in infant brain language processing with fNIRS. Specifically, we shall examine voice recognition and responses to emotional speech between the two risk groups and healthy controls between 9-18 months.

Study Aims and Hypotheses:

1. To test the feasibility of our recently piloted longitudinal fNIRS paradigm in infants with severe maternal mental illness in order to detect changes in language development.
   We hypothesise:
   a) That neural responses to the vocal paradigm will correlate with existing measures of infant neurocognitive development
2. To discover infant biomarkers of atypical language development in CAPRI using fNIRS.
   We hypothesise:
   a) Children of mothers with SMI would experience delays in vocal and affect recognition at 9 months compared to children of healthy mothers.
   b) Children of mothers with SMI would experience atypical neural connectivity compared to children of healthy mothers
3. To stratify infants within a risk subset into highest and lowest risk using epidemiologically-derived resilience and risk predictors for child neurocognitive outcomes (ADHD, ASD, intellectual disability & cognitive ability). To compare between these assigned groups emergence of voice recognition over three time points (9 months, 12 months & 18 months), using fNIRS.
   We hypothesise:
   a) That there is an interaction with adversity and parental mental illness such that children exposed to parental mental illness and adversity experience the largest developmental delays.

4. To discover objective early indicators of atypical brain development of voice recognition for use in routine clinical settings in order to target CAPRI at greatest risk for early specialist intervention

METHODS AND ANALYSIS

Design

This study is a novel longitudinal infant brain imaging study to assess whether fNIRS can locate a neuro-biomarker of early language development in children at high and low risk of cognitive

impairment. The study is taking place across the UK, but is based in Greater Manchester. The research is funded by the European Research Council (ERC, 682741). It was approved by North West – Greater Manchester West Research Ethics Committee (17/NW/0074). The current protocol version is Version 1.9 (19/06/19).

Sample Size

Over four years (September 2017-April 2021), we aim to recruit and test 100 infants of mothers with mental illness; alongside 50 infants of healthy mothers acting as controls. Both cohorts of infants will be aged between 9-18 months old (+/-1 month).

Patient and Public Involvement

At the final session, all mothers will be asked to think about the effectiveness of the study's recruitment strategies, the burden of time and emotional strain on those that take part, dissemination, and any other suggestions.

Participants and Recruitment Procedures

Mothers with SMI will be recruited from primary and secondary care settings, outpatient services and mother and baby units (MBUs). In addition, we will advertise the study on CAPRI-Voc social media channels and targeted online advertising so that women may self-refer. Mental health NHS trusts will be brought on board as research sites to ensure full engagement with study recruitment. The research team will advertise the research at meetings of ward managers, clinicians, nurses, care coordinators and specialist midwives. Leaflets, posters and eligibility checklists will be distributed in these meetings for further circulation among staff. NHS Staff will provide eligible women with a brief overview of the study along with participant information sheets. Women will inform their NHS contact if they are interested in participating and provide their consent for the research team to contact them. There will be appointed study champions within each trust whose role it is to promote the study and contact the research team to pass across all relevant information pertaining to potential recruits; primary psychiatric diagnosis, infant date of birth, risk information and contact details. The research team will contact the potential recruit (usually via telephone) to confirm continued interest in the research, address any queries arising from the information sheet and to arrange a visit for the first session. Consent for participation will be agreed at least 24 hours after the information sheet has been read.

Healthy mothers will be recruited through leaflets and posters placed in and around The University of Manchester buildings, Manchester Foundation Trust NHS buildings and Sure Start Centres, alongside digital advertising via the CAPRI-Voc social media pages. Women can contact the research team if they

are interested in the study via the contact details placed on the advertising materials. Potential participants will be provided with participant information sheets and allowed a minimum of 24 hours to consider their decision and ask any questions of the research team. A visit would then be arranged to gain informed consent to participate in the study and begin session one.

Inclusion/Exclusion Criteria

SMI is defined as a severe psychiatric disorder that requires intervention, hospitalisation or ongoing treatment. Mothers with a primary diagnosis of schizophrenia, schizoaffective disorder, bipolar disorder, severe recurrent unipolar depression, psychotic depression, severe anxiety, obsessive compulsive disorder (OCD) and post-traumatic stress disorder (PTSD) are sought. Mothers with a current diagnosis of a severe psychiatric disorder with a minimum requirement of scheduled follow up with secondary care services will be eligible for study inclusion. Primary substance misuse disorders and primary eating disorders are excluded as any related gestational effects on the development of the infant cannot be ruled out.

All mothers will be aged 16 or over, fluent in the English language and able to give written, informed consent. Care coordinators will assess capacity to consent of their clients with SMI, and capacity considered throughout by the experienced research team in collaboration with the CI.

Figures 1 and 2 illustrate the flow of both SMI and healthy participants through the study, based on the ESMI[37] protocol (Grant Reference: RP-DG-1108-10012) and the CONSORT diagram[38]

FIGURE 1 placement

FIGURE 2 placement

Sessions

Measures

The research team designed a bespoke 50 page interview workbook that has two main sections; section one contains researcher administered questionnaires and section two contains self-complete questionnaires for the mother to undertake. The remaining measures across all study time points, along with the interview workbook are briefly described in Table 1 below. Healthy mothers will complete a modified version of all measures because of non-applicability of certain clinical questions/measures (see Table 1). Prior to the baseline session, section two of the workbook (self-report questionnaires) will be sent to the mothers to complete in their own time in order to reduce the time burden on the baseline assessment session.

'9 months' refers to the time period where the infant is aged 9 months (+/- 1 month). 9 month data are collected at the study baseline interview session. SMI mothers will have certain aspects of these data collected via medical records, if consent has been granted. '12 months' refers to the time period when the infant is aged 12 months (+/- 1 month). 12 month data are collected at the first follow-up face-to-face session. '18 months' refers to the time period where the infant is aged 18 months (+/- 1 month). 18 month data are collected at the second follow-up face-to-face session. The reason for utilising medical records where possible is to decrease any potential burden of recall on the SMI mothers so as to increase the likelihood of continued participation.

The baseline face-to-face session takes up to two hours and includes assessments for both mothers and their infants. The follow-up sessions take up to 1 hour and 30 minutes. Visits will either take place at the women's homes, a local NHS facility, or at The University of Manchester, whichever is most convenient for the participant. Based on preference, the women can complete the face-to-face sessions in one or two parts. Women with older children who require childcare to take part may be reimbursed for the costs of childcare. Women are offered £50 worth of shopping vouchers as reimbursement for their time and inconvenience at their final session (18 month).

Mother Only Measures						
Type of measure/ Name of Instrument	**Instrument Details**	**Healthy Mother Modification**	**Data Relating To**			**Hypothesis type [primary, secondary] and label [a,b,c…]**
			Session One (Infant age 9m +/- 1m)	**Session Two (Infant age 12m +/- 1m)**	**Session Three (Infant age 18m +/- 1m)**	
Background and Socio-Demographic Information	Questions about the mother's demographic background (age, ethnicity, social class, income, partner status) and previous parenting experience	**5a-5b removed**	**X**			**3a**
Obstetric History	Questions about the mother's pregnancy and birth in relation to the infant involved in the current study	**n/a**	**X**			**3a**
Medical History	Questions about the mother's physical health	**n/a**	**X**			**3a**
Substance Use	Questions about the mother's use of alcohol, cigarettes, and drugs. Some items can be taken from/supplemented by medical records if consent is given	**n/a**	**X**			**3a**
Psychiatric History	Questions relating to the mother's psychiatric history. Some items can be taken from/supplemented by medical records if consent is given	**All Questions removed**	**X**			**2a, 2b, 3a**
Brief Psychiatric Rating Scale (BPRS)	This is a 24-item measure that assesses positive, negative and affective symptoms among people with a mental illness. The 24 items include somatic concern, anxiety, emotional withdrawal, depressive mood, hostility, blunted affect, excitement and disorientation. The BPRS is scored by summing the items, with scores ranging from 18-126; a higher score is indicative of more severe symptomology[39].	**All Questions removed**	**X**			**3a**

