A randomised-controlled trial of a pre-emptive intervention for infants showing early behavioural risk signs of autism spectrum disorder

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Abstract

Background: There is great interest in the potential efficacy of pre-diagnostic intervention within the Autism Spectrum Disorder (ASD) prodrome. Current evidence relates to samples selected based on family-history risk. We designed the largest pre-emptive RCT of a clinically-indicated sample of infants with early ASD behavioural signs.

Methods: In this two-site randomised-controlled trial, infants (9-14 months-old) were enrolled based on the presence of early signs of ASD. Between June 9th 2016 and March 30th 2018, we randomly assigned (1:1) 50 infants to receive a parent-mediated video-aided intervention (iBASIS-VIPP) and 53 infants to receive treatment as usual only (TAU). Group allocation was by minimization, stratified by site, sex, age, and early ASD behavioural markers. Assessments were conducted at baseline (prior to treatment allocation) and at a six-month endpoint. The primary outcome was a measure of early behavioural signs associated with ASD (Autism Observation Scale for Infants); secondary outcomes were a range of developmental skills. Trial registration: ANZCTR12616000819426.

Outcomes: There was no significant effect of treatment group on early ASD behavioural signs (β=-0·74, 95%CI=-2·47,0·98). However, the iBASIS-VIPP group was significantly improved compared to TAU on parent-reported receptive (β=37·17, 95%CI=10·59, 63·75), and expressive vocabulary count (incidence rate ratio=2·31, 95%CI=1·22,4·33) and functional language use (β=6·43, 95%CI=1·06,11·81).

Interpretation: A pre-emptive intervention for infants showing early signs of ASD had no immediate treatment effect on early ASD symptoms, but a positive effect on parent-rated communication skills.

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Autism Spectrum Disorder (ASD) is not typically diagnosed until after 2-years of age. However, there is now robust evidence that certain behavioural features – for instance, reduced social attention[1] and communication behaviours[2] – are often apparent before the first birthday. The identification of infants presenting with these behaviours prior to the full ASD syndrome emerging provides a potential opportunity to apply interventions to mitigate long-term symptom severity and disability.

Although genetic variation is known to play a major role in the aetiology of ASD, there is emerging evidence that the biological susceptibility may be modified by the quality of the social environment in early development.[3] 'Interactive specialisation' theory proposes that the quality of an infant's early social interactions has a major influence on the developing brain structures that underpin social behaviour.[4] Early infant interactions, most typically with parents/caregivers, are critical in creating an optimal social environment to support the development of neural pathways associated with social behaviours.[5] Consistent with this theory are findings that parental interaction styles that are sensitive and responsive to child cues assist are associated with more favourable long-term social and communicative outcomes for children experiencing typical[6] or atypical[7] development.

Infants are typically born with biases to attend to and learn from social stimuli.[8] By contrast, there is good evidence that some infants later diagnosed with ASD have reduced sensitivity in underlying biasing mechanisms at both the behavioural[1] and neural[9] level. These differences may lead to changes in parent interaction styles, such as increased directiveness during play and less sensitivity to their infant's behavioural cues,[10] and there is evidence that these parent behaviours are associated with ASD diagnostic status at age 3 years.[11] This does not imply that parents are in any way a 'cause' of ASD, but rather that atypical communication and social cues among infants may induce differences in parent interaction styles, which in turn, may modify the quality of social input that the infant receives.

This literature has created significant clinical and scientific interest in whether parent interaction styles provide a malleable target for interventions aimed at enhancing developmental outcomes for infants showing early signs of ASD. However, there have been few randomised trials.[12] One small randomised-controlled trial (RCT), examined the efficacy of adaptive responsive teaching (ART), a parent-mediated therapy targeting parental responsiveness to infant interaction. The group receiving ART (n = 11) showed reduced

parent directiveness during infant play and improved infant receptive language compared to community treatment as usual (TAU; n = 5). A second RCT compared the effect of an intensive ART protocol (30 home-based sessions over a 6 month period) and community TAU in 87 infants with early behavioural signs of ASD.[14] While parents in the ART group showed significantly greater increases in responsiveness to their infants, there were no treatment effects observed over TAU in child developmental outcomes.

Elsewhere in developmental science – such as child attachment – there is evidence of the particular effectiveness of video feedback in increasing parental sensitivity and non-directiveness.[15] Video-feedback provides parents an opportunity to reflect on their infants' behaviours, and their own interactive responses to these behaviours. Video-feedback is a core component of the Video Interaction for promoting Positive Parenting (VIPP) program,[16] and iBASIS-VIPP[17] is a protocol adaptation designed specifically for infants in the ASD prodrome. An RCT of 54 infant siblings of children with ASD (aged 6-9 months) found iBASIS-VIPP led to improvements at immediate follow-up (mean age 15 months) in parental non-directiveness, with a trend also toward reduced ASD symptomatology.[17] Follow-up assessments at two timepoints up to 2 years after the end of intervention found a sustained treatment effect over time in reducing ASD symptoms.[18] This study provided the critical first evidence that pre-emptive ASD interventions may alter longer-term symptom trajectory, but two study design elements tempered possible conclusions. First, a relatively modest sample size reduced the precision of treatment estimates. Second, in the familial high-risk selection strategy, only a minority of infant siblings would be expected to be on a developmental trajectory toward ASD, limiting the potential to extrapolate findings to infants showing clinically-relevant early signs of ASD.

The aim of this study was to provide the first well-powered test of the efficacy of iBASIS-VIPP with a sample of infants (9-14 months) showing early behavioural signs of ASD. The hypothesis was that, compared to TAU, the iBASIS-VIPP intervention would reduce the severity of ASD symptoms, increase the quality of parent-child interactions, and improve infant communication and social skills at treatment endpoint (6-months post baseline) and developmental follow-up (18 months post-baseline). The current report is of findings at treatment endpoint.

