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Supplementary appendix

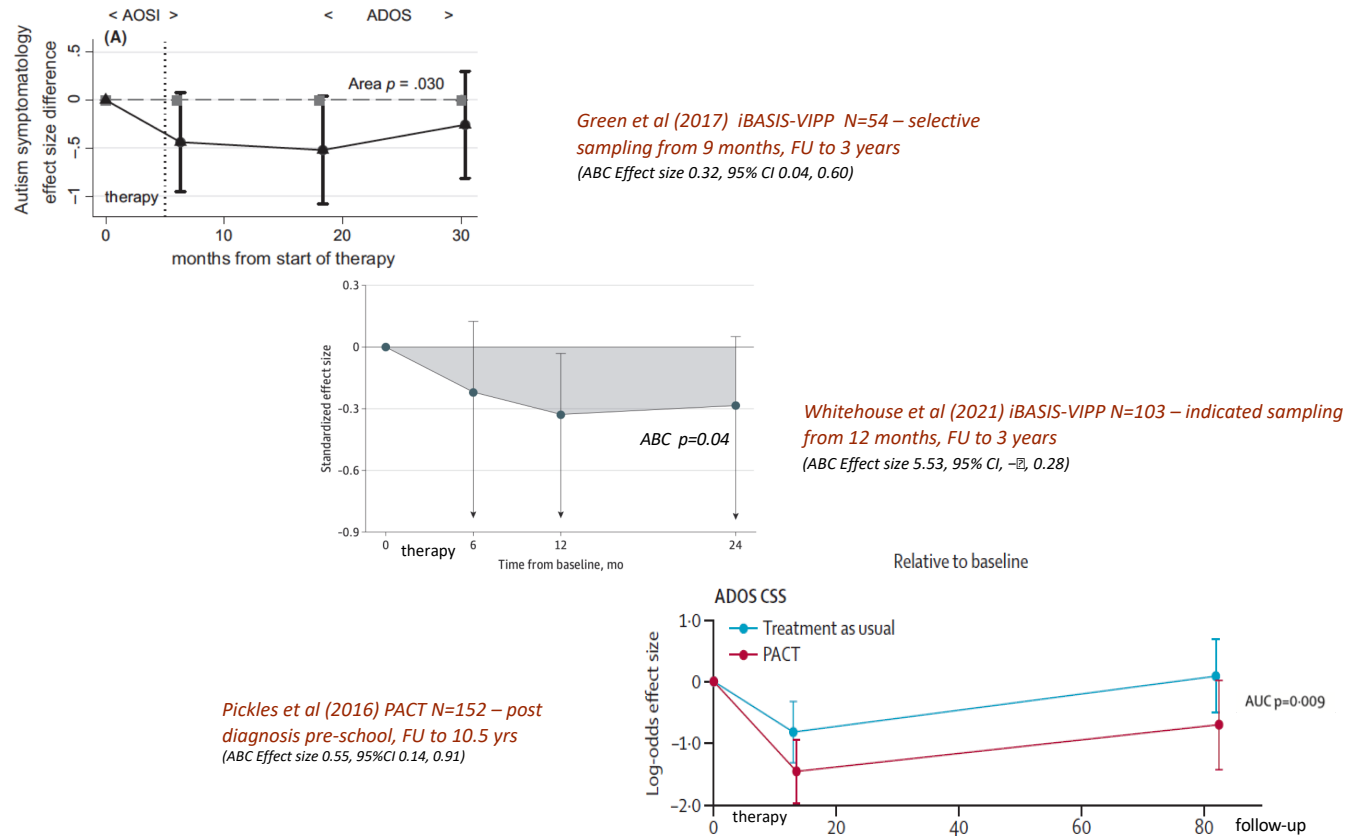
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AN INTEGRATED EARLY CARE PATHWAY FOR AUTISM

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Figure 1 Long-term developmental outcomes from three parent-mediated intervention trials. Showing replicated effects at different stages in early development to improve a combination of social communication skills, behavioural rigidity and sensory sensitivities; improvements sustained after the end of therapy



Reproduced from Green et al. 2017, Whitehouse et al. 2021, Pickles et al. 2016 – see main text. ABC/AUC = Area between curves estimation over time. These estimates provide a principled basis for an overall mean effect for unequally spaced measures that summarise treatment effect over the whole trial from baseline to follow-up.