Hospital Anxiety and Depression Scale (HADS)	This is a 14-item measure that assesses anxiety and depression in a general population of both patients and the general population[40–42]. There are seven items relating to anxiety, and seven relating to depression. Items are rated on a four-point likert scale with 0 representing the least symptomatology and 3 representing the highest; there are six reverse scored items in total. The HADS is scored by summing the items relating to anxiety and depression separately, for both scales a score of seven or less indicates feelings are in the normal range.	**n/a**	**X**			**3a**
General Health Questionnaire (GHQ)-12	This is designed to screen for non-psychotic and minor psychiatric disorders, comprising two sections: (1) ability to carry out normal functions and (2) appearance of distress[43,44].	**n/a**	**X**			**3a**
The Postpartum Bonding Questionnaire (PBQ)	This is a 25 item self-administered measure designed to detect issues within mother-infant relationships[45]. Items are rated on a six-point scale with 0 representing the least cause for concern and 5 representing greater issues in the mother-infant bond. There are 15 reverse scored items. The 25 items encompass four sub-scales: (1) a general impairment scale (12 items, scores ranging from 0 to 60), (2) rejection and anger (7 items, scores ranging from 0 to 35), (3) anxiety concerning the infant (4 items, scores ranging from 0 to 20), and (4) developing risk of abuse (2 items, scores ranging from 0 to 10). Total scores are calculated by summing the 25 items (scores range from 0 to 125). Analysis of the scale includes both total and subscale scores[45].	**n/a**	**X**			**3a**
Childhood Trauma Questionnaire (CTQ)	This is designed to assess adults and adolescents for a history of childhood trauma using a 28-item retrospective self-report questionnaire[46]. This contains five subscales: (1) physical abuse, (2) sexual	**n/a**	**X**			**3a**

	abuse, (3) emotional abuse, (4) physical neglect, and (5) emotional neglect[46]. Each subscale has five questions; the additional three questions are designed to detect individuals who may under report their trauma. Items are rated on a five point scale with 1 = "never true" when they were growing up, to 5= "very often true" when they were growing up. Thus, scores range from 5 to 25 for each of the abuse types. The CTQ has demonstrated reliability and validity in both patient and community populations[47,48] .					
EQ-5D-5L	This measures health-related quality of life across five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression), each rated on five levels (no problems, slight problems, moderate problems, severe problems, and extreme problems)[49]. The participant indicates their health state by ticking the box next to the most appropriate statement, and rates their health today on a scale of 0 (the worst health you can imagine) to 100 (the best health you can imagine). The scores from each of the dimensions are combined to form a unique health state from a possible 3125 combinations[49].	**n/a**	**X**			**3a**
Composite Abuse Scale (CAS)	This is designed to measure partner abuse over the past year. The 30-item self-administered questionnaire is rated from 1= 'Never' to 5= 'Daily', with total scores ranging from 0-150. There are four dimensions within the scale; severe combined abuse, emotional abuse, physical abuse, and harassment[50]. The CAS has been validated for patient and community populations[50,51].	**n/a**	**X**			**3a**
Infant Medical Notes and Growth Trajectories	Using information from the 'little red book' to record data on infants APGAR scores and early weight measurements.	**n/a**	**X**			**3a**

Qualitative Questionnaire	Research team designed topic guide to be administered at the final (18m) session. This consists of open ended questions relating to the mothers' experience of the study as a whole and in particular their understanding and feelings towards the fNIRS process.	**n/a**			**X**	
Mother / Infant Measures						
Manchester Assessment of Caregiver-Child Interaction (MACI)	Mother-infant interactions are captured in a six-minute video clip taken during unstructured play [52]. Coding of the interaction is completed by a trained rater and assesses two caregiver scales (sensitive responsiveness and non-directedness), four infant scales (attentiveness to caregiver, positive affect, negative affect, and liveliness), and two dyadic scales (mutuality and intensity of engagement)[52]. This measure has been validated and utilised within both patient and community populations[53,54].	**n/a**	**X**			**3a**
Bayley Scales of Infant and Toddler Development	Researcher-administered scales that examine motor (fine and gross), language (receptive and expressive) and cognitive development of infants and toddlers alongside their social-emotional and adaptive behaviour[55]. These scales have been used to assess general development and as a test for neurodevelopmental delay across both western and non-western cohorts[56,57]. The scales are flexible enough to use the subtests independently based on research question[55]. The full Bayley assessment will be completed at the nine month time point, following time points will only use the cognitive and language subscales.	**n/a**		**X**	**X**	**1a**
fNIRS Assessment	Design – based on published pilot [28] – created to capture changes in infant neural responses to vocal and non-vocal sounds across 9, 12, and 18 months. Infants listen to vocal and non-vocal sounds with different	**n/a**	**X**	**X**	**X**	**1a, 2a, 2b**

	emotional valences whilst sat on mum's lap for a maximum of 15 minutes. The fNIRS equipment uses near infrared light to capture changes in blood oxygenation in response to the stimuli which is analogous to brain function. This will be used to assess whether fNIRS can detect early biomarkers of language delay in high risk children.					

Table 1. Description of study measures by cohort

fNIRS vocal processing

In order to assess whether fNIRS is able to detect early biomarkers of atypical language development in children with maternal mental illness, we have developed a study design based on research in healthy mothers and their infants completed at The University of Manchester (Novel biomarkers in infants: developing optical imaging solutions for the measurement of early vocal brain development). Infants wear a custom-made head cap (array) covering bilateral anterior and posterior temporal and temporoparietal junction (TPJ) regions and 24 measurement points relevant for recognition of dynamic vocal and emotional expressions (happy, angry, neutral) and their interaction across these regions. Two back-to-back up to 9 minute sessions include repeated blocks with the infant watching cartoons on the mother's lap while listening to auditory stimuli. The first session comprises neutral vocal interjections: 'a' and neutral non-vocal environmental sounds such as fire crackling and running water. Pitch contours were matched to ensure a consistent neutral valence and intensity manipulated to 70dB (average for radio or TV sounds) using Praat software [58]. The second session comprises a single female speaker saying the sentence 'dogs are sitting by the door' in a neutral, happy, and angry prosody. As with the first session, intensity was manipulated to 70dB. The pitch contour of the neutral speech was matched to that in the first session, again to ensure that all neutral valence stimuli were equal in pitch. Each sound track, and, therefore, block was set to 8 seconds using Audacity software [59]. As differences in pitch are inherent to differing emotional prosodies, the happy and angry speech stimuli were not matched for this. Neutral vocal stimuli were taken directly from the above mentioned study from The University of Manchester. Neutral non-vocal stimuli were taken from the Voice Localiser Database [60], animal sounds were removed from these stimuli as there is debate around their definition as 'vocalisation' [61] as they may elicit brain responses in language areas. The speech stimuli were taken from the RAVDESS database [62]. During this task the infants will be videoed to provide real-time visualisation of motion artefacts during data analysis. The fNIRS testing sessions last approximately 30 minutes, which includes introducing parents to the set-up and placing the head cap/array onto the infant.

Power Calculations

Based on prior research conducted on awake infants, we expect a 20-28% attrition rate from motion artefacts [26,28]. Prior studies using fNIRS have established a difference using roughly 20 infants in each comparator group [26]; therefore, we expect to need an overall sample of 60 in order to achieve sufficient power (approx. 25 with healthy mothers; 25 with mentally ill mothers).