Methods

Study design and participants

This was a two-site (Perth and Melbourne, Australia), single-blind RCT: participants were randomly allocated to receive either iBASIS-VIPP therapy (iBASIS-VIPP group) or community treatment as usual (TAU group) over a 5-month period. In Perth, infants were recruited through the metropolitan Government service for children with developmental delays, to which children are typically referred via a health professional or parent/caregiver self-referral. A study team member telephoned parent(s)/caregiver(s) of newly-referred infants in the age range to screen for study eligibility. In Melbourne, community Maternity and Child Health nurses directly referred potentially eligible infants to the study team, a member of which then telephoned the parent(s)/caregiver(s) to screen for eligibility.

Families were invited into the trial if: (a) the infant was in the age range of 9 months to 14 months, 31 days (corrected for prematurity) at eligibility screening; (b) the infant displayed at least three of the five key 'ASD risk' behaviours on the Social Attention and Communication Surveillance-Revised (SACS-R) 12-month checklist,[19] and (c) the primary caregiver spoke sufficient English to participate fully in therapy sessions. Exclusion criteria were: (a) diagnosed comorbidity known to affect infant neurological and developmental abilities (including birth <32 weeks' gestation); and/or (b) the family did not intend to remain living in the local area for the trial duration. (See Supplementary Material for the full trial protocol.) The study was approved by the Child and Adolescent Health Service Ethics Committee (2016008EP, June 8th, 2016), and each family provided written informed consent.

Baseline assessments typically took place within 4 weeks of eligibility screening (Mean=2·53 weeks; SD=1·50; range=0·29-8·71). While this time-period could not be achieved for one participant (8·71weeks) for logistical reasons (infant illness), age eligibility requirements for this infant were still met. Treatment endpoint assessments typically occurred within 2 weeks of the baseline assessment 6-month anniversary (Mean=6·22 months; SD=0·60; range=4·4–9·2), and all occurred after completion of the treatment protocol (in the iBASIS-VIPP group). Trial registration is available at: ANZCTR12616000819426.

Randomisation and masking

After consenting and baseline assessment, participant details were sent to the randomisation centre (Telethon Kids Institute), where the study coordinator (who was not involved in the administration or coding of assessments) randomly assigned (1:1 via computer algorithm) participants to either iBASIS-VIPP or TAU groups. Randomisation was by minimisation, stratified by site (Perth, Melbourne), infant sex (male, female), number of SACS-R risk behaviours (3, 4, 5 key items endorsed) and age band at recruitment (9-11 months, 12-14 months, corrected for prematurity), with assignment determined by a 'biased coin' of probability 0.7. Research staff conducting baseline and endpoint assessments were independent of clinical teams conducting the iBASIS-VIPP therapy, housed in separate buildings and unaware of treatment allocations and randomization methods. Given the parent-mediated nature of the intervention, group allocation could not be masked from families.

Procedures

Intervention

The manualised iBASIS-VIPP intervention involves up to 12 individual sessions (one introductory, six core, and up to five booster sessions) delivered in family homes by a therapist (here, speech and language therapist or psychologist) at fortnightly intervals over a 5-month period. In this study, three booster sessions were offered to all participants, for 10 sessions in total. The primary caregiver is asked to participate in all therapy sessions, during which parent and infant are videotaped engaging in everyday interactions, which form the basis of a video feedback discussion. Core methods include: (a) a focus on the communicative aspects of each parent-infant dyad; (b) viewing videotaped interaction excerpts providing positive examples of a sensitive interaction style; and (c) a trained therapist framing observations, assisting with self-reflection, and focusing on behavioural change. Parents were asked to undertake 15-minutes daily home practice in interacting with their infant using the newly learned skills. Two therapists at each site were trained to protocol fidelity by experts from the iBASIS and VIPP development teams. (See Supplementary Material for the intervention manual.)

All intervention sessions were videotaped. Therapist fidelity to the manual was assessed on 40 sessions (35 participants) randomly selected to balance timepoint and therapist. These were double-coded with a 21-item pass/fail measure of therapeutic skills and specific iBASIS-VIPP strategy by the originating UK iBASIS-VIPP team (CT, JG, VS). The mean

fidelity score was 20·5 passed items/session (range=18–21); only one of 40 sessions was below the 80% fidelity threshold. (See Supplementary Material for the fidelity measure.)

Infants receiving community therapy were not excluded. Parents in both treatment groups completed a weekly diary, recording all contact with health professionals between baseline and endpoint assessments.

Measures

Baseline and endpoint assessments took place in a research setting at the Telethon Kids Institute (Perth) and La Trobe University (Melbourne).

Screening identification

The SACS-R is administered by health professionals to identify infants/children showing early behavioural signs of ASD.[19] The SACS-R 12-month version checklist includes five key ASD risk behaviours: spontaneous eye contact, proto-declarative pointing, social gestures, imitation, and response to name. Infants considered at increased likelihood for ASD demonstrate a pattern of 'atypical' behaviour on at least three of these key items.[19,20] When administered by Maternal and Child Health nurses, the original SACS tool has high positive predictive value (>70%) at 12 months for later ASD diagnosis.[19] The original SACS was recently revised,[19] and the revised tool (SACS-R, as described above) was used in the current study. At the Melbourne site, Maternal and Child Health nurses within the community completed the SACS-R assessments as part of their routine practice, following training led by JB. At the Perth site, a trained Speech and Language Therapist (MR) administered the SACS-R via a phone interview with the primary caregiver. (See Supplementary Material for further information.)

