Project Title: Music-assisted programmes: Developing communication in autism spectrum disorder through music making
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Principle Investigator: **Dr Fang Liu**, Associate Professor
School of Psychology and Clinical Language Sciences
University of Reading
f.liu@reading.ac.uk

Co-Investigators: **Dr Tom Loucas**, Associate Professor
School of Psychology and Clinical Language Sciences
University of Reading
t.loucas@reading.ac.uk

Dr Tim Williams, Associate Professor
School of Psychology and Clinical Language Sciences
University of Reading
timothy.williams@reading.ac.uk

Dr Jacqueline Sin, Associate Professor
School of Psychology and Clinical Language Sciences
University of Reading
jacqueline.sin@reading.ac.uk

Researchers: **Melissa Knight,** Research Paediatric Speech and Language Therapist, School of Psychology and Clinical Language Sciences, University of Reading,
M.Knight@student.reading.ac.uk

Georgia Aslett, UROP (Undergraduate Research Opportunities Programme) placement student, School of Psychology and Clinical Language Sciences, University of Reading, G.Aslett@student.reading.ac.uk

Sara Fincham Majumdar, Highly Specialist Speech and Language Therapist, School of Psychology and Clinical Language Sciences, University of Reading, s.c.finchammajumdar@reading.ac.uk

1. Introduction

This project is funded by a European Research Council Proof of Concept Grant (ERC-POC-2018, 838787, MAP, 2019-2021, https://cordis.europa.eu/project/rcn/222085/factsheet/en) to Fang Liu (PI).

The proposed research aims to develop a set of music-assisted intervention programmes to increase spoken language ability in 2-4-year-old, nonverbal or minimally verbal children with autism spectrum disorder (ASD), a neurodevelopmental disorder characterized by atypical social communication and interaction, and repetitive and restricted behaviours, activities and interests (American Psychiatric Association, 2013). Randomised controlled trials (RCTs) will be conducted to assess and validate the effectiveness of our intervention programmes through

the comparison of the outcomes of the treatment group (who receives music-assisted language interventions) with a control group (who receives traditional speech and language therapy).

2. Participants

1.1 Participant recruitment

Participants will be 2-4-year-old, nonverbal or minimally verbal children with ASD. They will be primarily recruited through the independent paediatric clinic (https://www.reading.ac.uk/Psychology/Clinics/SLT-Independent-Paediatric-Clinic.aspx) and the Centre for Autism (https://www.reading.ac.uk/autism/) at the University of Reading. We will also post or send our recruitment flyers/emails to local nursery schools (e.g., http://www.newbridgenursery.reading.sch.uk/The-Snowflake-Centre) and charities (e.g., http://www.autismberkshire.org.uk/). Internet postings (e.g., Facebook, Twitter), word-of-mouth, local media, newspaper advertisements, and parent support groups will also be used.

To screen for eligible participants, we will use an online registration form to collect basic background information (https://reading.onlinesurveys.ac.uk/registration-form, content to be revised for this project) about our potential participants. Formerly hosted by Bristol Online Surveys (https://www.onlinesurveys.ac.uk/) for which the University of Reading has a license, this online survey is fully compliant with all UK and EU data protection laws.

1.2 Participant characteristics

Following Dawson et al. (2010: e18), our participant exclusion criteria will include:

(1) "a neurodevelopmental disorder of known etiology (e.g., fragile X syndrome),
(2) significant sensory or motor impairment,
(3) major physical problems such as a chronic serious health condition,
(4) seizures at time of entry,
(5) use of psychoactive medications,
(6) history of a serious head injury and/or neurologic disease,
(7) alcohol or drug exposure during the prenatal period, and
(8) ratio IQ below 35 as measured by mean age equivalence score/chronological age on the visual reception and fine motor subscales of the Mullen Scales of Early Learning (Mullen, 1995)."

Participant inclusion criteria will include:

(1) aged between 2-4 at entry,
(2) nonverbal or minimally verbal, with fewer than 20 functional words (Kasari, Brady, Lord, & Tager-Flusberg, 2013),
(3) meeting criteria for ASD on the Toddler Module of the ADOS-2 (Autism Diagnostic Observation Schedule, Second Edition; Esler et al., 2015; Luyster et al., 2009; Randall et al., 2018), and a clinical diagnosis based on the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5; American Psychiatric Association, 2013) criteria using all available information,
(4) willingness to complete the intervention.

Race, ethnicity, and gender are not taken into consideration during participant recruitment. To minimize risks and to ascertain interpretability of the data, participants will be assessed for Significant Medical History, Peripheral Hearing, and Cognitive Abilities as indicated below in detail. Only the minimum necessary number of participants will be recruited.

Significant Medical History. For participants who come to our laboratory to take part in the intervention programmes, their medical history will be assessed to ensure that they fulfil our exclusion and inclusion criteria mentioned above.

