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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 UK and European Union. 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 National Health Service (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. The study was approved through North West–Greater Manchester West Research Ethics Committee (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. 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.

INTRODUCTION

The number of children and adolescents living with parental mental illness (CAPRI) is 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 with 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 of a growing number of vulnerable children.

Functional near infrared spectroscopy and CAPRI-Voc

Functional near infrared spectroscopy (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 and 1150 nm. 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 MRI (fMRI), using blood oxygen level-dependent 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 10 Hz) allowing for detailed analysis of the haemodynamic response function of both HbO and HHb associated with neural activity, for example, latency effects.

This study will use 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 (eg, electroencephalography, 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 General Practitioner (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 and 18 months (±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 and 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 and 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 (ie, Bayley III).
2. To discover infant biomarkers of atypical language development in CAPRI using fNIRS. We hypothesise:
   a. Children of mothers with serious mental illness (SMI) would experience delays in vocal and affect recognition at 9 months compared with children of healthy mothers.
   b. Children of mothers with SMI would experience atypical neural connectivity compared with 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 (attention deficit hyperactivity disorder (ADHD), Autistic Spectrum disorder (ASD), intellectual disability and cognitive ability). To compare between these assigned groups emergence of voice recognition over three time points (9 months, 12 months and 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 neurobiomarker 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 (05/07/2021).

Sample size

Over 5 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 and 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. 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 and post-traumatic stress disorder 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 years 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 Consolidated Standards of Reporting Trials diagram.[35]

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 2 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 time point. Infants are aged 9 months (±1 month) at session one (baseline), aged 12 months (±1 month) at session two and aged 18 months (±1 month) at session three. Mothers with SMI will have data on prescription medications and substance use collected via medical records, if consent has been granted. The reason for using medical records where possible is to decrease any potential burden of recall on the mothers with SMI so as to increase the likelihood of continued participation.

The baseline face-to-face session takes up to 2 hours and includes assessments for both mothers and their infants. The follow-up sessions take up to 1 hour and 30 min. Visits will either take place at the women's homes, a local NHS facility or at the University of Manchester, whichever is