Primary outcome

The *Autism Observation Scale for Infants* (AOSI) is a measure of early behavioural signs associated with ASD,[20] including response to name, social reciprocity and imitation. An assessor trained to fidelity codes observed behaviours as 0, 1, 2 or 3, with a higher score indicating a greater level of ASD-like atypicality. The Total Score is the sum of all items (1 through 18), with a range of 0-38. A Total Score of ≥ 9 at 12 months is predictive of an ASD diagnosis at age 3 years.[20] The AOSI Total Score has strong inter-rater reliability (≥ .92).[21] Studies of infant siblings of children with ASD have reported higher AOSI Total scores for 8-

and 14-month-old infants who later receive an ASD diagnosis compared to infants who do not,[22] but there are no data currently available for clinically-indicated infants. The AOSI was administered by one research assistant at each site, blind to participant group. Each assessment was filmed, and a random subset (20%) of AOSI recordings (baseline and endpoint) was coded by the trained research assistant at the other study site. This double-coding showed good inter-rater agreement on the AOSI Total Score; single measures intraclass correlations (ICC), two-way mixed effects model for absolute agreement =.78.

Blinded secondary outcome

The *Manchester Assessment of Caregiver-Infant interaction (MACI)*[23] is a global rating measure of the quality of parent-infant interactions. It is blind video-coded from a 6-minute play session between parent/caregiver and infant. The MACI was specifically designed for the ASD prodrome, and MACI measures of infant behaviour at 14 months have been found to be associated with ASD diagnosis at 3 years.[11] Four scales showing the greatest predictive validity[11] were pre-defined as the scales of interest for the current study: Caregiver Sensitive Responsiveness, Caregiver Nondirectiveness, Infant Attentiveness, and Infant Positive Affect. Each scale involves rating on a 7-point scale (range=1-7). Within-trial independent double coding of 15% of recordings (baseline and endpoint assessments) – by independent UK trainer MWW – showed good to high inter-rater agreement; single measures ICC, two-way mixed effects model range .67-.80.

The Mullen Scales of Early Learning (MSEL)[24] is a standardised developmental assessment of early motor and cognitive development from 0-68 months. We pre-defined the subscales of interest for this study as Receptive Language, Expressive Language, Visual Reception, and Fine Motor. T-scores for each MSEL subscale are provided, but raw scores were used in the presence of floor effects, as is common for children with ASD.[25]

Unblinded (parent-report) secondary outcomes

The *Vineland Adaptive Behavior Scales–2nd edition (VABS-2)*[26] is a measure of functional skills relevant for everyday living. We predefined the subscales of interest as Communication and Socialization, using standard scores (M=100, SD=15).

The *Words and Gestures version of the MacArthur-Bates Communicative Development Inventory (MCDI)*[27] is a measure of early vocabulary. Caregivers endorse the number of

words the child understands or both understands and says among an inventory spanning different semantic categories (maximum=396 words). The outcomes of interest were an Expressive Vocabulary Count (total of all items endorsed 'understands and says'), a Receptive Vocabulary Count (combined total of all items endorsed 'understands' and 'understands and says') and a Total Gestures score.

The *Parenting Sense of Competence (PSOC) scale*[28] is a measure of the caregiver's own sense of parenting efficacy. Each item is rated on a 6-point scale (range=1-6). Endorsed PSOC items are summed to yield three subscales: Satisfaction (range=6-36), Efficacy (range=5-30) and Interest (range=3-18).

Statistical analyses

We report full pre-planned analyses, which were written and registered prior to linkage of the treatment allocation variable to outcome data and treatment unblinding. The target number of participants was n=132, which would provide 85% power to detect a 0.52 SD difference (α=·05) in change in AOSI Total Score (independent samples-t-test). Slower than anticipated recruitment at the Melbourne site led to a smaller final sample of n=103, which, from post-hoc power calculation, provides 85% power to detect a 0.60 SD difference in AOSI Total Score change.

Data preparation was undertaken with treatment assignment masked, and analyses were performed with uninformative labels for the treatment groups. A visual inspection was conducted of each outcome measure distribution. Floor effects were observed for MSEL T-scores; hence, raw scores were analysed with adjustment for chronological age (weeks) and prematurity (weeks), calculated as 40 minus gestational age (weeks).

All analyses were conducted as intention-to-treat with effect estimates generated from an ANCOVA regression model. Effect estimates (95% confidence interval) are reported as the between-groups comparison of a given test measure at endpoint, adjusted for pre-randomisation baseline score, study site, infant sex, number of SACS-R key items endorsed and chronological age (weeks). Statistical significance was denoted as α <·05. Residuals from regression models were visually inspected to ensure modelling assumptions were satisfactorily met. These assumptions were not met for the MCDI Expressive Vocabulary and PSOC Interest subscales, therefore, a negative binomial model (reported as an incidence rate

ratio (IRR) with 95% confidence interval) and a tobit regression model were used, respectively. As is best practice, a forest plot was also generated to present the effect size (Cohen's d) of the unadjusted treatment effect (between-groups comparison at endpoint). Change scores (difference between baseline and endpoint) and between group differences in these change scores are presented as Supplementary Material, but no analyses were undertaken on these post-hoc descriptive statistics. (For the full statistical analysis plan, see Supplementary Material.)

Role of the funding source

The funders of the study had no role in the study design, data collection, analysis or interpretation, or writing of the report.

Results

Figure 1 presents the trial CONSORT diagram. Between June 9th 2016 and 30th March 2018, 104 families (Perth, n=66; Melbourne, n=38) were enrolled and randomised. One infant randomised to the iBASIS-VIPP group was excluded post-randomisation, due to not meeting the English language requirement. This left a total sample size of 103 infants/families; n=50 for the iBASIS-VIPP group and n=53 for the TAU group. The two groups had similar characteristics at baseline (Table 1). Six/104 (6%) infants were lost to the study from baseline to endpoint, 5 in the TAU group and 1 in the iBASIS-VIPP group.