In addition, the paradigm creation has taken note of limitations in previous studies such as lengthy paradigms; it will also employ a mixture of motion artefact detection and correction algorithms such as principal component analysis (PCA) to help minimise effects of the motion artefacts that may occur and to reduce attrition as much as possible.

fNIRS data analysis

fNIRS signals are contaminated by physiological confounds such as respiratory and cardiovascular oscillations, and movement artefacts generated by participants. In infants these artefacts are more common, take up a larger proportion of recorded data, and thus make data cleaning and analysis harder. The study team will assess the video recordings of the fNIRS sessions to identify and remove artefacts created by movement such as spikes and baseline shifts as a result of the cap being relocated. In order to remove the majority of these artefacts we will apply a PCA algorithm. PCA uses the variance in data to find independent signals; these signals can then be divided into separate components which account for varying proportions of the overall signal variance. We will use PCA during preprocessing in order to remove the component that explains the majority of the variance. The data will be translated in to optical density using the modified beer lambert law, and then finally the GLM will be applied using the AR-IRLS method. This method is particularly suited to infant data, and helps to resolve issues with artefacts and serial correlations in the data due to physiology through auto-regressive pre-whitening and iteratively weighted least squares[63]. Using MATLAB© (The Mathworks Inc., Natick, Massachusetts, USA) and the NIRs Toolbox [64] stimulus-evoked micromolar changes in HbO and HHb can then be calculated compared to baseline, testing individual and group responses for significant differences. Therefore, notwithstanding potential data loss through these mechanisms, we are confident that our planned recruitment is sufficient to detect significant differences in neural responses to vocal and speech sounds.

The primary hypothesis is that there will be a statistically significant difference in neural responses to vocal sounds between infants of healthy mothers compared to those whose mothers have SMI. General linear models appropriate to the distribution of micromolar changes in HbO and HHb will be used to assess differences between groups. age, childhood trauma, substance abuse and social adversity (e.g. income, employment).

In addition, we hypothesise that there will be a statistically significant difference in neural responses to vocal sounds between infants at low and high risk of long term cognitive impairment based on the epidemiological research from Work Package 1 and 2 of the CAPRI programme.

To address potential modification of the effects of serious mental illness by level of adversity and we will combine potential sources of adversity into a single score to reduce the chance of overfitting the data. Adversities include maternal substance and alcohol abuse, childhood trauma and indicators of social and economic deprivation collected at baseline. An interaction term (parental mental illness*adversity) will be entered into the model to test its association with neural response.

Ethical Considerations

The 16 participating NHS trusts have granted Research and Development (R&D) approval for the CAPRI-Voc study. To ensure all researchers are able to complete research with participants to a high standard, training is provided in all relevant measures e.g. fNIRS (data collection and analysis), Bayley Scales of Infant and Toddler Development (administration and scoring), Good Clinical Practice, and Information Governance training in line with the General Data Protection Regulation (GDPR).

Some of the participants will be categorised as vulnerable; as such, researchers will complete level three safeguarding courses for both adults and children. Alongside this training, there are detailed SOPs which outline how to ensure our participants' welfare is maintained. These SOPs also cover the process to follow if and when any safeguarding concerns arise (i.e. researchers will contact the CI, KA, to discuss these concerns and to decide upon a plan of action).

As we expect to collect the majority of data at participants' homes, a lone working SOP was developed to ensure the safety of the research team, whereby researchers provide details of the session location, date and time to a colleague within CAPRI. If no contact has been made within these time-frames, the colleague will contact the lone worker and escalate if necessary.

Dissemination

This study will provide further knowledge about where fNIRS can be used reliably, and potentially in a routine clinical setting, as a new and inexpensive early screening tool for infants at risk of atypical language development, linked to cognitive impairment. By using the behavioural measure of the Bayley Scales of Infant and Toddler development at concurrent time points, alongside fNIRS, we aim to be able to see if, and how, fNIRS may locate biomarkers of atypical developmental before behavioural measures are reliably able to do so. With this insight, infants at risk of atypical development could be identified early and preventative measures put in place for those that would benefit most. We aim to produce regular newsletters for participants throughout the project, as well as presentations at national and international conferences. The main study findings will be reported in peer-reviewed journals; and we shall ensure that relevant resources (e.g. Public Health England Perinatal and Infant Mental Health eBulletin) are updated with these findings.

Study Status

Recruitment and data collection are ongoing from September 2017 until April 2021.

Author Contributions

KA and DD created, designed, and applied for funding for the study. DD drafted the original protocol. KA, DD, HH, RE and CZ developed the original fNIRS study paradigm, LS and CH aided in the revision of this paradigm. KA has given final approval for the protocol manuscript to be published and is accountable for all aspects of the work. LS led the write up of the protocol manuscript, with the help of AK, JC, CH, HH and AE under the supervision of KA. KA is the Chief Investigator, AE and HH Research Associates, and LS, AK and JC are Research Assistants on the project. All authors read and approved the final manuscript.

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Conflicts of Interest

The authors declare no conflicts of interest

Data Statement

Not applicable

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FIGURE LEGENDS

Figure 1. CONSORT flow of SMI participants

Figure 2. CONSORT flow of healthy participants

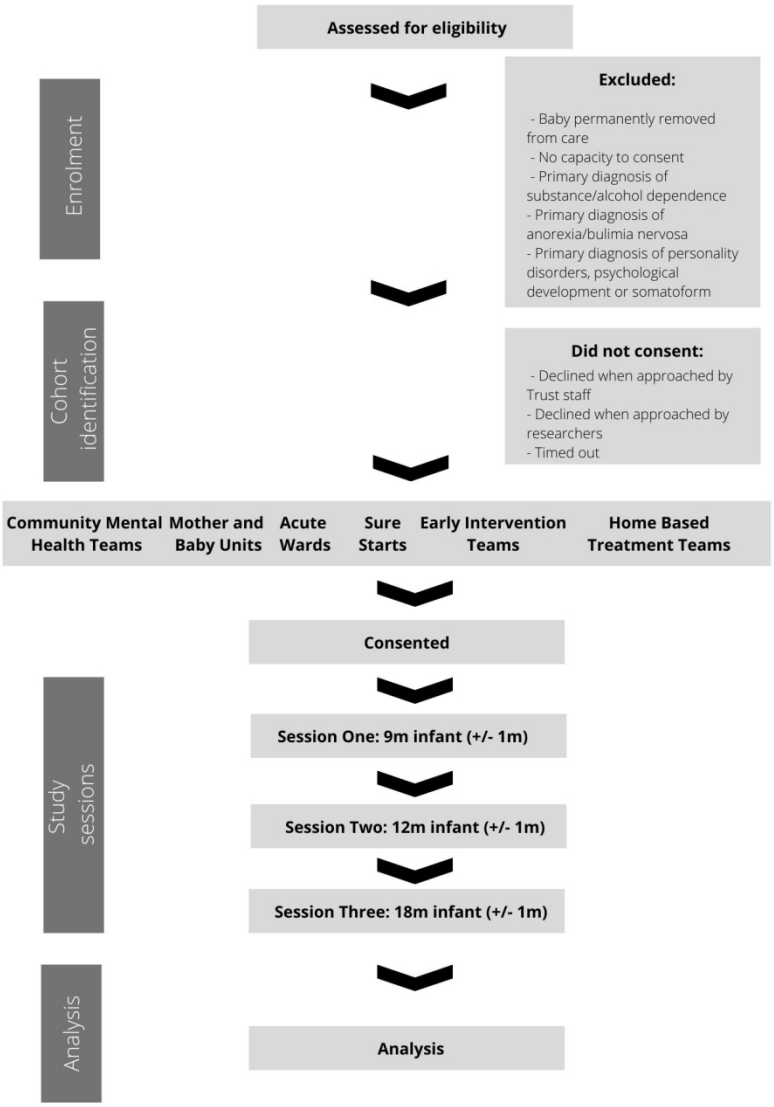

Figure 1. CONSORT flow of SMI participants

210x297mm (171 x 171 DPI)