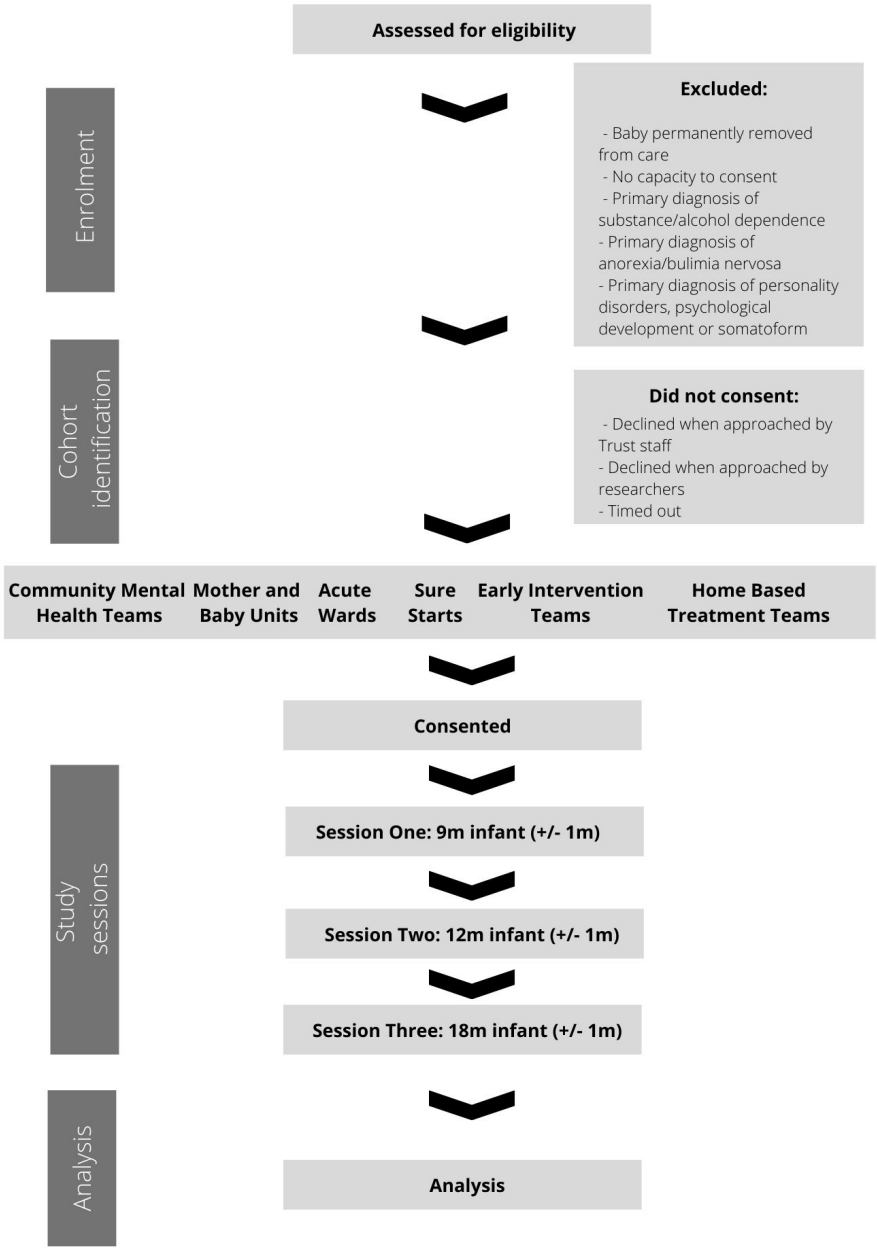

Figure 1 CONSORT flow of participants with SMI. CONSORT, Consolidated Standards of Reporting Trials; SMI, serious mental illness.

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 Manchester Assessment of Caregiver-Child Interaction (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 sociocommunicative input to their infants affecting language development.[38] Previous work links mother–infant interactions to vocal fNIRS at 6 months.[25] As the current study

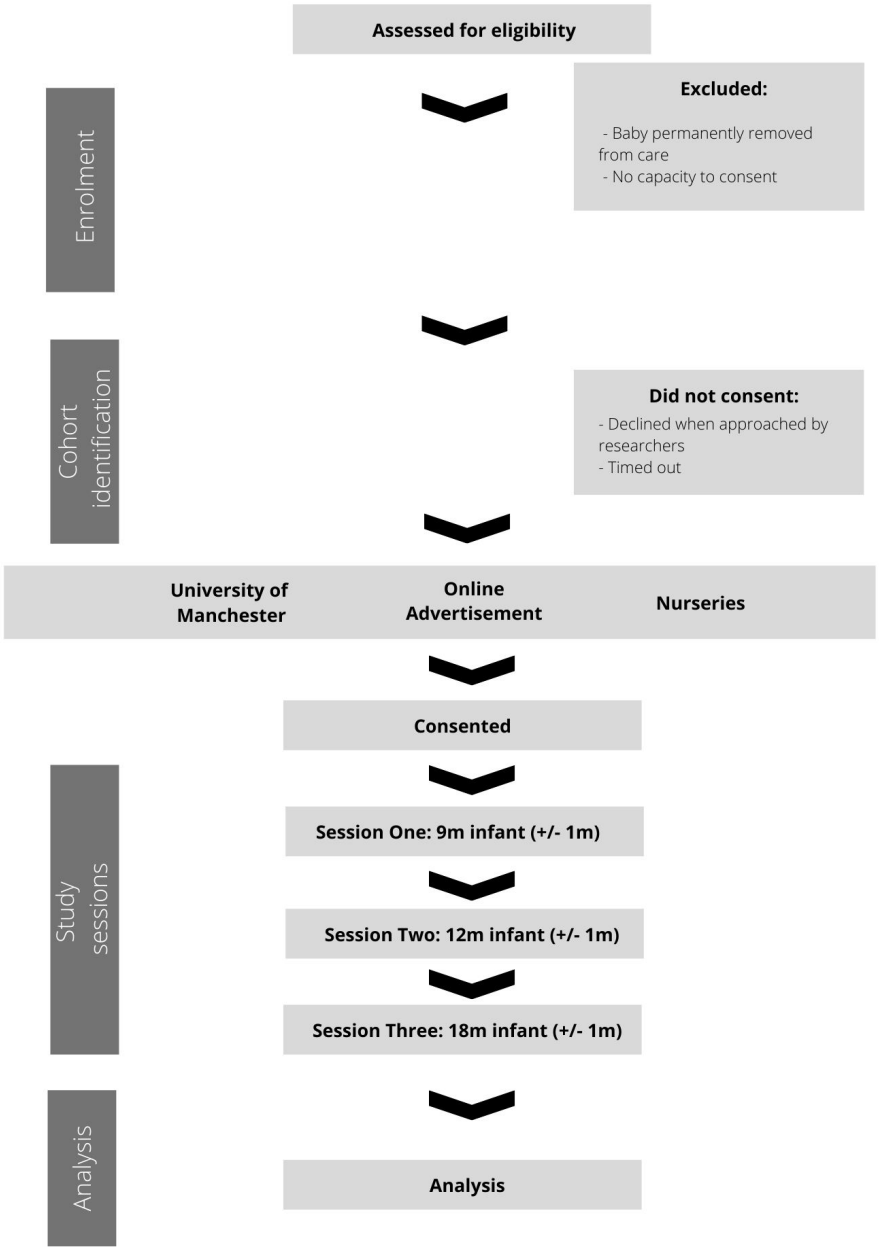

Figure 2 CONSORT flow of healthy participants. CONSORT, Consolidated Standards of Reporting Trials.