Infant baseline characteristics

There was a relatively even split of infants presenting with 3 (n=32, 31%), 4 (n=34, 33%) and 5 (n=37, 36%) key ASD 'risk' behaviours on the SACS-R. Over half of the sample (59/103, 57%) scored ≥ 9 on the AOSI at baseline. Approximately 20% (20/103) of the sample were siblings of children with ASD, and there was no difference between these infants and the remainder of the sample on baseline characteristics. (For further information on participant characteristics at baseline assessment, see Supplementary Material).

Intervention dosage and compliance

Compliance by the iBASIS-VIPP group for the iBASIS-VIPP intervention was high: all 50 participants completed the pre-specified minimum sessions (introductory and six core) and at least one booster session. No adverse effects from intervention were reported.

Treatment as Usual

A greater proportion of infants in the TAU group (59%) received community therapy compared to the iBASIS-VIPP group (35%), particularly Psychology and Speech and Language Therapy (TAU=50%; iBASIS-VIPP=12·2%). Mann-Whitney tests indicated that, compared to the iBASIS-VIPP group, the TAU group had significantly more Psychology and Speech and Language Therapy sessions, U = 738.5, Z=3.55, p<.01, and more minutes of this type of therapy, U=729.5, Z=3.50, p<.01. The receipt of these therapies was particularly unbalanced across treatment groups at the Perth (TAU=63%; iBASIS-VIPP=3%), but not at the Melbourne (TAU=21%; iBASIS-VIPP=29%) site. (See Supplementary Material for an analysis of community therapy received.)

Outcome estimation

Figure 2 presents the effect size (Cohen's d) of the unadjusted treatment effect. Table 2 shows mean baseline, endpoint, and difference scores for all outcomes by treatment group, including the adjusted mean difference between groups at endpoint. For the primary outcome (AOSI), adjusted analysis indicated a difference between groups at endpoint of -0·74 (-2·47,0·98) suggesting no statistically significant treatment effect. A post-hoc examination of the primary outcome by site (see Supplementary Material) showed a larger mean change from baseline to endpoint (favouring iBASIS-VIPP) at the Melbourne site, unadjusted mean difference -2·70 (-5·44,0·04), in comparison to the Perth site, unadjusted mean difference -0·23 (-2·71,2·25).

There was no observable treatment effect for three of the four MACI scales (Infant Attentiveness, Caregiver Sensitive Responding and Caregiver Non-directiveness), but the iBASIS-VIPP group had significantly lower scores on Infant Positive Affect at endpoint than the TAU group, -0·69 (-1·28,-0·11). An effect favouring the iBASIS-VIPP group was observed for the MSEL Receptive Language subscale, 1·30 (-0·48,3·08), but the confidence intervals overlapped with zero indicating a statistically non-significant treatment effect.

Adjusted analysis of unblinded parent-report variables showed a statistically significant positive treatment effect on the VABS Communication subscale, 6·43 (1·06,11·81), the MCDI Receptive Vocabulary subscale, 37·17 (10·59,63·75), and the MCDI Expressive Vocabulary subscale, (IRR) 2·31 (1·22,4·33). Effects favouring the iBASIS-VIPP group

were also observed for the VABS Socialization scale, 3·72 (-1·30,8·74), and the MCDI Gestures subscale, 3·22 (-0·60,7·04), but these comparisons were not significant. There was no treatment effect for any of the PSOC subscales.

Discussion

This was the largest RCT to date of a pre-emptive intervention for clinically-indicated infants showing early behavioural signs of ASD. The pre-specified analyses revealed no statistically significant treatment effect on the measures of early ASD symptoms and the quality of parent-child interactions. Significant treatment effects of iBASIS-VIPP were observed on a range of parent-reported expressive and receptive language outcomes, including vocabulary count and functional language use. These provide the first indications from a well-powered RCT that a parent-mediated intervention may have effects on developmental outcomes for infants showing early signs of ASD.

An intriguing aspect of the study findings is that group differences were observed in parent-reported measures of infant development, but not in measures assessing the hypothesised treatment mechanism (parent sensitive responding or non-directiveness during infant interactions). There are several possible explanations for this pattern of findings. First, the lack of treatment effect for the MACI Caregiver Sensitive Responding and Caregiver Non-directiveness measures may reflect the similar degree of improvement observed for both the iBASIS-VIPP and TAU groups. A substantial proportion of participants in the TAU group received community therapy, particularly at the Perth site. TAU at the Perth site predominately occurred through one service (Child Development Service), and most often comprised individual intervention sessions. A review of the intervention manuals for this service showed similarities between its therapy principles and the hypothesised treatment mechanism of the iBASIS-VIPP – enhancing parental awareness of infant communication signals, and practicing strategies for increasing parental responsiveness. (See Supplementary Material.) The similarities in treatment targets may explain the comparable levels of improvement by the two treatment groups on the MACI caregiver measures.

Second, it is possible that our method for assessing parent behaviour during infant interactions – a video recording of an example interaction within the laboratory environment

at baseline and treatment endpoint assessments – may not reflect these behaviours as they are experienced on a day-to-day basis, including how much time the parent actually spends interacting with their infant. It is also possible that the intervention altered parenting behaviours that were more specific than could be measured by two global rating scales (i.e. MACI sensitive responsiveness and non-directiveness). However, we note that previous studies have observed a treatment effect on parental non-directiveness as measured by the MACI,[17] suggesting that this subscale is sensitive to change.

A third explanation is the possible presence of bias in the parent-reported outcomes. Given the parent-mediated nature of the intervention, parents were not blinded to the treatment condition, which raises the possibility that the treatment effects identified by parent-report measures of infant communication ability may be due to their knowledge of the intervention, and an improved ability to recognise infant communication signs. While the treatment effect for the blind-administered MSEL Receptive Language subscale was in the same direction as those from the parent-reported assessments, albeit with confidence intervals crossing the null, there was no such effect for the MSEL Expressive Language subscale. Based on this pattern of findings, it is possible that a parent report bias may have influenced the treatment effects observed.