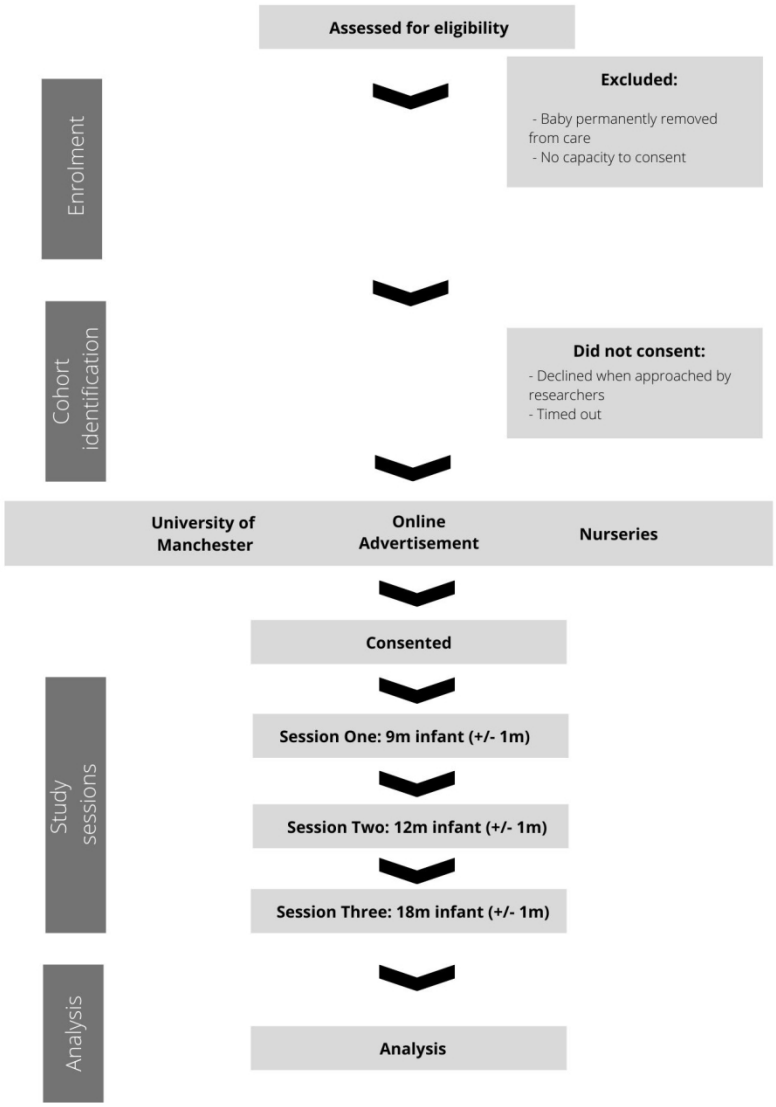

Figure 2. CONSORT flow of healthy participants

210x297mm (171 x 171 DPI)

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Vocal Brain Development in Infants of Mothers with Serious Mental Illness (CAPRI-Voc) - study protocol

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Vocal Brain Development in Infants of Mothers with Serious Mental Illness (CAPRI-Voc) - study protocol

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ABSTRACT

Introduction

Improving the lives of children and adolescents with parental mental illness (CAPRI) remains an urgent political and public health concern for the United Kingdom (UK) and European Union (EU). Recurrent parental mental illness is believed to lead to fractures in the family, academic and social lives of these children yet interventions are poorly targeted and non-specific. Part of an interdisciplinary programme of work (the CAPRI Programme. Grant number: 682741), CAPRI-Voc aims to achieve two goals: First, to test the feasibility of our longitudinal imaging paradigm in mother-infant pairs where the mother has a diagnosis of severe mental illness. Second, to compare development of vocal processing in these infants with infants in the general population.

Methods and Analysis

Recruitment of 100 infants of mothers with mental illness, alongside 50 infants of healthy mothers. Both cohorts of infants will undergo functional near infrared spectroscopy (fNIRS) brain imaging at three time points: 9, 12 and 18 months to explore differences between cohorts in their neural responses to vocal stimuli in our language paradigm. Mothers will complete an interview and psychological questionnaires. We shall also complete an infant developmental battery and mother-child interaction play session. Data on recruitment, retention and dropout will be recorded.

Ethics and Dissemination

It will be made clear that fNIRS is a safe, non-invasive technology widely used in infant clinical and psychological research. We shall reassure mothers that no definitive causal link exists between maternal mental illness and language development in infants, and that individual data will only exist as part of the wider dataset. As the study includes both children and vulnerable adults, all research staff will complete NHS Safeguarding level 3 training. Dissemination will be via direct feedback to stakeholders, patient and advisory groups, and through presentations at conferences, journal publications and University/NHS trust communications. Study approved through North West-Greater Manchester West REC (17/NW/0074) and Health Research Authority (212715).

Strengths and Limitations of this study

- CAPRI-Voc will provide the first national study to investigate early language networks measured by functional near infrared spectroscopy (fNIRS) in infants of mothers with serious mental illness (SMI). Our longitudinal methodology allows us to follow changes in neural

responses over time in the same infant, providing stronger evidence of typical or atypical developmental trajectories.

- The group we wish to recruit raises challenges, including recruitment and attrition
- This fNIRS imaging protocol is untested within the ecologically valid setting of the home which may affect data analysis and thus inference to the wider population

Key Words: CAPRI, infant, parental mental illness, resilience, risk, language development, fNIRS

INTRODUCTION

The number of children living with parental mental illness (CAPRI) are increasing[1]. Numerous studies illustrate the risk of CAPRI developing their own mental illness[2–7]. However, risk of mental illness is likely to be relatively rare compared to other more common outcomes including behavioural, educational, social and other difficulties [5,8–15]. Some evidence suggests that paternal and maternal depression is associated with atypical cognitive development in CAPRI, with significantly delayed expressive language and lower IQ [10,11,16], particularly in exposed boys [15].

In spite of this, most CAPRI will remain resilient. Social support and education about mental illness may improve resilience [17–21], but little reliable information exists to help parents and clinicians understand better which children in the risk-set are likely to be at greatest risk and which may be resilient; this lack of understanding creates a challenge for services with limited resources. This is important not only for economic reasons, but also because those at greatest risk are also those likely to be most sensitive to intervention[22]. Identifying a biomarker in infants for greatest risk of later cognitive deficits might allow early intervention or even prevention and improve the quality of life for a growing number of vulnerable children.

fNIRS and CAPRI-Voc

fNIRS is a relatively new functional imaging technique, particularly suited for use in infants, due to its ease of use, portability, tolerance of movement and non-invasive nature. It is based on the principle that many biological tissues are relatively transparent to light in the near infrared ranges between 700-1150nm. Chromophores, molecules that absorb light, such as oxygenated (HbO) and deoxygenated haemoglobin (HHb) absorb specific wavelengths in this range offering an 'optical window' for non-invasive assessment of these compounds in the brain. Using multiple light emitting sources and detectors allows for topographic maps of changes in HbO and HHb to be generated across the illuminated region. Analogous to functional magnetic resonance imaging (fMRI), using blood oxygen level dependent (BOLD) changes, fNIRS provides an index of functional brain activity via

downstream cortical blood flow and neuronal activity. Evidence supports reasonable concordance between fMRI and fNIRS measures, although they are best viewed as complementary methodologies[23]. fNIRS lacks the spatial resolution of fMRI, in that it is limited to measuring superficial cortical areas close to the scalp. It is, however, a low cost, portable, safe, quick and extremely well tolerated 'bedside' technology that allows neuroimaging to be carried out when fMRI scanning is difficult or contraindicated. fNIRS provides greater temporal resolution than fMRI (data acquisition typically in the order of 10Hz) allowing for detailed analysis of the haemodynamic response function of both HbO and HHb associated with neural activity, e.g. latency effects.