Peripheral Hearing Testing. All participants will be screened for possible hearing loss by play audiometry, during which they will respond to an auditory stimulus through play activities, such as putting a ball in a bucket when a sound is heard through earphones (Harlor & Bower, 2009). Eligible participants will need to meet normal-range standards, having air-conduction hearing threshold levels of less than 20 dB between the frequencies of 250 and 8000 Hz. If a hearing problem is uncovered, the participant will not be able to take part in the study, but will still be entitled to payment for their time and their parent/guardian/carer will be advised to contact their doctor or a paediatric audiologist.

Cognitive Screening. All participants will be assessed for normal cognitive functioning appropriate for their age using the IQ test, *Mullen Scales of Early Learning* (Mullen, 1995). Those with ratio IQ below 35 will be excluded to ensure that all participants will be able to follow instructions and participate in the intervention programmes without difficulties.

Justification for the Minimum Number of Participants Needed. Although participation in this research poses very minimal risk, we will only run the minimum number of participants to minimize any risks. We anticipate to include 30 2-4-year-old, nonverbal or minimally verbal children with ASD in our randomised controlled trials (RCTs), 15 in the treatment group and 15 in the control group. This would be a sufficient number for our proof of concept study. However, considering the possible attrition and drop-out of the participants, we aim to recruit 50 participants at the outset.

3. Informed Consent

All participants will go through a consent process approved by the University Research Ethics Committee (UREC) at the University of Reading. Since 2-4-year-old children are unable to give informed assent, consent will be sought from their parents, legal guardians, or carers. Our procedure is as follows. First, the parent/guardian/carer will be verbally briefed and given a written copy of the information sheet to read. They will then be given the opportunity to ask any questions they may have and discuss the intervention procedure. If they agree for their child to take part in the study, they will then be given a consent form to sign. Before each session, the children will be verbally briefed in an appropriate manner, with delivery of information assisted by the PECS (Picture Exchange Communication System) or body language where appropriate. Given the limited communicative abilities of the children, children's assent will be managed by monitoring their behaviour and responses towards the researchers throughout each session. Testing will cease immediately if children become disengaged or agitated. On the very rare occasions that children refuse to take part, or express explicit or implicit desire to withdraw from the study at any time, no further attempts will be made to ensure their cooperation. Measures will be taken to prevent any psychological, emotional, cognitive, or physical harm to the participants. The parents/guardians/carers will be asked to be present during the study at all times.

4. Data Protection

This study will be performed in accordance with the spirit and the letter of the declaration of Helsinki, the ICH (International Conference on Harmonization) Good Clinical Practice Guidelines (Grimes et al., 2005), the CONSORT (Consolidated Standards of Reporting Trials) statement (Moher, Schulz, & Altman, 2001; Schulz, Altman, & Moher, 2010), the regulatory requirements and laws in the UK and EU, such as the General Data Protection Regulation

(GDPR) (https://www.gov.uk/government/publications/guide-to-the-general-data-protection-regulation), the ethical standards and guidelines of Horizon 2020 (http://ec.europa.eu/research/participants/data/ref/h2020/grants_manual/hi/ethics/h2020_hi_ethics-data-protection_en.pdf), and this protocol.

Sources of Materials. The research data obtained from our participants will be in the form of cognitive and behavioural data (in text or spreadsheet format) and audio and video recordings. Participants will be able to request their scores on the tests they have completed. Data collection and analyses will be done in the PI's lab or a clinic room in the School of Psychology and Clinical Language Sciences at the University of Reading. We will adhere to the standards of the European Data Protection Regulation (https://gdpr-info.eu/) and the UK Data Protection Act 2018 (https://www.gov.uk/government/collections/data-protection-act-2018) at all stages of our research and post-research. We will participate in the Open Research Data Pilot (ORD Pilot) of Horizon 2020, providing other researchers in the world access to and reuse of our anonymised research data. Unless participants revoke their permission for us to use and analyse their data, the data will not expire. Participants are free to choose to notify the study research staff in writing or verbally informing for stopping being in the study at any time and they may notify the study research staff in writing or verbally to request that their data not be used in any future study. If participants withdraw from the study, their data will be destroyed. Physical destruction will be used to erase files and dispose of data. We will physically destroy the computers/drives using a secure destruction facility approved by our institution when data need to be destroyed. Shredders certified to an appropriate security level will be used for destroying paper and CD/DVD discs.