The only previous RCT of iBASIS-VIPP[16] found a more pronounced treatment effect on autistic-behaviours (AOSI) at treatment endpoint (d= 0·50, 95%CI=-0·15 to 1·08) compared to those observed in the current study (d=0.22, 95%CI=-0.19, 0.63). Two key differences in study designs may have contributed to these findings. First, in contrast to the current Australian study, the previous study was conducted in the UK where the TAU group had minimal access to community therapy. While it was unethical for the current study to restrict access to community interventions, this regional difference in health care provision led to an imbalance between studies in the amount of intervention received by the TAU groups. Second, the two studies differed in terms of their infant selection strategies; in the current study, infants were recruited on the basis of early behavioural risk signs of ASD, whereas infants in the previous study were recruited on the sole basis of having a sibling with ASD, and the majority did not show ASD risk behaviours. These differences in selection strategies are evident in the baseline characteristics of the two samples, whereby infants in the current study had equivalent or lower raw scores on the MSEL Receptive and Expressive Language subscales, and equivalent AOSI Total scores, despite being an average of 5 months older (see

Supplementary Material). The comparably lower communicative abilities and persisting ASD signs observed in the current sample may be associated with different treatment responses, and this will be critical to monitor in the planned longer-term follow-up of this participant sample.

An unexpected finding was the greater improvement in infant positive affect for the TAU group compared to the iBASIS-VIPP group. This measure was coded from parent-infant interaction videos and assesses the level of infant enjoyment during these interactions. Although both treatment groups had increased scores on this measure from baseline to endpoint, it appears the effect was driven by a particularly large increase in the TAU group at the Melbourne site (Table 2). Given the stratification of treatment groups on key infant variables, the inter-rater reliability achieved on MACI coding, and the minimal community therapy received by the Melbourne TAU group, there is no obvious explanation for the greater observed improvement among these infants. Examination of the longitudinal trajectory of this outcome across groups and sites will provide important data to further understanding of this finding.

The findings from the study are strengthened by the RCT design, which included balancing key infant variables across groups, the blinding of the assessors conducting follow-up assessments and coding assessment videos, and the pre-specified analysis plan. A limitation of the study design was that we did not include an activity for the TAU group that served as a control for the attention paid to parents in the iBASIS-VIPP group. However, we note that approximately 60% of the TAU group received some form of community intervention, and around half of the TAU group received speech and language therapy, which are activities that will also have increased the attention of parents to the development of their infant. The study design also incorporated different recruitment protocols between sites. The SACS-R measures early ASD risk behaviours and was designed to be a direct observation assessment. The Melbourne site employed this assessment procedure, but there were logistical reasons that prevented this at the Perth site, and SACS-R screening occurred via a telephone interview. However, we believe that these different procedures had minimal influence on the internal validity of the study given that the treatment groups were stratified by both site and the number of SACS-R ‘risk markers’, and no differences between treatment groups were observed at baseline in the primary outcome measure, AOSI, a direct observation measure of early ASD risk behaviours. (See Supplementary Material.)

The current study findings represent an important step in increasing our understanding of how to provide optimal clinical care to infants presenting with early emerging signs of ASD. Currently, it is common for clinical systems to adopt a 'wait and see' approach in terms of ASD concerns,[29] whereby infants are monitored until behavioural measurement and diagnostic formulation are considered to have greater stability, typically no earlier than 2 years of age. In the current study, infants showed early ASD risk behaviours at a mean age of 12 months, and responded to a moderate-intensity intervention as shown by significant improvements in parent-reported developmental outcomes. While the strength of these findings do not yet warrant a change in healthcare policy, a critical next step for this research is to determine the endurance of treatment effects, particularly into the third and fourth years of life, when developmental abilities provide greater predictive power for outcomes in middle childhood. These data will help determine whether this clinical model represents a cost-effective approach to improving long-term developmental abilities in children with neurodevelopmental differences.[30]

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Contributors:

AW, KH, JG, JW designed the study, and KV coordinated the trial. JB designed and implemented the SACS-R training for recruitment into the study. MG, MR, CR and SW delivered the treatment under supervision of JD, VS, and CT. MB, LC, SD and SP undertook the research assessments. SP, LC, SD, SP and KV undertook data preparation, and MC conducted the analyses. CB and AD performed the coding of parent-child interaction videos under the direction of MWW. All authors contributed to data interpretation. AW, KH, KV, JG and JW led the writing of the report with review from all authors.

Declaration of interests

We declare no competing interests.

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Research in context

Evidence before this study

There have been repeated theoretical arguments that pre-diagnostic intervention for ASD very early in its prodrome may provide enhanced opportunity for interventions to exert developmental effects, but there remains relatively little evidence-base. Targeting the ASD prodrome can be 'selective', based on familial risk status, or 'indicated', based on early emerging ASD signs in infants in the community We searched PubMed (November 8th 2018) using the terms "autism, "autism spectrum disorder", "intervention", "very early intervention", "infant", "prodrom*", "randomised controlled trial" and "clinical trial". Our search did not have any language or date restrictions, and we also searched the reference lists of selected articles for other relevant publications. A recent systematic review identified four RCTs for infants at high risk of ASD prior to 18 months of age, and a fifth RCT has been published subsequently. These trials are characterised by small sample sizes, unclear concealment of treatment group allocation, and lack of clarity about hypothesised treatment mechanisms. One treatment model (iBASIS-VIPP) to date has shown evidence of an enduring and positive impact on ASD symptoms over early development, in a trial based on a selective prevention strategy, where a majority of infants did not develop atypically. The current study is the first study to test the efficacy of iBASIS-VIPP using a clinically-indicated strategy, with infants identified in the community as showing early emerging signs of ASD.

