Parent-mediated Intervention in Infants with an Elevated Likelihood for Autism Reduces Dwell Time during a Gaze Following Task

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Data availability statement: Data are available upon request to the authors.

Funding statement: The research was supported by awards from the BASIS funding consortium led by Autistica (No: 7267), The Waterloo Foundation and Autism Speaks US; and from the UK Medical Research Council (MR/T003057/1) and the NIHR Biomedical Research Centre for Mental Health at the South London and Maudsley NHS Foundation Trust and King's College London. JG and AP are National Institute for Health Research (NIHR) Senior Investigators (NIHR NF-SI-0617-10168 and NF-SI-0617-10120 respectively). The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care.

Conflict of Interest Disclosure: Authors have no conflict of interest to declare.

Ethics approval statement: The study was approved by NHS Health Research Authority (NHS RES London REC 06/MRE02/73) and London Research Ethics Committee (Ref: 09/H0718/14).

Patient consent statement: parents provided written informed consent.

Clinical trial registration: This study is registered as ISRCTN 87373263 (https://www.isrctn.com/ISRCTN87373263); the trial protocol is available at **http://www.bbmh.manchester.ac.uk/ibasis/protocol/**. The current work is an exploratory secondary analysis of this trial dataset.

Abstract

Cognitive markers may in theory be more sensitive to the effects of intervention than overt behavioural measures. The current study tests the impact of the *Intervention with the British Autism Study of Infant Siblings – Video Interaction for Promoting Positive Parenting* (iBASIS-VIPP) on an eye-tracking measure of social attention: dwell time to the referred object in a Gaze Following Task. The original two-site, two-arm, assessor-blinded randomised controlled trial (RCT) of this intervention to increase parental awareness and responsiveness to their infant, was run with infants who have an elevated familial likelihood for autism (EL). Fifty-four EL infants (28 iBASIS-VIPP intervention, 26 no intervention) were enrolled, and the intervention took place between 9 months (baseline) and 15 months (endpoint), with gaze following behaviour measured at 15 months. Secondary intention to treat (ITT) analysis showed that the intervention was associated with significantly reduced dwell time to the referent of another person's gaze (beta=-.32, SE=.14, p=.03) at 15-month treatment endpoint. Given the established link between gaze following and language, the results are considered in the context of a previously-reported, non-significant and transient trend towards lower language scores at treatment endpoint (Green et al., 2015). Future intervention trials should aim to include experimental cognitive measures, alongside behavioural measures, to investigate mechanisms associated with intervention effects.

Lay summary

The current study tests the impact of the *Intervention with the British Autism Study of Infant Siblings - Video Interaction for Promoting Positive Parenting* (iBASIS-VIPP) on an eye-tracking measure of social attention: looking time to the object of another person's gaze. Infants who received the iBASIS-VIPP intervention spent *less* time looking to the object of

another person's gaze. This may be linked to the previously-reported trend of slightly lower language scores immediately after the intervention. These findings emphasise the need for future trials to include more fine-grained, experimental measures of social interaction, alongside broad assessment measures, to better understand how the intervention might change behaviour.

Introduction

There has been growing interest in identifying early neural and cognitive phenotypes for neurodevelopmental conditions such as autism, which may be evident before the onset of overt clinical symptoms (Dawson, Rieder & Johnson, 2023; Johnson et al., 2015; Visser et al., 2016). Neurocognitive markers are intermediate between genes and behaviour and are thus potentially closer to the underlying causal mechanism of atypicality, with clinically observable behaviours being a downstream consequence. Such neurocognitive markers may prove to be useful indicators of the effects of early pre-emptive intervention before they become evident in behaviour (Insel, 2007). They may also help indicate the underlying mechanisms of how interventions work, what they change, and how they lead to particular downstream behavioural outcomes; as well as helping to identify any potential harms or adverse events – all important considerations for ethical pre-emptive intervention (see Manzini et al., 2021).