This study will utilise a bespoke fNIRS imaging paradigm and array design, previously piloted in young infants of 40 healthy mothers to assess early language development[24,25]. fNIRS is particularly suited to infants as it does not require the infrastructure, cost or tolerance of MRI or the addition of conductive gels (e.g. EEG) in order to acquire data. The fNIRS system (mini-NTS, Gower labs, UCL, UK) is a bedside, portable imaging system that can be operated in participants' homes or at a familiar clinical setting such as a GP surgery or health centre, allowing the research team greater scope to recruit new mothers and infants and perform those assessments in familiar environments. The fNIRS system provides a 48-channel array for topographical coverage of bilateral superior temporal cortices.

Several brain imaging studies agree that healthy infants can discriminate speech/vocalisations from other sounds by around 6 months old, through differential responses viewed within the frontal, temporal and parietal cortices[26–28]. By recruiting infants aged between 9-18months (+/- 1 month), we aim to capture vocal developmental changes, not only between healthy and at-risk infants, but also in within-subject longitudinal data. Voice recognition is a precursor of early language acquisition[29] which, in turn, is a key predictor of a range of subsequent life outcomes. Previous 'high risk' studies[30,31] in older children have reported abnormalities in speech and language using observer-rated measures. Similar behavioural assessments cannot distinguish infants at low and high-risk of autism, whereas fNIRS studies were able to reliably identify differences in brain function of very young infants [32,33]. Work packages 1 & 2 explore epidemiological data that will allow work package 3 (CAPRI-Voc) to stratify infants into higher and lower risk sets for atypical neurocognitive outcomes. We shall validate this grouping by examining differences in infant brain language processing with fNIRS. Specifically, we shall examine voice recognition and responses to emotional speech between the two risk groups and healthy controls between 9-18 months.

Study Aims and Hypotheses:

1. To test the feasibility of our recently piloted longitudinal fNIRS paradigm in infants with severe maternal mental illness in order to detect changes in language development.
   We hypothesise:
   a) That neural responses to the vocal paradigm will correlate with existing measures of infant neurocognitive development (i.e. Bayley III)
2. To discover infant biomarkers of atypical language development in CAPRI using fNIRS.
   We hypothesise:
   a) Children of mothers with SMI would experience delays in vocal and affect recognition at 9 months compared to children of healthy mothers.
   b) Children of mothers with SMI would experience atypical neural connectivity compared to children of healthy mothers
3. To stratify infants within a risk subset into highest and lowest risk using epidemiologically-derived resilience and risk predictors for child neurocognitive outcomes (ADHD, ASD, intellectual disability & cognitive ability). To compare between these assigned groups emergence of voice recognition over three time points (9 months, 12 months & 18 months), using fNIRS.
   We hypothesise:
   a) That there is an interaction with adversity and parental mental illness such that children exposed to parental mental illness and adversity experience the largest developmental delays.

4. To discover objective early indicators of atypical brain development of voice recognition for use in routine clinical settings in order to target CAPRI at greatest risk for early specialist intervention

METHODS AND ANALYSIS

Design

This study is a novel longitudinal infant brain imaging study to assess whether fNIRS can locate a neuro-biomarker of early language development in children at high and low risk of cognitive impairment. The study is taking place across the UK, and based in Greater Manchester. The research is funded by the European Research Council (ERC, 682741), and approved by North West – Greater Manchester West Research Ethics Committee (17/NW/0074). The current protocol version is 2.0 (05/07/21).

Sample Size

Over five years (September 2017-October 2022), we aim to recruit and test 100 infants of mothers with mental illness; alongside 50 infants of healthy mothers acting as controls. Both cohorts of infants will be aged between 9-18 months old (+/-1 month).

Patient and Public Involvement

At the final session, all mothers are asked to think about the effectiveness of the study's recruitment strategies, the burden of time and emotional strain on those that take part, dissemination, and any other suggestions.

Participants and Recruitment Procedures

Mothers with SMI will be recruited from national primary and secondary care settings, outpatient services and mother and baby units (MBUs). In addition, we will advertise the study on CAPRI-Voc social media channels and targeted online advertising so that women may self-refer. Mental health NHS trusts will be brought on board as research sites to ensure full engagement with study recruitment. The research team will advertise the research at meetings of ward managers, clinicians, nurses, care coordinators and specialist midwives. Leaflets, posters and eligibility checklists will be distributed in these meetings for further circulation among staff. NHS Staff will provide eligible women with a brief overview of the study along with participant information sheets. Women will inform their NHS contact if they are interested in participating and provide their consent for the research team to contact them. There will be appointed study champions within each trust whose role it is to promote the study and contact the research team to pass across all relevant information pertaining to potential recruits; primary psychiatric diagnosis, infant date of birth, risk information and contact details. The research team will contact the potential recruit (usually via telephone) to confirm continued interest in the research, address any queries arising from the information sheet and to arrange a visit for the first session. Consent for participation will be agreed at least 24 hours after the information sheet has been read.

Healthy mothers will be recruited through leaflets and posters placed in and around The University of Manchester buildings, Manchester Foundation Trust NHS buildings and Sure Start Centres, alongside digital advertising via the CAPRI-Voc social media pages. Women can contact the research team if they are interested in the study via the contact details placed on the advertising materials. Potential participants will be provided with participant information sheets and allowed a minimum of 24 hours to consider their decision and ask any questions of the research team. A visit would then be arranged to gain informed consent to participate in the study and begin session one.

Inclusion/Exclusion Criteria

SMI is defined as a severe psychiatric disorder that requires intervention, hospitalisation or ongoing treatment. Mothers with a primary diagnosis of schizophrenia, schizoaffective disorder, bipolar disorder, severe recurrent unipolar depression, psychotic depression, severe anxiety, obsessive compulsive disorder (OCD) and post-traumatic stress disorder (PTSD) are sought. Mothers with a current diagnosis of a severe psychiatric disorder with a minimum requirement of scheduled follow up with secondary care services will be eligible for study inclusion. Primary substance misuse disorders and primary eating disorders are excluded as any related gestational effects on the development of the infant cannot be ruled out.

All mothers will be aged 16 or over, fluent in the English language and able to give written, informed consent. Care coordinators will assess capacity to consent of their clients with SMI, and capacity considered throughout by the experienced research team in collaboration with the Chief Investigator (CI).

Figures 1 and 2 illustrate the flow of both SMI and healthy participants through the study, based on the ESMI[34] protocol (Grant Reference: RP-DG-1108-10012) and the CONSORT diagram[35]

FIGURE 1 placement

FIGURE 2 placement

Sessions

Measures

Our bespoke 50 page interview workbook contains researcher administered questionnaires and self-complete questionnaires for the mother to undertake. The remaining measures across all study time points, along with the interview workbook are briefly described in Table 1 below. Healthy mothers will complete a modified version of all measures because of non-applicability of certain clinical questions/measures (see Table 1). Up to two weeks prior to the baseline session, the self-report questionnaires are sent via royal mail to the mothers to complete in their own time in order to reduce the time burden on the baseline session.