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 (12-month and 18-month) time points 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

Table 1 Description of study measures by cohort

Mother-only measures

Type of measure/ name of instrument	Instrument details	Data relating to				Hypothesis type (primary, secondary) and label (a, b, c…)
		Healthy mother modification	Session one (infant aged 9 months±1 month)	Session two (infant aged 12 months±1 month)	Session three (infant aged 18 months±1 month)	
Background and sociodemographic 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 to 126; a higher score is indicative of more severe symptomatology.[53]	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.[54–56] There are seven items relating to anxiety, and seven relating to depression. Items are rated on a 4-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 7 or less indicates feelings are in the normal range.	n/a	X			3a
General Health Questionnaire-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.[57 58]	n/a	X			3a
The Postpartum Bonding Questionnaire	This is a 25-item self-administered measure designed to detect issues within mother–infant relationships.[59] Items are rated on a 6-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 subscales: (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.[59]	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.[60] This contains five subscales: (1) physical abuse, (2) sexual abuse, (3) emotional abuse, (4) physical neglect and (5) emotional neglect.[60] 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 5-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.[61 62]	n/a	X			3a

Continued

Table 1 Continued

Type of measure/ name of instrument	Instrument details	Data relating to: Healthy mother modification	Session one (infant aged 9 months±1 month)	Session two (infant aged 12 months±1 month)	Session three (infant aged 18 months±1 month)	Hypothesis type (primary, secondary) and label (a, b, c…)
Mother-only measures						
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).[63] 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.[63]	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 to 150. There are four dimensions within the scale: severe combined abuse, emotional abuse, physical abuse and harassment.[64] The CAS has been validated for patient and community populations.[64 65]	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
Qualitative questionnaire	Research team designed topic guide to be administered at the final (18-month) 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/iInfant measures						
Manchester Assessment of Caregiver-Child Interaction	Mother–infant interactions are captured in a 6 min video clip taken during unstructured play.[66] 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).[66] This measure has been validated and used within both patient and community populations.[67 68]	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 socioemotional and adaptive behaviour.[69] These scales have been used to assess general development and as a test for neurodevelopmental delay across both western and non-western cohorts.[70 71] The scales are flexible enough to use the subtests independently based on research question.[69]	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 while sitting on mum's lap for a maximum of 15 min. 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.	n/a	X	X	X	1a, 2a, 2b

fNIRS, functional near infrared spectroscopy; n/a, not applicable.

(02 August 2021) and approved by the Health Research Authority (HRA, 17 September 2021) 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 regard to public safety, including the use of personal protective equipment (PPE) for both researcher and participant.

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 regions and 24 measurement points relevant to 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, that is, '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 70 dB (average for radio or TV sounds) using Praat software.[40] 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 70 dB. 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 soundtrack, and, therefore, block was set to 8 s using Audacity software.[41] 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,[42] animal sounds were removed from these stimuli as there is debate around their definition as 'vocalisation'[43] as they may elicit brain responses in language areas. The speech stimuli were taken from the RAVDESS Database.[44] 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 min, 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 (approximately 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 preprocessing

fNIRS signals are contaminated by physiological noise arising from components that include respiration and cardiac pulsation, as well as motion 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 more challenging.[45] Preprocessing will follow the most up-to-date recommendations from literature,[46 47] and will be performed with custom scripts in MATLAB (The Mathworks, Natick, Massachusetts, USA) based on functions from Homer2[48] and the Brain AnalyzIR Toolbox.[49] 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 SD, and corrected using the Wavelet-based filtering alone[50] or in combination with other methods, as suggested in.[46] 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 (GLM), using the different stimuli as regressors; in particular, it will be fitted using the auto-regressive prewhitening iteratively reweighted least squares method,[51] which has been shown to be helpful in mitigating the impact of serial correlations and residual artefacts in the data.[52] Stimulus-evoked changes in HbO and HHb can then be compared with 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 with 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 (eg, 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 packages 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 significance 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 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, for example, 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.

Some of the participants will be categorised as vulnerable; as such, researchers will complete level 3 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 (ie, researchers will contact the CI, KMA, to discuss these concerns and to decide on 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 (eg, 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.

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