The prospective study of infants with a family history of autism, henceforth infants with an elevated likelihood (EL), enables the study of early cognitive markers that are associated with emerging symptoms of autism (Jones et al., 2014; Elsabbagh, 2020; Wolff & Piven, 2020), as approximately ~20% of infants with an EL for autism go on to develop autism themselves (Ozonoff et al., 2011; Szatmari et al., 2016). Over the past decade, several

intervention studies have been carried out with infants with an EL for autism, measuring the long-term effects on social and non-social attention, language development and autism outcomes. While the clinical purpose of such early intervention is often to support development or longer-term outcomes, this randomised control trial methodology also represents a developmental experiment, which enables the causal effect of changing the early environment to be measured. As such, these studies can inform our understanding of developmental mechanisms.

To date, there have been several 'pre-emptive' interventions with infants who have an EL for autism. A recent meta-analysis (Hampton et al., 2022) suggested that across studies, while there were strong effects for changes in parent behaviours there was no evidence for direct alterations in child behaviours. However, Yoder, Stone and Edmunds (2021) found that increased intervention fidelity (i.e. parent use of intervention strategies) significantly mediated the impact on child outcomes. The Intervention with the British Autism Study of Infant Siblings - Video Interaction for Promoting Positive Parenting (iBASIS-VIPP), the intervention used in the current study, showed a significant *cumulative effect* (i.e. area under the curve) on child autism outcomes across the period of developmental follow-up (Green et al., 2017; Whitehouse et al., 2021), see Figure S1. This area under the curve method exploits repeated observations to increase power; it also acts to reflect the sustained impact of such an intervention over developmental time, important conceptually for developmental interventions. It is possible that, particularly early in development, fine-grained neurocognitive markers may be more sensitive to the earlier effects of intervention. For instance, in a parent-delivered infancy intervention, 'promoting first relationships', Jones et al. (2017) showed a pattern of neural responses to social stimuli in the 12-month-old EL sample which were more akin to typically developing infants.

The iBASIS-VIPP intervention, uses video-based feedback with parents of 9- to 14-month-old infants who have an elevated likelihood for autism (Green et al., 2015; Green et al., 2017). This intervention builds on developmental theory, which suggests that aspects of parent-child interaction, including the increased parental 'directiveness' found in the first year for infants with an EL for autism compared to low likelihood community controls (Papageorgopoulou et al., 2024; Wan et al., 2012; Wan et al., 2013), are potentially modifiable, allowing amplification of the beneficial effects of the infant's early environment. At treatment endpoint (Green et al., 2015), the iBASIS intervention was associated with reduced parental directiveness (i.e. reduced parental demands, intrusions and criticisms) and with non-significant trends towards reduced autism behavioural markers (ES = 0.50; CI -0.15 to 1.08). These effects were maintained at 3-year follow-up (Green et al., 2017) with a significant cumulative treatment effect (i.e. area under the curve) for increased child attentiveness and initiation during parent-child interaction, as well as fewer autism symptoms measured with an observational clinical assessment (Green et al., 2017; *Figure S1*, Supplementary Materials). A later trial of the same intervention in Australia with a cohort of community-identified infants between 9 and 15 months who showed early markers of autism (Whitehouse et al., 2021), similarly showed fewer autism symptoms in the intervention arm.

The prospective study of infant siblings has identified many early natural history 'precursors' to autism behaviours (Johnson, Gliga, Jones & Charman, 2015). Such early markers are measurable before the onset of overt clinically defining behaviours. Joint attention behaviours, for instance have been widely studied in infants with an elevated likelihood for autism, with behavioural studies showing reduced joint attention from towards the end of the first year of life (Presmanes et al., 2007). Eye-tracking studies enable a more fine-grained approach to studying the components of responding to joint attention, including gaze following and the distribution of attention to the referred-object compared to other parts

of the screen. Several studies in EL infants have shown that while there are no significant differences between EL and typical likelihood groups in the ability to correctly orient in response to another person's gaze cue, there are associations between reduced attention to the referent (i.e. less 'dwell time' to the gazed-at object) and later autism behavioural outcome (Bedford et al., 2012; Parsons et al., 2019; Thorup et al., 2016).