Further information on iBASIS-VIPP and PACT parent-mediated interventions

Background theory and developmental science The logic for this work stems from the multifaceted importance of caregiver-infant interaction in the early months of life; effects that impact on the fine-tuning of brain and perceptual system specialisation, capacity for joint attention, intersubjectivity; and specifically here, as an interpersonal platform for infant social and communication development. Empirical evidence suggests altered early parent-infant interaction dynamics in the context of infant's increased familial likelihood of later autism ('infant siblings'), with overall increased in 'directiveness' of parental responses from 7 months infant age, linked in early data to altered infant visual processing (Elsabbagh et al 2015). This pattern of parental responsiveness continues to be seen at infant age 14 months, plus additional changes in infant dyadic response in reduced attentiveness to parent, affect sharing and mutuality. These infant dyadic behaviours at 14 months then predict autism diagnosis at three years (Wan et al 2013). This and other evidence is compatible with the idea of a transactional cascade arising in early infancy, with amplifying divergence in dyadic interaction during the latter part of the first year as part of a potential trajectory towards autistic development. The parent-mediated developmental interventions described here specifically target these early transactional interactions with the aim of supporting later child development trajectories. Mechanistic trial evaluations of such interventions with mediation analysis (as below) can in turn then test this developmental hypothesis. Further background context for this intervention approach can be found in Green (Green, 2020).

iBASIS-VIPP pre-diagnostic intervention This intervention was designed to be applied to infants in the first 18 months of life, who are at increased likelihood of autism development. The intervention protocol was developed out of the original 'Video Interaction for Positive Parenting' (VIPP) method, developed in the context of children and families' social rather than neuro developmental risk (Juffer et al 2008). Since, in any pre-emptive intervention programme, a proportion of participants will go on to have neurotypical development, it was important ethically to design an intervention with this background evidence of acceptability, safety and effectiveness in a neurotypical development context. The substantive adaptations for early neurodevelopmental divergence included doubling the length of the intervention to 12 sessions over 5 months, and adaptation of intervention methods to early signs of infant neurodivergence. In a series of home-based sessions, the therapist uses video-feedback to help parents recognise their baby's communication cues so they can respond in a way that builds their social communication development. Parents are videoed interacting with their baby in everyday situations, such as feeding and playing. The therapist then provides guidance to the parent about how their baby is communicating with them, and they can communicate back to have back-and-forth conversations. The focus is first on interpretation of the infant's behaviour and recognising their intentions, then working on sequences of sensitive responding during everyday activities, emotional attunement, and patterns of verbal and nonverbal interaction. This therapy focuses on supporting parent-child interactions as a way of enriching their social environment, creating learning opportunities for the child in a way that is tailored to the child's unique abilities. It is emphasised that these parent-infant interactions are not a primary 'cause' of autism, since child neurodivergence is highly heritable, but rather a way of valuing and enriching the potentially neurodivergent infant's early social experience. The feasibility and acceptability of the method was shown in a pilot case series (Green et 2012); followed by RCTs of the method applied to infants at familial high likelihood in the latter part of the first year (Green et al 2017) and to infants identified in the community as showing early evidence of possible autistic development (Whitehouse et al 2021). In both these RCTs the infants were then followed after the end of therapy till diagnostic evaluation at 3 years. The studies followed therapy impact on parent-infant dyadic interaction over time, and independently assessed child development and emerging autistic-related behaviours. Figure 1 above shows the sustained effect of the therapy on these child outcomes; cumulatively significant over time as measured by the resulting area between the curves of therapy vs usual care.

Further information about iBASIS-VIPP therapy and future professional training can be obtained from the corresponding author, Prof Jonathan Green jonathan.green@manchester.ac.uk.

PACT post-diagnostic intervention The Paediatric Autism Communication Therapy (PACT) is a 12 month family-focussed programme with a similar theoretical rationale. The developmentally staged manual builds on developmental precursor skills to social facility and communication through a parent mediated approach. The rationale is that autistic children will respond to carer communication adapted to their individual communication style, with enhanced social engagement, communication ability and social development. The intervention consists of 1:1 clinic sessions between therapist and parent with child. The therapist uses specific video feedback techniques to help parents/carers recognise, respond to, and enhance their child's social communication. After an initial orientation meeting, families attended bi-weekly 1 ½ hour clinic sessions for 6 months followed by a 6-month period of monthly booster sessions, used flexibly to continue generalising the communication techniques in daily routines. Within each session, the therapist reviews short video clips of the