Table 1 outlines data collected at each timepoint. Infants are aged 9m (+/- 1m) at session one (baseline), aged 12m (+/- 1m) at session two, and aged 18m (+/- 1m) at session three. SMI mothers will have data on prescription medications and substance use collected via medical records, if consent

has been granted. The reason for utilising medical records where possible is to decrease any potential burden of recall on the SMI mothers so as to increase the likelihood of continued participation.

The baseline face-to-face session takes up to two hours and includes assessments for both mothers and their infants. The follow-up sessions take up to 1 hour and 30 minutes. Visits will either take place at the women's homes, a local NHS facility, or at The University of Manchester, whichever is most convenient for the participant. fNIRS equipment can be transported within a safely padded travel case via researcher car to any location other than the University of Manchester. At the time of writing 100% of participants completed their sessions within their own home, further illustrating the benefit of fNIRS as a portable imaging tool. Based on preference, the women can complete the face-to-face sessions in one or two parts. Women with older children who require childcare to take part may be reimbursed for the costs of childcare. Women are offered £50 worth of shopping vouchers as reimbursement for their time and inconvenience at their final session (18 month).

In addition to the fNIRS main outcome measure, the current study will use both the MACI assessment of mother and child interaction and the Bayley scales of infant and toddler development, both explained in greater detail in Table 1. There is a wealth of research reporting maternal behaviour and attachment affecting child social and cognitive development [36,37]. In addition, mothers with mental illness may provide less socio-communicative input to their infants affecting language development [38]. Previous work links mother-infant interactions to vocal fNIRS at 6m [25], as the current study follows infants over time we will only use the MACI at the baseline session due to changing trajectories of mother infant interactions over more than a few months. Overall, we aim to assess if and how mother-infant interactions, in this at risk group, affect neural responses to language.

The current study aims to assess whether fNIRS is sensitive to neural atypicalities in an at risk group. In order to validate this we will use the Bayley III as a concurrent behavioural assessment of cognitive and language development. Currently, behavioural assessments pick up delays too late , or not at all, and may be affected by subjective bias of the rater [39]. We will administer the Bayley III at our later (12m & 18m) timepoints due to its greater sensitivity to delay in older infants. We aim to see whether the fNIRS assessments can locate atypical development in line with or prior to these behavioural tools.

COVID-19

The Coronavirus pandemic effectively halted all study activities from March 2020 to March 2021. Viral infections (such as coronaviruses) during pregnancy affect infant development. Therefore, any further CAPRI-Voc recruitment requires Covid-19 data on exposure and/or infection be collected to understand this new potential risk factor. A substantial amendment was submitted (02/08/21) and

approved by the HRA (17/09/21) and the sponsor to reopen the study to recruitment of healthy (control) participants only, and to reflect the extended study end date of October 2022 following a no-cost extension from the ERC.

Covid-19 reopen protocol changes:

- Reopening of recruitment to healthy control participants only.
- The utilisation of a study website containing all regulatory study documentation and links to Sponsor approved online data collection platform Qualtrics for the administration of informed consent, interview workbook and self-report questionnaires.
- Face-to-face study sessions resume as per standard protocol. Additionally, all national and local guidelines will be followed with regards to public safety, including the use of PPE for both researcher and participant.

Mother Only Measures						
Type of measure/ Name of Instrument	**Instrument Details**	**Healthy Mother Modification**	**Data Relating To**			**Hypothesis type [primary, secondary] and label [a,b,c…]**
			Session One (Infant age 9m +/- 1m)	**Session Two (Infant age 12m +/- 1m)**	**Session Three (Infant age 18m +/- 1m)**	
Background and Socio-Demographic Information	Questions about the mother's demographic background (age, ethnicity, social class, income, partner status) and previous parenting experience	**5a-5b removed**	**X**			**3a**
Obstetric History	Questions about the mother's pregnancy and birth in relation to the infant involved in the current study	**n/a**	**X**			**3a**
Medical History	Questions about the mother's physical health	**n/a**	**X**			**3a**
Substance Use	Questions about the mother's use of alcohol, cigarettes, and drugs. Some items can be taken from/supplemented by medical records if consent is given	**n/a**	**X**			**3a**
Psychiatric History	Questions relating to the mother's psychiatric history. Some items can be taken from/supplemented by medical records if consent is given	**All Questions removed**	**X**			**2a, 2b, 3a**
Brief Psychiatric Rating Scale (BPRS)	This is a 24-item measure that assesses positive, negative and affective symptoms among people with a mental illness. The 24 items include somatic concern, anxiety, emotional withdrawal, depressive mood, hostility, blunted affect, excitement and disorientation. The BPRS is scored by summing the items, with scores ranging from 18-126; a higher score is indicative of more severe symptomology[40].	**All Questions removed**	**X**			**3a**

Hospital Anxiety and Depression Scale (HADS)	This is a 14-item measure that assesses anxiety and depression in a general population of both patients and the general population[41–43]. There are seven items relating to anxiety, and seven relating to depression. Items are rated on a four-point likert scale with 0 representing the least symptomatology and 3 representing the highest; there are six reverse scored items in total. The HADS is scored by summing the items relating to anxiety and depression separately, for both scales a score of seven or less indicates feelings are in the normal range.	**n/a**	**X**			**3a**
General Health Questionnaire (GHQ)-12	This is designed to screen for non-psychotic and minor psychiatric disorders, comprising two sections: (1) ability to carry out normal functions and (2) appearance of distress[44,45].	**n/a**	**X**			**3a**
The Postpartum Bonding Questionnaire (PBQ)	This is a 25 item self-administered measure designed to detect issues within mother-infant relationships[46]. Items are rated on a six-point scale with 0 representing the least cause for concern and 5 representing greater issues in the mother-infant bond. There are 15 reverse scored items. The 25 items encompass four sub-scales: (1) a general impairment scale (12 items, scores ranging from 0 to 60), (2) rejection and anger (7 items, scores ranging from 0 to 35), (3) anxiety concerning the infant (4 items, scores ranging from 0 to 20), and (4) developing risk of abuse (2 items, scores ranging from 0 to 10). Total scores are calculated by summing the 25 items (scores range from 0 to 125). Analysis of the scale includes both total and subscale scores[46].	**n/a**	**X**			**3a**
Childhood Trauma Questionnaire (CTQ)	This is designed to assess adults and adolescents for a history of childhood trauma using a 28-item retrospective self-report questionnaire[47]. This contains five subscales: (1) physical abuse, (2) sexual	**n/a**	**X**			**3a**

	abuse, (3) emotional abuse, (4) physical neglect, and (5) emotional neglect[47]. Each subscale has five questions; the additional three questions are designed to detect individuals who may under report their trauma. Items are rated on a five point scale with 1 = "never true" when they were growing up, to 5= "very often true" when they were growing up. Thus, scores range from 5 to 25 for each of the abuse types. The CTQ has demonstrated reliability and validity in both patient and community populations[48,49] .					
EQ-5D-5L	This measures health-related quality of life across five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression), each rated on five levels (no problems, slight problems, moderate problems, severe problems, and extreme problems)[50]. The participant indicates their health state by ticking the box next to the most appropriate statement, and rates their health today on a scale of 0 (the worst health you can imagine) to 100 (the best health you can imagine). The scores from each of the dimensions are combined to form a unique health state from a possible 3125 combinations[50].	**n/a**	**X**			**3a**
Composite Abuse Scale (CAS)	This is designed to measure partner abuse over the past year. The 30-item self-administered questionnaire is rated from 1= 'Never' to 5= 'Daily', with total scores ranging from 0-150. There are four dimensions within the scale; severe combined abuse, emotional abuse, physical abuse, and harassment[51]. The CAS has been validated for patient and community populations[51,52].	**n/a**	**X**			**3a**
Infant Medical Notes and Growth Trajectories	Using information from the NHS provided Personal Child Health Record (aka 'the little red book') to record data on infants APGAR scores and early weight measurements.	**n/a**	**X**			**3a**