The aim of the current study is to further investigate the effect of the iBASIS-VIPP intervention, which represents a therapeutic alteration in the child's early developmental environment. Specifically, we examine a cognitive measure of social attention - dwell time to the referred-object in a Gaze Following Task (Parsons et al., 2019). Dwell time to the referent may represent a proximal marker of the iBASIS-VIPP intervention, which aims to promote social interaction by reducing parental directiveness and increasing child initiations. Given the association between autism outcome and reduced dwell time to the referred-object (Bedford et al., 2012; Parsons et al., 2019) we aimed to test whether the cumulative reduction in autism behaviours following the iBASIS-VIPP intervention (Green et al., 2017) is preceded by an *increase* in dwell time toward the referent in the intervention arm.

Materials and Methods

Design

The iBASIS study was a two-site, single (rater)-blinded RCT of two parallel groups: intervention and no intervention, with participants randomly assigned to arm between April 2011 and December 2012. Research assessments took place at the Centre for Brain and Cognitive Development, at pre-randomisation baseline (9 months), following 5 months of intervention (15 months; Green et al., 2015), and at 27- and 39-month follow-up (Green et al., 2017). We monitored the use of other treatments in both arms of the trial; there was only one parent, in the no-intervention group, who reported any additional interventions (1 hour/week of speech and language therapy between the 15-month and 27-month assessments). The study

was approved by NHS Health Research Authority (NHS RES London REC 06/MRE02/73) and London Research Ethics Committee (Ref: 09/H0718/14) and parents provided written informed consent. This study is registered as ISRCTN 87373263 (https://www.isrctn.com/ISRCTN87373263); the trial protocol is available at **http://www.bbmh.manchester.ac.uk/ibasis/protocol/**. The current work is an exploratory secondary analysis of this trial dataset.

Participants

Infant siblings of children with autism were sampled within the context of the British Autism Study of Infant Siblings (BASIS), a prospective, longitudinal observational study. In the overall Phase 2 cohort there were 143 infants, 116 with elevated likelihood for autism, due to an older sibling with a diagnosis, and 27 with typical likelihood. Of this overall Phase 2 sample, a subsample of N=54 took part in the iBASIS-VIPP trial (28 intervention, 26 no intervention, see randomisation below). Infants were 7- to 10-months at the baseline visit. Exclusion criteria included: substantial medical disorder in the infant, being a twin, prematurity <34 weeks, or birthweight <5 lbs. The families were approached in order of identification and infants were not selected on the basis of developmental characteristics or atypicality. Families were paid travel expenses for research visits.

*Randomisation and masking (*see *Green et al., 2015 for full details)*

Families were randomly assigned (1:1) to either intervention or no intervention, stratified by centre (London or Manchester), using a permuted block approach within the two strata with random block sizes of four or six generated by the Clinical Trials Unit statistician. Treatment allocation could not be masked from families and therapists, but assessors and supervising research staff (including those administering the eye-tracking tasks) were

unaware of treatment allocation and the method of randomisation. All measures analysed in this paper were administered and coded naïve to other information, including group allocation.

Intervention

The 'intervention arm' received the *Intervention with the British Autism Study of Infant Siblings - Video Interaction for Promoting Positive Parenting (iBASIS-VIPP)*, which was based on VIPP (Juffer, Bakerman-Kranenburg & Van Ijzendoorm, 2008) and modified for the early autism prodrome (see Green et al., 2015; Green et al., 2017). VIPP aims to promote social-communication development by using video-feedback with parents/caregivers to increase their ability to understand and adapt to their infant's individual communication style. Therapy sessions were every 2 weeks, and in addition to the 6 therapy sessions in VIPP, iBASIS-VIPP added up to a further 6 booster sessions, depending on the families' need, giving a total of up to 12 sessions. Additional therapeutic procedures were also added to address any emerging signs of atypicality, for example, to address barriers to reciprocity and facilitate interaction (see Green et al., 2013 for full details). During the therapy sessions, which took place in participants' homes, the therapist uses video excerpts of parent-child interactions as a basis for increasing parents' ability to identify and interpret infant behaviour, increase sensitive responding, emotional attunement and patterns of verbal and non-verbal interaction. The 'no intervention arm' had no planned intervention, and no parents reported their child to be receiving any community-based intervention before the 15-month outcome.