Participant Confidentiality. To protect against any breach in confidentiality, each participant will be assigned a participant code which has no resemblance to his/her name, and only the investigators and authorized personnel have access to the link codes. Codes instead of names of participants will be used on data files, disks, publications, and reports. Data collected specifically for this project will not be part of the participant's record but will be maintained separately. Since the data, research results, and the medical information used in these studies are not labelled with any personal identification, there is little risk that the results can be linked to the participants. Any individually identifying information is kept in a secure location with restricted access and any such physical documentation is kept in a locked cabinet at a secure location with restricted access. All individually identifying information will either be stored in electronic form in a secure location with limited access and/or stored in a locked file cabinet with restricted access. To ensure data integrity and security, we will lock our computer systems with passwords and install firewall systems. We will also protect our servers by power surge protection systems through line-interactive uninterruptible power supply (UPS) systems. With participants' permission, we may want to use an extract of the audio recording for teaching, conferences, presentations, publications, and/or thesis work. These materials will be managed under the described data retention and destruction policy, and they will not be used in any way that will violate participant confidentiality and privacy.

Video Recordings of Testing and Intervention Sessions. It is valuable to be able to video the testing and intervention sessions, in particular the Autism Diagnostic Observation Schedule (Esler et al., 2015; Luyster et al., 2009), which is a standardised clinical interview. Video allows us to check the diagnosis and the consistency of the researcher's behaviour, and the child's progress throughout the intervention period. Video data can never be fully anonymised because a person's face is visible. The consent form seeks explicit consent for using video. After the study is completed, video will be stored in an encrypted format on a password protected computer in a locked office. It will never be shared outside the research group, even with

collaborators.

5. Methods

Randomised Controlled Trials (RCTs)

We will conduct our randomised controlled trials (RCTs) following the CONSORT (Consolidated Standards of Reporting Trials) statement (Moher, Schulz, & Altman, 2001; Schulz, Altman, & Moher, 2010). The detailed procedure is outlined in the CONSORT checklist (Appendix A) and flow diagram (Appendix B). Everyone agreeing to take part will have a 50:50 chance of receiving the music-assisted (MAP) intervention or treatment as usual (TAU). A computer will be used to allocate participants (stratified for gender) randomly to one of the study arms, which will not have any identifying information about the participants apart from gender.

Experimental Procedure

Participants and their parents/guardians/carers will come to the School of Psychology and Clinical Language Sciences at the University of Reading for one to two hours for consent, IQ and hearing screening, and handedness assessment. They may participate in the interventions either in the treatment or the control group.

Background Measures

The treatment and control groups will be matched on the presence of echolalia (van Santen, Sproat, & Hill, 2013), IQ (*Mullen Scales of Early Learning, 1995)*, receptive and expressive language (*Receptive and Expressive One-Word Picture Vocabulary Tests, Fourth Edition; ROWPVT-4, EOWPVT-4*), and ASD symptomatology (checked using *ADOS-2* and meeting the *ICD-10* or *DSM-5* criteria for ASD).

Intervention Programmes

After assessing the receptive and expressive language level of each participant, 36 target words will be chosen for all participants to learn during the intervention sessions. These target words will relate to naturalistic, everyday activities that the child spontaneously engages in, so the adult can follow the child's lead or focus of attention and the child's activities can be turned into a social routine, with music.

All intervention sessions will be videotaped, individually delivered in a quiet room. Each intervention session will last about 45 minutes, happening 2 days a week, for 18 weeks. For the music-assisted (MAP) language interventions, we will use a structured protocol, delivered through naturalistic strategies such as incidental learning, high-density repetition, time-delay and mand-modelling. For each of the 36 target words, we will create a set of songs defining its meaning and the contexts where it occurs. During each session, the songs will be delivered using a digital piano or a guitar, and a range of music instruments commonly used in music therapy. The children will be taught to sing the songs, where the target words will be occurring repetitively, together with other engaging and interactive activities such as dancing, vocalizing, improvising, and playing musical games. For the treatment-as-usual (TAU) control group, regular speech and language therapy sessions will be delivered, focusing on the learning of the 36 target words using conventional methods, in line with the PACT approach (Green et al., 2010) and the NICE guideline on psychosocial interventions (https://www.nice.org.uk/guidance/cg170/chapter/1-Recommendations#specific-interventions-for-the-core-features-of-autism).

Outcome Measures

Primary outcome will be measured using the production of the 36 target words at baseline, post-intervention, and 1-month follow-up, assessed by a blinded outcome data assessor.

Secondary outcomes will include the following at baseline, post-intervention, and 1-month follow-up, assessed by a blinded outcome data assessor:

- IQ is measured using Mullen Scales of Early Learning, 1995.
- Receptive and expressive language is measured using Receptive and Expressive One-Word Picture Vocabulary Tests, Fourth Edition; ROWPVT-4, EOWPVT-4.
- ASD symptomatology is measured using the ADOS-2.
- Vocal production throughout 3 days is measured using audio recordings.