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Qualitative Questionnaire	Research team designed topic guide to be administered at the final (18m) session. This consists of open ended questions relating to the mothers' experience of the study as a whole and in particular their understanding and feelings towards the fNIRS process.	**n/a**			**X**	
Mother / Infant Measures						
Manchester Assessment of Caregiver-Child Interaction (MACI)	Mother-infant interactions are captured in a six-minute video clip taken during unstructured play [53]. Coding of the interaction is completed by a trained rater and assesses two caregiver scales (sensitive responsiveness and non-directedness), four infant scales (attentiveness to caregiver, positive affect, negative affect, and liveliness), and two dyadic scales (mutuality and intensity of engagement)[53]. This measure has been validated and utilised within both patient and community populations[54,55].	**n/a**	**X**			**3a**
Bayley Scales of Infant and Toddler Development	Researcher-administered scales that examine motor (fine and gross), language (receptive and expressive) and cognitive development of infants and toddlers alongside their social-emotional and adaptive behaviour[56]. These scales have been used to assess general development and as a test for neurodevelopmental delay across both western and non-western cohorts[57,58]. The scales are flexible enough to use the subtests independently based on research question[56].	**n/a**		**X**	**X**	**1a**
fNIRS Assessment	Design – based on published pilot [25] – created to capture changes in infant neural responses to vocal and non-vocal sounds across 9, 12, and 18 months. Infants listen to vocal and non-vocal sounds with different emotional valences whilst sat on mum's lap for a maximum of 15 minutes. The fNIRS equipment uses near infrared light to capture changes in blood oxygenation in	**n/a**	**X**	**X**	**X**	**1a, 2a, 2b**

	response to the stimuli which is analogous to brain function. This will be used to assess whether fNIRS can detect early biomarkers of language delay in high risk children.					

Table 1. Description of study measures by cohort

fNIRS vocal processing

In order to assess whether fNIRS is able to detect early biomarkers of atypical language development in children with maternal mental illness, we have developed a study design based on previous research[24,25]. Infants wear a custom-made head cap (array) covering bilateral anterior and posterior temporal and temporoparietal junction (TPJ) regions and 24 measurement points relevant for recognition of dynamic vocal and emotional expressions (happy, angry, neutral) and their interaction across these regions. Two back-to-back up to 9 minute sessions include repeated blocks with the infant watching cartoons on the mother's lap while listening to auditory stimuli. The first session comprises neutral vocal interjections, i.e. 'ah' sounds and neutral non-vocal environmental sounds such as fire crackling and running water. Pitch contours were matched to ensure a consistent neutral valence and intensity manipulated to 70dB (average for radio or TV sounds) using Praat software [59]. The second session comprises a single female speaker saying the sentence 'dogs are sitting by the door' in a neutral, happy, and angry prosody. As with the first session, intensity was manipulated to 70dB. The pitch contour of the neutral speech was matched to that in the first session, again to ensure that all neutral valence stimuli were equal in pitch. Each sound track, and, therefore, block was set to 8 seconds using Audacity software [60]. As differences in pitch are inherent to differing emotional prosodies, the happy and angry speech stimuli were not matched for this. Neutral vocal stimuli were taken directly from the above mentioned study from The University of Manchester. Neutral non-vocal stimuli were taken from the Voice Localiser Database [61], animal sounds were removed from these stimuli as there is debate around their definition as 'vocalisation' [62] as they may elicit brain responses in language areas. The speech stimuli were taken from the RAVDESS database [63]. During this task the infants will be videoed to provide real-time visualisation of motion artefacts during data analysis. The fNIRS testing sessions last approximately 30 minutes, which includes introducing parents to the set-up and placing the head cap/array onto the infant.

Power Calculations

Based on prior research conducted on awake infants, we expect a 20-28% attrition rate from motion artefacts [23,25]. Prior studies using fNIRS have established a difference using roughly 20 infants in each comparator group [23]; therefore, we expect to need an overall sample of 60 in order to achieve sufficient power (approx. 25 with healthy mothers; 25 with mentally ill mothers).

In addition, the paradigm creation has taken note of limitations in previous studies such as lengthy paradigms

fNIRS data pre-processing

fNIRS signals are contaminated by physiological noise arising from components that include respiration and cardiac pulsation, as well as motion artfacts generated by participants. In infants these artfacts are more common, take up a larger proportion of recorded data, and thus make data cleaning and analysis more challenging [64]. Pre-processing will follow the most up-to-date recommendations from literature [65,66], and will be performed with custom scripts in MATLAB© (The Mathworks Inc., Natick, Massachusetts, USA) based on functions from Homer2 [67] and the Brain AnalyzIR Toolbox [68]. After pruning low quality channels, raw data will be converted into optical densities; then, motion artefacts (spikes, baseline shifts) will be detected with *ad*-hoc thresholds on signal changes and standard deviation, and corrected using the Wavelet-based filtering alone [69] or in combination with other methods, as suggested in [65]. After removing trials showing residual artefacts, data will be band-pass filtered, in order to remove physiological noise at high and very low frequencies, and converted to haemoglobin concentration changes using the modified Beer Lambert law. Subject-level statistical analysis will involve modelling the data with a General Linear Model, using the different stimuli as regressors; in particular, it will be fitted using the *auto-regressive pre-whitening iteratively reweighted least squares* (AR-IRLS) method [70], which has been shown to be helpful in mitigating the impact of serial correlations and residual artifacts in the data [71]. Stimulus-evoked changes in HbO and HHb can then be compared to baseline, testing individual and group responses for significant differences. Therefore, notwithstanding potential data loss through these mechanisms, we are confident that our planned recruitment is sufficient to detect significant differences in neural responses to vocal and speech sounds.

Statistical analysis

The primary hypothesis is that there will be an overall difference in neural responses to vocal sounds between infants of healthy mothers compared to those whose mothers have SMI. This shall be tested using linear mixed effects models that include random effects to account for longitudinal measurements belonging to the same child. Models will be fitted to the coefficients of the regressors obtained with the subject-level GLM, and/or the metrics derived from the individual block averages (e.g. the average activation after stimulus onset). These models will include variables for both whether the mother has an SMI and the type of vocal sounds. Our secondary hypothesis is that the response to the type of vocal sound will be different according to maternal SMI. This shall be tested using an interaction between the variables for maternal SMI and type of vocal sound.

In addition, we hypothesise that there will be a difference in neural responses to vocal sounds between infants with maternal SMI at low and high risk based on their long term cognitive impairment risk, as predicted from Work Package 1 and 2 of the CAPRI programme.

We shall also examine the extent that the impact of SMI is independent of adversity by including the following variables in the model: maternal substance and alcohol abuse, childhood trauma and indicators of social and economic deprivation collected at baseline. P-values will be calculated using likelihood ratio tests and significant will be set using the p-value threshold of $p<0.05$, estimated using a likelihood ratio test.

Ethical Considerations

The 16 participating NHS trusts granted Research and Development (R&D) approval for the CAPRI-Voc study. To ensure all researchers are able to complete research with participants to a high standard, training is provided in all relevant measures e.g. fNIRS (data collection and analysis), Bayley Scales of Infant and Toddler Development (administration and scoring), Good Clinical Practice, and Information Governance training in line with the General Data Protection Regulation (GDPR).

Some of the participants will be categorised as vulnerable; as such, researchers will complete level three safeguarding courses for both adults and children. Alongside this training, there are detailed standard operating procedures (SOPs) which outline how to ensure our participants' welfare is maintained. These SOPs also cover the process to follow if and when any safeguarding concerns arise (i.e. researchers will contact the CI, KA, to discuss these concerns and to decide upon a plan of action).