Outcome measures

Experimental stimuli and procedure

The Gaze Following Task (see Figure 1) was run as part of a battery of eye-tracking tasks at endpoint only (15 months). Infants were seated on their mother's lap, at approximately 60cm from a Tobii T120 screen. A five-point calibration routine was run. The

experiment was started only after at least four points were properly calibrated for each eye. Infant behaviour was monitored by a video camera placed above the Tobii monitor. Stimuli were presented with TobiiStudio software.

Figure 1 Example stimuli from the Gaze Following Task

Gaze Following Task – Proportion of dwell time to the referent (see Parsons et al., 2019)

The gaze following component of this task was embedded within a word learning paradigm. There were four pseudo-words (kobe, toma, sefo, dax) presented during teaching trials in two, fixed word-object mapping pairs: kobe/toma and sefo/dax. *Teaching* trials began with direct gaze from the actress accompanied by a greeting (e.g. 'hello') the actress then exclaimed 'look' and shifted her gaze towards one of two objects (the referent), labelled it (e.g. 'kobe') and then returned to central direct gaze. There were then two further gaze shifts, in which the same object was labelled using different exclamations ('wow, a kobe'; 'see, a kobe'). After the third and final gaze shift, the trial ended with the actress looking at the referent. *Testing* trials showed only two objects - the referent object alongside the distractor object it had been paired with during the teaching trial.

There were two different formats for the teaching and testing trials: one-word and two-word test trials. For one of the object pairs, one object was labelled and then immediately followed by a test trial (one-word test trial). For the other object pair both objects were

labelled before being followed by the corresponding test trials (two-word test trials). Two-word test trials were harder since the infant could only succeed if they associated the words and the objects. When only one object in the pair was labelled, infants could perform correctly during testing (i.e., look longer at the referent of the label) by simply remembering which object had been labelled, without explicitly mapping the word and object. The word used in teaching to refer to the gazed at object, was heard four times in the one-word test trials and three times in the two-word test trials. Data from the word learning part of this task were not analysed for the current study as the task was unsuccessful in measuring word learning (see Parsons et al., 2019).

Data were extracted from Tobii Studio using the ClearView filter to identify fixations as stable gaze within a 100-pixel radius with >60ms duration. AOIs were defined around the face, referent, and distractor. Fixation points (x and y co-ordinates) were assigned to AOIs using Matlab R2016b. Where samples were missing for fewer than 200ms and data from immediately before and after missingness indicated the same AOI, missing data were set to that same AOI. AOI dwell time proportions for each AOI were calculated from the beginning of the first gaze shift to the end of the trial.

The variable analysed in the current study is *proportion of dwell time to the referent* compared to dwell time on the rest of the screen (including the other object, 'distractor'; the actress' 'face'; and 'other' parts of the background, i.e., actress' top and black screen), during the teaching phase of the trial (calculated across both one-word and two-word teaching trials) see Parsons et al. (2019). This measure is one of several gaze following metrics and was chosen because reduced dwell time to the referent relates to autism outcome in Parsons et al. (2019) and Bedford et al. (2012) and lower language scores (Parsons et al., 2019). See Supplementary Materials for the proportion of dwell time across all regions (see Table S3).

Mullen Scales of Early Learning (*MSEL;* Mullen, 1995).

The *MSEL* is a standardised developmental assessment, which examines early motor and cognitive development. The assessment is comprised of five subscales: gross motor (GM), visual reception (VR), fine motor (FM), receptive language (RL) and expressive language (EL). Data were collected at baseline (9 months) and outcome (15 months). Non-verbal IQ was calculated by summing FM and VR subscales and checked for imbalance at baseline (see statistical analysis).

Statistical analysis

Statistical analysis using intention-to-treat (ITT) was run in Stata (Stata 15, 2017). Standardised beta estimates and SEs were obtained using the stdBeta command. Estimates are reported which correspond to group differences from regression analyses of the endpoint variable, covarying for age at endpoint assessment. None of the potential baseline variables checked (maternal mental health, ethnicity and qualifications, household income, child's sex, age at baseline, non-verbal IQ, and number of autistic siblings) showed imbalance >0·5 SD (corresponding to a medium group difference; Cohen, 1992). A sensitivity analysis, using a propensity matching approach was also run to account for all variables with a smaller degree of imbalance (0.25 SD): these were mother's ethnicity, mother's highest qualification, child's age at baseline and child's non-verbal IQ. Quantile-quantile plots of residuals indicated a single residual outlier in the non-intervention arm (4.06 SD above the mean) for 'dwell time' in the Gaze Following Task, and analyses were therefore repeated without this outlier.