Added value of the study

The findings suggest that iBASIS-VIPP may not significantly reduce early ASD symptoms immediately following treatment. However, this intervention does significantly improve parent-reported language and communication outcomes compared to standard care. This is the first study to provide evidence that a parent-mediated intervention for infants showing early symptoms of ASD can improve parent-reported developmental outcomes immediately following treatment among a community-referred sample of infants showing emerging signs of ASD.

Implications of all the available evidence

Future research that examines whether these developmental improvements endure over time will help determine the long-term efficacy and cost effectiveness of a novel clinical model that applies pre-emptive intervention to infants showing early behavioural risk signs of ASD.

Table 1. Participant characteristics at baseline by treatment group.

	Treatment as Usual (n = 53)	iBASIS-VIPP (n = 50)
Family characteristics		
Annual household income ≥$50,000[a]	44 (88%)	40 (95%)
Mother completed university degree	29 (55%)	33 (63%)
Infant living with both biological parents	52 (98%)	49 (98%)
Infant characteristics		
Male	32 (60%)	38 (76%)
Older sibling with ASD	10 (19%)	10 (20%)
Chronological age in months	12.38 (2.02)	12.40 (1.93)
Adjusted age in months	12.31 (2.00)	12.12 (1.98)

Data are n (%) or mean (SD) for available cases

[a]Household income data were not reported for 3 cases in the Treatment as Usual Group (total n for this variable, n=50), and 8 cases in the iBASIS-VIPP group (total n for this variable=42).

Table 2. Mean (SD) baseline, endpoint and difference scores, and beta co-efficient (95%CI) data for each assessment by treatment group.

	Perth		Melbourne		Total		
	iBASIS-VIPP	TAU	iBASIS-VIPP	TAU	iBASIS-VIPP	TAU	Treatment effect estimate[a]
AOSI Total							
Baseline	9·00 (3·70)	9·47 (4·16)	11·00 (4·01)	8·89 (5·21)	9·72 (3·90)	9·26 (4·52)	
	n = 32	n = 34	n = 18	n = 19	n = 50	n = 53	
Endpoint	8·84 (4·13)	9·38 (5·27)	9·65 (4·76)	9·86 (4·70)	9·12 (4·33)	9·52 (5·05)	
	n = 31	n = 32	n = 17	n = 14	n = 48	n = 46	
Difference	-0·32 (4·98)	-0·09 (4·85)	-1·06 (3·96)	1·64 (3·50)	-0·58 (4·62)	0·43 (4·51)	-0·74 (-2·47, 0·98)
	n = 31	n = 32	n = 17	n = 14	n = 48	n = 46	
MACI Caregiver Nondirectiveness							
Baseline	4·25 (1·55)	4·24 (1·46)	4·17 (1·89)	3·84 (1·61)	4·22 (1·66)	4·09 (1·51)	
	n = 32	n = 34	n = 18	n = 19	n = 50	n = 53	
Endpoint	4·88 (1·26)	4·58 (1·39)	4·76 (1·09)	4·93 (1·49)	4·84 (1·20)	4·68 (1·42)	
	n = 32	n = 33	n = 17	n = 14	n = 49	n = 47	
Difference	0·62 (1·64)	0·33 (1·31)	0·41 (1·62)	0·57 (1·99)	0·55 (1·62)	0·40 (1·53)	0·16 (-0·33, 0·65)
	n = 32	n = 33	n = 17	n = 14	n = 49	n = 47	
MACI Caregiver Sensitive Responding							
Baseline	4·38 (1·58)	4·62 (1·30)	4·11 (1·37)	3·68 (1·49)	4·28 (1·50)	4·28 (1·43)	
	n = 32	n = 34	n = 18	n = 19	n = 50	n = 53	
Endpoint	5·12 (1·01)	4·85 (1·03)	4·88 (0·70)	4·71 (1·14)	5·04 (0·91)	4·81 (1·06)	
	n = 32	n = 33	n = 17	n = 14	n = 49	n = 47	
Difference	0·75 (1·74)	0·24 (1·20)	0·65 (1·22)	0·57 (2·03)	0·71 (1·57)	0·34 (1·48)	0·24 (-0·15, 0·63)
	n = 32	n = 33	n = 17	n = 14	n = 49	n = 47	
MACI Infant Positive Affect							
Baseline	3·34 (1·47)	3·79 (1·59)	3·28 (1·64)	3·00 (1·86)	3·32 (1·52)	3·51 (1·72)	
	n = 32	n = 34	n = 18	n = 19	n = 50	n = 53	
Endpoint	3·75 (1·50)	4·21 (1·19)	3·59 (1·66)	4·86 (1·56)	3·69 (1·54)	4·40 (1·33)	
	n = 32	n = 33	n = 17	n = 14	n = 49	n = 47	
Difference	0·41 (1·76)	0·42 (1·90)	0·18 (1·59)	1·36 (2·53)	0·33 (1·69)	0·70 (2·13)	-0·69 (-1·27, -0·10)