Protection against Risks

There are no or only minimal risks involved in our intervention programmes, such as possible fatigue, anxiety, or frustration. Appropriate care will be taken to avoid or minimize these risks, including the following: 1) Participants can take as many breaks as necessary during the intervention sessions; 2) Children will be accompanied by parents/guardians/carers during all sessions; 3) We will take the incidental learning approach and make the sessions enjoyable, engaging, and fun for children; 4) Children and parents/guardians/carers can choose to withdraw from the study at any point or not to participate; 5) All sessions will follow appropriate health and safety guidelines including testing during office hours, keeping doors to testing rooms ajar, and allowing an easy exit route, etc.; 6) Before coming in and again upon arrival, children will be provided with a social story, pictures of what the procedures involve. The procedures will be explained in simple terms and it will be made clear that they can stop at any time. Given the limited communicative abilities of the children, children's assent will be managed by monitoring their behaviour and responses towards the researchers throughout each session. Caregivers will be present to inform researchers as well if they think their child is in any form of distress. Testing will cease immediately if children become disengaged or agitated. On the very rare occasions that children refuse to take part, or express explicit or implicit desire to withdraw from the study at any time, no further attempts will be made to ensure their cooperation; 7) We will follow the good practice guide when communicating with children with ASD and their family (Brown & Elder, 2014; Lee, Walter, & Cleary, 2012), and make every effort to ensure that our participants have a safe and pleasant experience with our intervention programmes.

All investigators on this project have obtained criminal record clearances through enhanced DBS (Disclosure and Barring Service) checks that cover vulnerable adults and children, and they have also been approved by the School to work with children. The researchers carrying out the interventions are appropriately qualified to do so.

If during the course of the trial, we make observations which raise concerns about the children's wellbeing and safety, we will follow the procedures and policies as outlined by the Keeping Children Safe Standards in the EU (https://ec.europa.eu/info/sites/info/files/standards_child_protection_kcsc_en_1.pdf), the Safeguarding Vulnerable Groups Act 2006 in the UK (http://www.legislation.gov.uk/ukpga/2006/47/contents), and the University of Reading DBS policy (http://www.reading.ac.uk/web/files/humanresources/DBS_Policy_FEB14.pdf) and safeguarding policy (https://www.reading.ac.uk/~/media/files/uor_safeguarding_policy_v7.ashx?la=en) to respond to any safeguarding concerns.

6. Findings

Incidental Findings. If during the hearing or cognitive screening we find that the participant may have potential hearing or cognitive deficits, we will recommend that they see an audiologist or their doctor for a full evaluation. Participants will be informed that the findings will be preliminary, inconclusive, and not necessarily valid for use by the participants' doctors in the management of their healthcare, so we do not expect to identify any incidental findings.

Potential Benefits of the Proposed Research to the Participants and Others. There may be direct benefit to the individual participant, since we will be delivering language intervention programmes to nonverbal or minimally verbal children with ASD during the study. We aim to use this Proof of Concept grant to develop a novel set of music-assisted programmes (MAP) to provide an easy-to-implement, individualised treatment for language impairments in nonverbal or minimally verbal ASD children in a relaxing, comforting, and stimulating setting. The project outcomes have the potential to break new ground and open up new possibilities for language and communication interventions in ASD.

7. Laboratory Health and Safety Procedures

1) **Fire safety** will be in line with the policy of the University of Reading and local fire departments.
2) **Electrical safety**: 1) All equipment will be checked for grounding and current leakage annually, and the results will be documented. 2) Precautions regarding electrical safety will be as per UK standards.
3) **Infection prevention and control**: We will follow the code of practice on the prevention and control of infections and related guidance in "The Health and Social Care Act 2008" in the UK (https://www.gov.uk/government/publications/the-health-and-social-care-act-2008-code-of-practice-on-the-prevention-and-control-of-infections-and-related-guidance).
4) **Medical emergencies**: Policies and procedures are in place at the University of Reading to deal with medical emergencies, e.g., a first aid officer will provide medical help whenever needed.

8. References:

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Appendix A. The CONSORT 2010 Checklist (http://www.consort-statement.org/).

CONSORT 2010 checklist of information to include when reporting a randomised trial

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	
	2b	Specific objectives or hypotheses	
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	
Participants	4a	Eligibility criteria for participants	
	4b	Settings and locations where the data were collected	
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	
	6b	Any changes to trial outcomes after the trial commenced, with reasons	
Sample size	7a	How sample size was determined	
	7b	When applicable, explanation of any interim analyses and stopping guidelines	
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	

Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	
	13b	For each group, losses and exclusions after randomisation, together with reasons	
Recruitment	14a	Dates defining the periods of recruitment and follow-up	
	14b	Why the trial ended or was stopped	
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	
Other information			
Registration	23	Registration number and name of trial registry	
Protocol	24	Where the full trial protocol can be accessed, if available	
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	

Appendix B. The CONSORT 2010 Flow Diagram (http://www.consort-statement.org/).

CONSORT 2010 Flow Diagram