Results

The CONSORT diagram (see Figure 2) shows the flow of participants through the study. Table S1 shows the baseline descriptive statistics for the intervention and no

intervention arms (Green et al., 2015) and Table S2 shows previously reported outcome measures, including child language scores (Green et al., 2017).

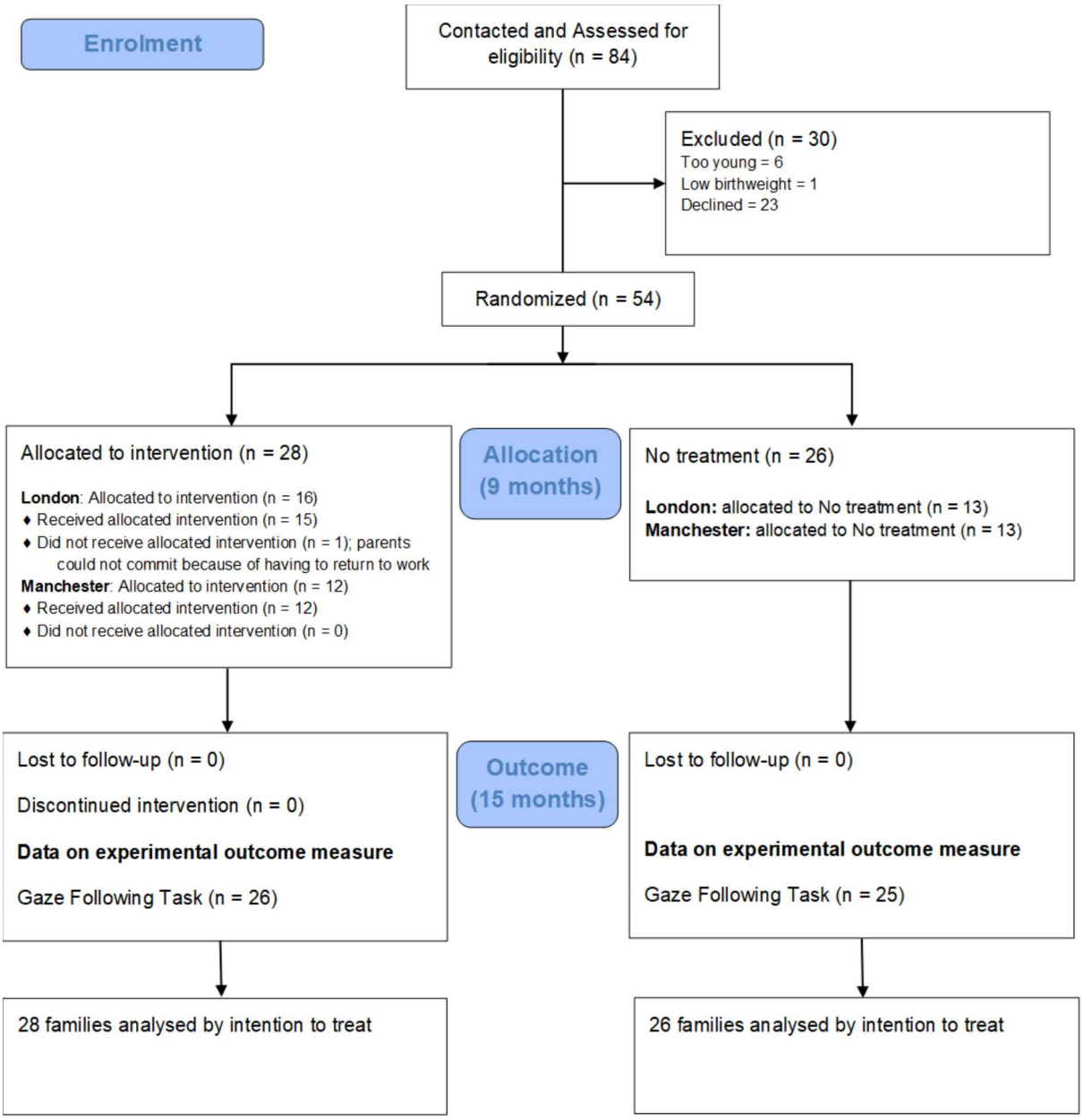

Figure 2: CONSORT Participant Flow Diagram

Dwell time to the Referent in the Gaze Following Task

A regression adjusting for age at outcome showed a significant effect of treatment group, beta=-.32, SE=.14, p=.03, with lower dwell time to the referent at endpoint in the intervention arm compared to the non-intervention arm (see Figure 3; intervention arm: mean proportion = .11, SD = .07; non-intervention arm: mean proportion = .18, SD = .11).

Results were similar when a residual outlier was removed (which corresponded to an outcome dwell time of 0.53, 4.06 SDs above the mean): beta=-.32, SE=.14, p=.03. Using a propensity score approach to account for