	n = 32	n = 33	n = 17	n =14	n = 49	n = 47	
MACI Infant Attentiveness							
Baseline	3·94 (1·27)	4·09 (1·29)	3·72 (1·13)	3·95 (1·51)	3·86 (1·21)	4·04 (1·36)	
	n = 32	n = 34	n = 18	n = 19	n = 50	n = 53	
Endpoint	4·50 (1·08)	4·70 (1·10)	4·29 (1·31)	4·71 (0·99)	4·43 (1·15)	4·70 (1·06)	
	n = 32	n = 33	n = 17	n = 14	n = 49	n = 47	
Difference	0·56 (1·29)	0·64 (1·39)	0·41 (1·42)	0·64 (1·82)	0·51 (1·32)	0·64 (1·51)	-0·19 (-0·63, 0·25)
	n = 32	n = 33	n = 17	n = 14	n = 49	n = 47	
MSEL Receptive Language							
Baseline	9·59 (2·35)	10·38 (2·66)	12·94 (2·48)	12·11 (3·00)	10·80 (2·88)	11·00 (2·88)	
	n = 32	n = 34	n = 18	n = 19	n = 50	n = 53	
Endpoint	15·38 (4·43)	15·03 (3·79)	19·29 (6·07)	16·13 (5·83)	16·73 (5·34)	15·38 (4·49)	
	n = 32	n = 33	n = 17	n = 15	n = 49	n = 48	
Difference	5·78 (3·76)	4·61 (3·66)	6·18 (4·95)	4·40 (4·36)	5·92 (4·16)	4·54 (3·84)	
	n = 32	n =33	n = 17	n = 15	n = 49	n = 48	1·30 (-0·48, 3·08)
MSEL Expressive Language							
Baseline	9·31 (1·93)	9·12 (2·09)	10·61 (2·55)	10·32 (3·07)	9·78 (2·23)	9·55 (2·52)	
	n = 32	n = 34	n = 18	n =	n = 50	n = 53	
Endpoint	14·78 (3·18)	15·03 (3·25)	16·41 (3·64)	14·80 (4·30)	15·35 (3·40)	14·96 (3·56)	
	n = 32	n = 33	n = 17	n =	n = 49	n = 48	
Difference	5·47 (2·54)	5·94 (3·05)	5·65 (3·30)	5·13 (3·46)	5·53 (2·79)	5·69 (3·17)	0·54 (-0·73, 1·80)
	n = 32	n = 33	n = 17	n =	n = 49	n = 48	
MSEL Visual Reception							
Baseline	14·12 (2·38)	14·15 (2·34)	17·89 (2·78)	17·39 (2·30)	15·48 (3·10)	15·27 (2·78)	
	n = 32	n = 34	n = 18	n = 18	n = 50	n = 52	
Endpoint	19·84 (2·68)	19·70 (3·39)	23·06 (2·61)	21·79 (2·89)	20·96 (3·05)	20·32 (3·36)	
	n = 32	n = 33	n = 17	n = 14	n = 49	n = 47	
Difference	5·72 (2·32)	5·52 (2·75)	4·94 (2·84)	4·50 (2·31)	5·45 (2·51)	5·21 (2·65)	0·31 (-0·77, 1·40)
	n = 32	n = 33	n = 17	n = 14	n = 49	n = 47	
MSEL Fine Motor							
Baseline	13·47 (3·01)	13·47 (2·69)	16·67 (2·03)	15·63 (2·61)	14·62 (3·09)	14·25 (2·83)	

	n = 32	n = 34	n = 18	n = 19	n = 50	n = 53	
Endpoint	18·78 (1·90)	18·61 (1·95)	21·53 (1·55)	19·67 (3·70)	19·73 (2·21)	18·94 (2·63)	
	n = 32	n = 33	n = 17	n = 15	n = 49	n = 48	
Difference	5·31 (2·51)	5·15 (2·85)	4·88 (2·96)	4·27 (1·87)	5·16 (2·65)	4·88 (2·60)	0·55 (-0·32, 1·41)
	n = 32	n = 33	n = 17	n = 15	n = 49	n = 48	
VABS Communication							
Baseline	77·68 (15·43)	81·26 (13·50)	74·11 (14·69)	78·12 (15·25)	76·37 (15·11)	80·05 (14·11)	
	n = 31	n = 27	n = 18	n = 17	n = 49	n = 44	
Endpoint	91·07 (15·41)	90·79 (14·61)	89·12 (14·84)	80·50 (17·33)	90·35 (15·07)	87·36 (16·12)	
	n = 29	n = 28	n = 17	n = 14	n = 46	n = 42	
Difference	12·59 (14·16)	8·12 (13·18)	15·35 (19·02)	5·29 (14·32)	13·61 (15·97)	7·10 (13·48)	6·43 (1·06, 11·81)
	n = 29	n = 25	n = 17	n = 14	n = 46	n = 39	
VABS Socialisation							
Baseline	87·59 (10·98)	90·93 (12·32)	82·39 (12·42)	91·65 (11·74)	85·60 (11·70)	91·20 (11·96)	
	n = 29	n = 27	n = 18	n = 17	n = 47	n = 44	
Endpoint	94·41 (13·62)	94·58 (12·29)	91·00 (9·43)	89·46 (11·98)	93·15 (12·24)	92·87 (12·27)	
	n = 29	n = 26	n = 17	n = 13	n = 46	n = 39	
Difference	7·30 (11·29)	4·25 (11·83)	9·06 (13·29)	0·92 (9·22)	7·98 (11·98)	3·08 (10·97)	3·28 (-1·43, 7·99)
	n = 27	n = 24	n = 17	n = 13	n = 44	n = 37	
MCDI Receptive Language							
Baseline	22·09 (31·68)	25·74 (35·85)	34·78 (36·56)	17·76 (16·69)	26·66 (33·71)	22·66 (29·94)	
	n = 32	n = 27	n = 18	n = 17	n = 50	n = 44	
Endpoint	119·97 (84·94)	100·10 (58·92)	133·18 (87·66)	72·36 (46·74)	124·85 (85·22)	91·07 (56·24)	
	n = 29	n = 29	n = 17	n = 14	n = 46	n = 43	
Difference	97·62 (70·67)	65·60 (48·14)	101·00 (77·81)	56·57 (45·66)	98·87 (72·55)	62·36 (46·86)	
	n = 29	n = 25	n = 17	n = 14	n = 46	n = 39	37·17 (10·59, 63·75)
MCDI Expressive Language							
Baseline	0·62 (1·13)	0·89 (1·83)	2·33 (3·22)	1·47 (2·37)	1·24 (2·25)	1·11 (2·05)	
	n = 32	n = 27	n = 18	n = 17	n = 50	n = 44	
Endpoint	24·48 (40·24)	19·86 (32·69)	31·88 (48·81)	9·93 (9·26)	27·22 (43·22)	16·63 (27·59)	
	n = 29	n = 29	n = 17	n = 14	n = 46	n = 43	