As we expect to collect the majority of data at participants' homes, a lone working SOP was developed to ensure the safety of the research team, whereby researchers provide details of the session location, date and time to a colleague within CAPRI. If no contact has been made within these time-frames, the colleague will contact the lone worker and escalate if necessary, first to the CI, who will deem if and when appropriate to notify local authorities.

Dissemination

This study will provide further knowledge about where fNIRS can be used reliably, and potentially in a routine clinical setting, as a new and inexpensive early screening tool for infants at risk of atypical language development, linked to cognitive impairment. Allowing for preventative measures for those that would benefit most. We aim to produce regular newsletters for participants throughout the project, as well as presentations at national and international conferences. The main study findings will be reported in peer-reviewed journals; and we shall ensure that relevant resources (e.g. Public Health England Perinatal and Infant Mental Health eBulletin) are updated with these findings.

Study Status

Recruitment and data collection are ongoing from September 2017 until July 2022.

Author Contributions

KA and DD created, designed, and applied for funding for the study. DD drafted the original protocol. KA, DD, HH, RE and CZ developed the original fNIRS study paradigm, LS and CH aided in the revision of this paradigm. JG and MP developed the statistical analysis plan. KA has given final approval for the protocol manuscript to be published and is accountable for all aspects of the work. LS led the write up of the protocol manuscript, with the help of AK, JC, CH, HH, JG, MP and AE under the supervision of KA. KA is the Chief Investigator, MP Research Fellow, AE and HH Research Associates, and LS, AK and JC are Research Assistants on the project. JG is a contributor to the fNIRS pre-processing and data analysis. All authors read and approved the final manuscript.

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Conflicts of Interest

The authors declare no conflicts of interest

Data Statement

Not applicable

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FIGURE LEGENDS

Figure 1. CONSORT flow of SMI participants

Figure 2. CONSORT flow of healthy participants

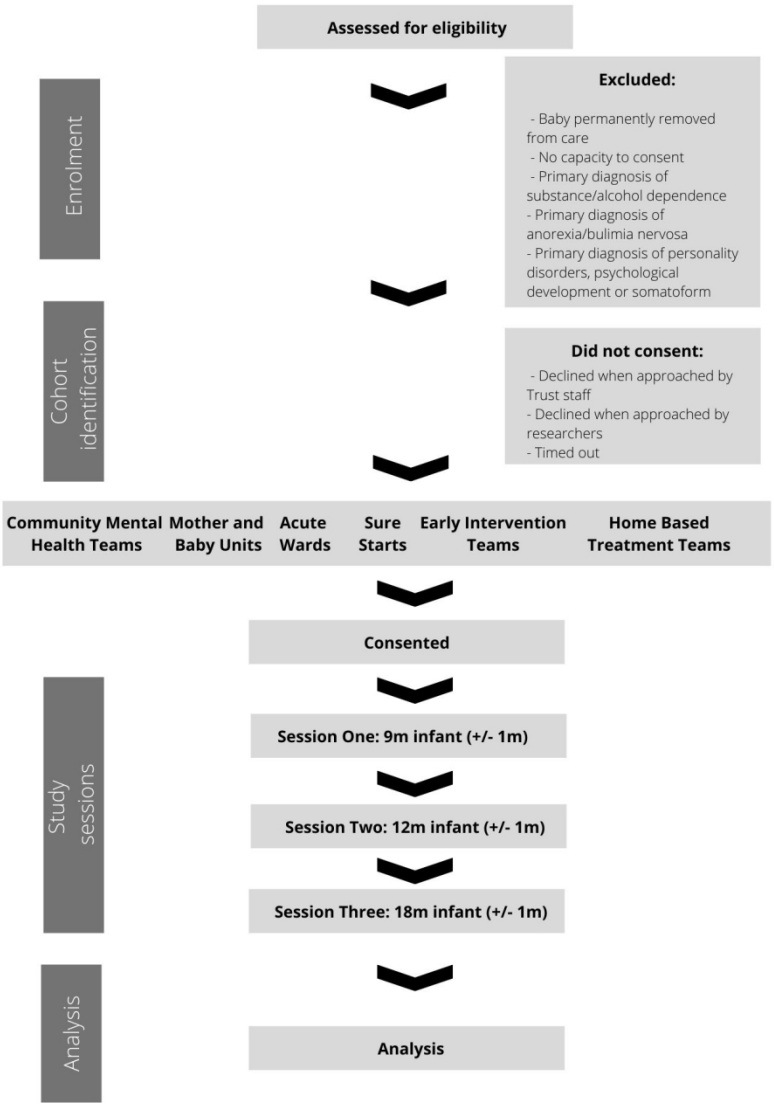

Figure 1. CONSORT flow of SMI participants

210x297mm (171 x 171 DPI)

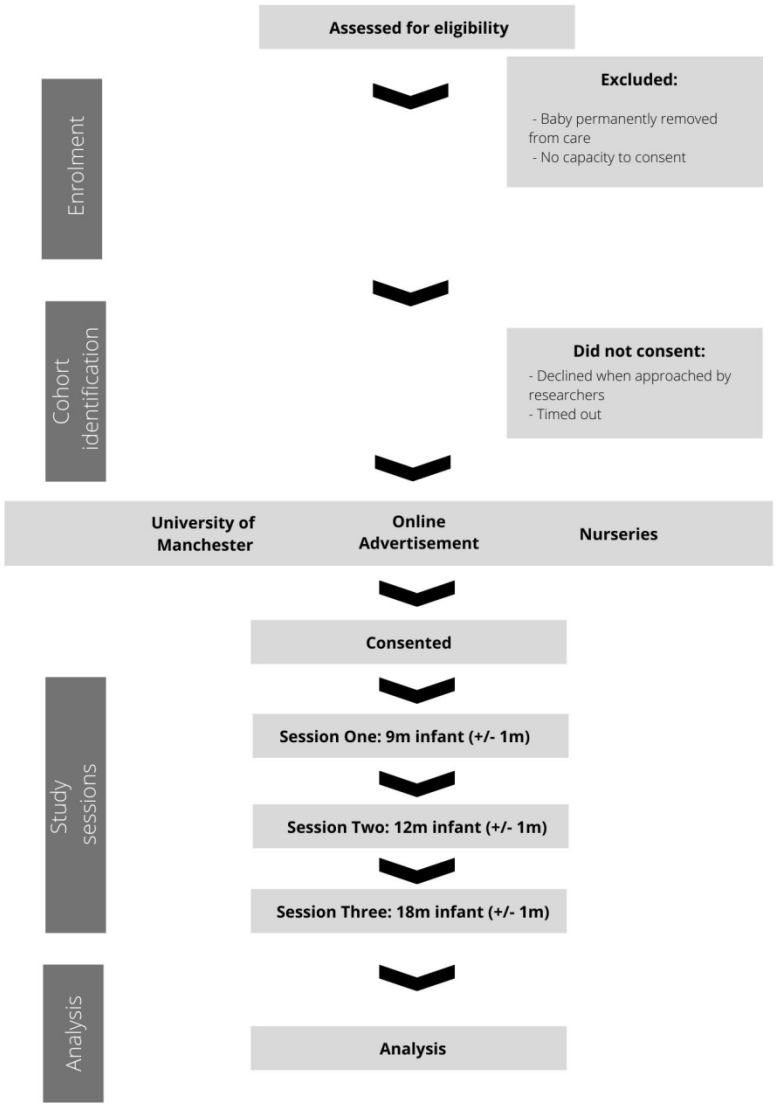

Figure 2. CONSORT flow of healthy participants

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