covariate imbalance (including variables showing a group mean difference >0.25 SDs) did not change the direction of effect or markedly decrease the magnitude of the coefficient, although the results no longer reached significance: beta=-.26, SE=.14, p=.08.

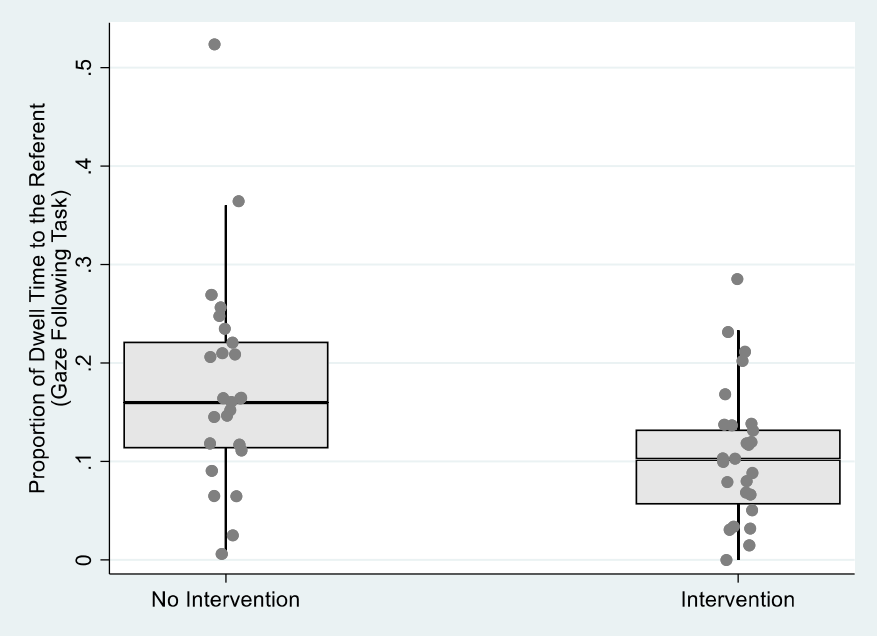

Figure 3: The Effect of Intervention on Proportion of Dwell Time to the Referent during a Gaze Following Task

Follow-up correlations:

Within the current RCT cohort, increased dwell time to the referent showed a positive association with Mullen language scores, but these did not reach significance either concurrently at 14 months (receptive language: r = .130, p = .364; expressive language: r = .161, p = .258) or longitudinally at 24 months (receptive language: r = .241, p = .103; expressive language: r = .173, p = .245) or 36 months (receptive language: r = .241, p = .096; expressive language: r = .181, p = .213). There was no significant correlation between dwell time and parental directiveness (r = -.04, p = .787).