adult and child interacting or playing together. This video is then jointly reviewed with the adult, using selected moments to identify and discuss the best individual communication strategies for the child. Between sessions, parents/carers are asked to practise PACT strategies with the child for around 30 minutes a day. PACT has been delivered in the clinic, on which most of the RCT evidence is based, but also online using video conference techniques, at home and in education (forthcoming trial results address efficacy in these latter settings). Other health, education or social interventions can be continued in parallel. The intervention is manualised and staged to reflect the developmental progression of pre-linguistic and early language skills. The intervention firstly aims to increase parental sensitivity and synchronous responsiveness to child communication, reducing mistimed parental responses. With achievement of greater shared attention and reciprocity, further incremental development of child communication is facilitated by promoting a range of strategies such as action routines, familiar repetitive language and pauses. An initial randomised trial of the intervention (Aldred et al 2004), showed evidence of effectiveness on symptom outcomes using the ADOS (total score). A subsequent larger RCT randomised trial involved 152 children with ‘core-autism’ in a parallel group randomised design (80% had learning difficulties and 25% phrase speech of baseline with an average age of 45 months). Children were assessed after one year of intervention and then after a further six years from the end of treatment at an average age 10.5 years, with 80% follow-up of the original sample followed at that time, assessed still blind to treatment allocation. The primary outcome result from the overall trial and follow-up (Pickles et al 2016) is summarised in Figure 1. The improvement in overall autism symptom levels seen at treatment endpoint is sustained during the next six years following the end of treatment. The area between curves (ABC) estimation on the cumulative effect of intervention over this time is significant. Parental report and the trend of teacher reports also support this effect (Pickles et al 2016, Leadbitter et al 2017). Parent experience of undertaking the PACT therapy has been reported (Leadbitter et al 2017, 2020). PACT has been adapted for delivery by non-specialist health workers in South Asia (Rahman et al 2016).

Treatment mechanism To address the question of the treatment mechanism underlying this effect, mechanistic analyses of both the original PACT pilot study (Aldred et al 2012) and the larger PACT RCT (Pickles et al 2015) have been undertaken. In both cases the mediation effects support improved parental synchrony as the proximal treatment target. In the detailed repeated measures mediation analysis (Pickles et al 2015), the impact of treatment on child communication initiation in the dyad is strongly mediated by the proximal targeted treatment effect on improving parental synchronous response (a specific effect, with no other measured parental behaviours contributing). This allows an inference that it is the change in parental synchrony that is responsible for the change in child communication. A second stage of mediation then is that the treatment effect on endpoint ADOS autism symptom level is strongly mediated by the prior change in child dyadic communication (Pickles et al 2015). This latter mediation effect implies that the child has been able to generalise its communication change in the dyadic across person and context into the interaction with a researcher in the ADOS examination.

Further information on the detail of PACT therapy and professional training can be obtained from <https://www.pacttraining.co.uk/>.

Further information on the Social Attention and Communication Surveillance (SACS) checklists and ASDetect app

The Social Attention and Communication Surveillance-Revised (SACS-R) with an additional preschool check (SACS-PR) is a developmental surveillance programme for the early identification of autism in infants, toddlers, and pre-schoolers. The SACS-R+PR is observationally based, requires training of child-health and education professionals, and works best when implemented in a setting that routinely monitors child development. Primary health practitioners (e.g., Maternal and Child Health nurses) are trained during a one-day workshop to use the SACS-R and SACS-PR checklists during their routine health checks with children at 12-, 18-, 24-, and 42-months. Parents are notified of the outcome of the assessment; that is, whether a child may be at a “higher” or “lower” likelihood of being on the autism spectrum, following a discussion of the child’s social-communication profile. Referrals to appropriate early intervention services and diagnosticians are made in collaboration with the parent/s. The efficacy of the SACS has been investigated in two large-scale studies in Victoria (SACS: 2006-08; SACS-R+PR: 2013-18) where ~36,000 children were monitored as part of their routine MCH health checks between 12-42-months of age by ~400 trained MCH nurses. The children referred as having a “high likelihood” of autism (based on 3 of 5 “key” behaviours) were referred to the SACS team at La Trobe University for a diagnostic assessment, followed-up every 6 months until 24-months, and again at 3.5 years (Barbaro & Dissanayake, 2010; Mozolic-Staunton et al., 2020). At 12-24 months, SACS-R showed high diagnostic accuracy with 82.92% positive predictive value (PPV); estimated negative predictive value (NPV);

98.72%) and specificity (99.56%) was high, with modest sensitivity (61.50%). Psychometric properties of the SACS-R+PR were excellent, with 82.92% PPV, 98.72% NPV; 99.56% specificity, and 96.13% sensitivity.

ASDetect is a free, video-led, mobile application based on the SACS research, and designed for parents to monitor their infants and toddlers for the early signs of autism. Parents are able to reference their own child's social-communication interactions against a illustrative library of neurotypical and neurodivergent videos alongside a guided checklist of behaviours. Parents receive an instant, on-screen result following completion of the questions, showing their child to be at "high" or "low" likelihood for autism; they also receive a detailed email with their child's results to be used in dialogue with family's professional support, at which time appropriate referrals to early supports and services can be made. Pilot data show that ASDetect has a PPV of 84% between 11-30-months of age (Barbaro & Yaari, 2020). ASDetect is available in English, Spanish and Chinese Mandarin, via the Android and Apple stores.

Further details on these instruments and SACS-R training can be obtained from Associate Professor Josephine Barbaro, OTARC, La Trobe University; j.barbaro@latrobe.edu.au.

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