Difference	23·86 (39·98) n = 29	9·08 (9·74) n = 25	29·53 (46·87) n = 17	9·00 (9·30) n = 14	25·96 (42·23) n = 46	9·05 (9·46) n = 39	2·31 (1·22,4·33)
MCDI Gestures							
Baseline	10·24 (5·20) n = 29	9·92 (6·46) n = 25	12·47 (6·76) n = 17	11·94 (5·81) n = 17	11·07 (5·86) n = 46	10·74 (6·22) n = 42	
Endpoint	30·72 (10·49) n = 29	28·66 (8·12) n = 29	30·62 (11·88) n = 16	25·43 (10·69) n = 14	30·69 (10·87) n = 45	(9·03) n = 43	
Difference	21·00 (9·20) n = 26	18·57 (7·86) n = 23	17·93 (9·06) n = 15	14·50 (8·85) n = 14	19·88 (9·15) n = 41	17·03 (8·36) n = 37	3·22 (-0·60, 7·04)
PSOC Interest							
Baseline	5·13 (0·85) n =	5·05 (0·76) n =	5·10 (0·70) n =	4·82 (0·90) n =	5·12 (0·80) n = 48	4·96 (0·81) n = 44	
Endpoint	4·98 (0·85) n =	5·30 (0·83) n =	5·19 (0·77) n =	4·71 (0·80) n =	5·05 (0·82) n = 47	5·10 (0·86) n = 42	
Difference	-0·15 (0·93) n =	0·11 (0·64) n =	0·07 (0·55) n =	0·05 (0·68) n =	-0·08 (0·83) n = 46	0·09 (0·65) n = 38	-0·23 (-0·62, 0·16)
PSOC Satisfaction							
Baseline	4·04 (0·76) n = 31	3·90 (0·92) n = 27	3·77 (0·86) n = 17	3·80 (0·95) n = 17	3·94 (0·80) n = 48	3·86 (0·92) n = 44	
Endpoint	4·07 (0·77) n = 31	3·78 (1·08) n = 28	3·70 (0·55) n = 16	3·58 (1·22) n = 14	3·94 (0·72) n = 47	3·71 (1·12) n = 42	
Difference	0·03 (0·61) n = 31	-0·19 (0·98) n =24	-0·06 (0·76) n = 15	-0·22 (0·70) n = 14	0·00 (0·66) n = 46	-0·20 (0·88) n = 38	0·21 (-0·09, 0·52)
PSOC Efficacy							
Baseline	4·27 (0·83) n = 31	4·33 (0·85) n = 27	3·82 (0·61) n = 17	4·25 (0·81) n = 17	4·11 (0·78) n = 48	4·30 (0·83) n = 44	
Endpoint	4·26 (0·88) n = 31	4·48 (0·81) n = 28	4·33 (0·46) n = 16	4·50 (0·96) n = 14	4·29 (0·75) n = 47	4·49 (0·85) n = 42	
Difference	-0·01 (0·91) n = 31	0·09 (0·66) n = 24	0·59 (0·57) n = 15	0·29 (0·66) n = 14	0·19 (0·86) n = 46	0·16 (0·66) n = 38	-0·08 (-0·38, 0·22)

Baseline and endpoint data are presented as means (SD) and number of cases available. Median and interquartile ranges for the PSOC Interest subscale and MCDI Expressive Language subscales are presented in the Supplementary Material.

[a]The treatment effect estimate is the beta coefficient of the ANCOVA analysis (linear regression, except for the PSOC Interest subscale where tobit regression was used) presented as the adjusted mean difference between groups at the endpoint (95%CI) for the Total sample. Incidence rate ratios (95%CI) are presented for MCDI Expressive Language.

AOSI: Autism Observation Scale for Infants; MACI: Manchester Assessment of Caregiver-Infant interaction; MSEL: Mullen Scales of Early Learning. MCDI: MacArthur-Bates Communicative Development Inventory, VABS: Vineland Adaptive Behavior Scales. A positive change score indicates skill improvement, except for AOSI Total score for which a negative change score reflects symptom improvement.

Figure captions

Figure 1. **CONSORT diagram of the trial.**

Figure 2. **Unadjusted effects of treatment group on the blinded primary (AOSI) and secondary (MACI, MSEL), as well as the unblinded parent-report outcomes (VABS, MCDI).**

Mean Cohen's d effect sizes (95% CI) are reported, with positive treatment effects of the iBASIS-VIPP compared to TAU shown as being to the right of the vertical dotted line. MACI=Manchester Assessment of Caregiver-Infant interaction; AOSI=Autism Observation Schedule for Infants; MSEL = Mullen Scales of Early Learning. MCDI = MacArthur-Bates Communicative Development Inventory; VABS=Vineland Adaptive Behavior Scales.

Data Sharing

Will individual participant data be available (including data dictionaries)?	Yes
What data in particular will be shared?	Individual participant data that underlie the results reported in this article, after de-identification (text, tables, figures, and Supplementary Material)
What other documents will be available?	Study protocol, statistical analysis plan
When will data be available (start and end dates)?	Immediately following publication; no end date
With whom?	Investigators whose proposed use of the data has been approved by an independent ethical review committee identified for this purpose
For what types of analyses?	For replication studies and individual participant data meta-analysis
By what mechanism will data be made available?	Proposals should be directed to Andrew.Whitehouse@telethonkids.org.au; to gain access, data requestors will need to sign a data access agreement