Discussion

This study investigates the effect of the iBASIS-VIPP intervention on an eye-tracking measure of responding to joint attention: dwell time to the referent. From a developmental science perspective, this intervention represents an experimental change in the early environment, which can provide evidence about the causal mechanisms underlying development. Generalisation of intervention strategies has been previously indicated by post-intervention changes in parent directiveness, measured objectively via a lab-based assessment of parent-child interaction (Green et al., 2015; Green et al., 2017). Here, we find that the iBASIS-VIPP intervention was associated with significantly *reduced* dwell time to the referent in a Gaze Following Task, in comparison to the control arm. This finding is in contrast to the predicted effect, given that decreased dwell time in other cohorts has been associated with increased autism outcomes (Bedford et al., 2012), and the iBASIS-VIPP intervention has been shown to significantly *decrease* autism behaviours longitudinally (Green et al., 2017).

What could explain reduced dwell time in the intervention arm in this cohort? We considered the possibility that by significantly reducing parental 'directiveness' and

increasing child attentiveness (Green et al., 2015; 2017), the intervention may nevertheless have had an unintended adverse effect of increasing child initiation but with less referential cues to follow have resulted in a re-adjustment in the parent-child interaction dynamics, with reduced directiveness increasing opportunities for the child to initiate, but potentially offering less referential cues to follow. However, the lack of correlation between parent directiveness and dwell time in the Gaze Following Task is not consistent with this idea.

In terms of relevant cues in the child's environment, it is plausible that decreased attention to the referent object is competitively reciprocal to increased attention to the face. Attention to the face in the Gaze Following Task was not significantly higher in the intervention arm (see Table S3) but Green et al. (2017) previously showed that, at an interactional level, child attentiveness to parents is significantly increased following the iBASIS-VIPP intervention (see Figure S1). Further, Jones et al. (2017) showed that another parent-mediated intervention with infants with an EL for autism was associated with increases in neural markers of social processing, including the P400 ERP to faces versus objects. This raises the possibility of a trade-off due to 'resource competition' between attention allocation to faces versus objects. Similar developmental trade-offs have been observed in other domains during the acquisition of new skills (i.e. motor and language; Berger, Cunsolo, Ali & Iverson, 2017)

Reduced dwell time to the gazed-at object has previously been associated with significantly lower language scores, both concurrently and longitudinally, in a cohort of infants at typical and increased familial likelihood for autism, which included the current sample (Parsons et al., 2019, total sample N=101, including N=51 infants from iBASIS-VIPP). Correlations between dwell time to the referent and objectively measured language scores in the intervention sample were in the same direction but did not reach significance (r values between .13 to .24). Green et al. (2015) previously reported a trend for lower language scores at treatment endpoint, which were non-significant but consistent across observational,

parent-report and ERP (auditory vowel discrimination) measures (with effect sizes spanning small: .17, through to moderate-large: .62). This direction of effects is in-line with the current finding of significantly reduced dwell time during the Gaze Following Task at 15 months. However, by 3-year follow-up (Green et al., 2017) the intervention arm showed a non-significant trend toward *increased* language scores (with scores for both arms within the average range), and significant language improvements were found in a replication trial (Whitehouse et al., 2021). This lagged reversal of effects on language might suggest later benefits to language associated with the increased early social engagement, as could be predicted by a more socially embedded, interpersonal account of language emergence (Tomasello, 2005).

Attentional control may play a role in the developmental timing of any socialisation/ language trade-off. Modulating attention to different facial features during peek-a-boo is predictive of increased language ability longitudinally in cohort studies of NT and EL infants (Elsabbagh et al., 2014). The iBASIS-VIPP intervention showed an increase in attention flexibility at endpoint (i.e. faster saccadic disengagement latency; Green et al. 2015). Future RCTs with larger sample sizes should embed neurocognitive measures to test mediation mechanisms toward longer-term developmental outcomes.

From a clinical perspective, monitoring of associated effects, including potentially unwanted effects, of any intervention is important (Bottema-Beutel, Crowley, Sandbank & Woynaroski, 2021). In this regard it is reassuring that the iBASIS trial follow-up through to three years-of-age showed a reversal of these trends, towards improved language outcomes; and moreover that a replication trial testing the iBASIS-VIPP intervention in a larger community sample of infants showing early autism signs (Whitehouse et al., 2019), did not replicate the apparent initial lower language scores at endpoint found in Green et al., (2015), and indeed showed significantly enhanced (unblinded) parent-reported language outcomes

over time (Whitehouse et al., 2021). We note that these two trials had different sampling strategies, 'selective' in the UK iBASIS sample with infant siblings at increased familial likelihood for autism compared to 'indicated' in Whitehouse et al. (2021) with community ascertained early markers for autism.

The results should be considered with respect to limitations of the current study. First, it is important to note that these analyses were not pre-specified as part of the original trial protocol. Second, the modest sample size should be noted, and as a field it is important to move towards large, well-powered RCTs and replicated findings. This is particularly relevant given the elevated familial likelihood design, which means the majority of children will go on to be typically developing. At present, larger-scale studies tend not to include neurocognitive measures for feasibility reasons. It will be important for future studies to provide a direct test of the sensitivity of neurocognitive versus observational markers. This is particularly important given the striking heterogeneity in the presentation of autism. Third, as is the case for all prospective sibling studies, the results cannot be generalised beyond infants with a family history of autism (e.g. to those associated with de novo mutations etc.). Finally, the Gaze Following Task was only completed at 15-month endpoint; without a baseline measure it is possible arms were not balanced at baseline, despite randomisation. Long-term follow-up is also important to understand the developmental trajectory of such experimental measures. A single outcome time-point limits our interpretation, as the iBASIS trial showed that these trends towards slowing effects on language were transient and the positive effects of intervention – namely reduced autism symptoms and increased child initiations - were strongest when measured across the following 2 years of development (Green et al., 2017).

Conclusions: In conclusion, the iBASIS-VIPP intervention was associated with reduced dwell time to the referent of another person's gaze at endpoint. Reduced attention to the referent can be understood in the context of our previously reported trend towards transiently

lower language scores at 15 months (Green et al., 2015) and potentially elucidates early developmental dynamics of social engagement and language learning in this cohort. The findings are compatible with a 'resource competition' trade-off model in development, with the intervention increasing social inputs for the infant, leading to increased social engagement but a simultaneous temporary lower language-specific development. The later reversal of this trend in language may be the result of this earlier increased social engagement, and future studies should aim to test this directly using mediation approaches.

Acknowledgements

The authors are grateful for the generous contributions BASIS families have made towards this study. They acknowledge with thanks the generous collaboration from the originators of the original VIPP intervention (Femmie Juffer, Marian Bakermans Kranenberg, Marinus van IJzendoorn) that forms the basis of our intervention model. The BASIS team was: Simon Baron-Cohen, Patrick Bolton, Rhonda Booth, Ami Brooks, Kim Davies, Janice Fernandes, Isobel Gammer, Clare Harrop, Samina Holsgrove, Michelle Liew, Janet McNally, Helena Ribeiro, Erica Salomone, Carol Taylor, Leslie Tucker.

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Supplementary materials

Table S1 Baseline descriptive statistics for the intervention and no intervention arms.

Reproduced from Green et al. (2015)

	No Intervention N = 26	**Intervention** N = 28*
Maternal medical history		
No disorder	15 (57.7%)	17 (60.7%)
Mental/physical disorder	11 (42.3%)	11 (39.3%)
Maternal ethnicity		
Caucasian	22 (84.6%)	18 (64.3%)
Other	4 (15.4%)	10 (35.7%)
Maternal qualifications		
> Degree	15 (57.7%)	10 (37.0%)
< Degree	11 (42.3%)	17 (63.0%)
Annual household income		
< £40,000	15 (57.7%)	16 (59.3%)
≥ £40,000	11 (42.3%)	11 (40.7%)
Biological Sex		
Male	12 (46.2%)	17 (60.7%)
Female	14 (53.8%)	11 (39.3%)
Typical older sibling(s)		
TD sib(s)	15 (57.7%)	14 (50.0%)
No TD sib(s)	11 (42.3%)	14 (50.0%)
Age/days		
Mean (SD)	276.58 (24.25)	267.14 (20.93)
MSEL Nonverbal T-score		
Mean(SD)	57.29 (10.69)	53.71 (12.73)

Data are the unimputed sample % or mean (SD) for available case. TD – typically developing; MSEL – Mullen Scales of Early Learning. * N = 27 for Maternal qualifications and annual household income.

Table S2 Baseline, 15 month, 27 month and 39 month follow-up data by intervention group.

Reproduced from Green et al. (2017)

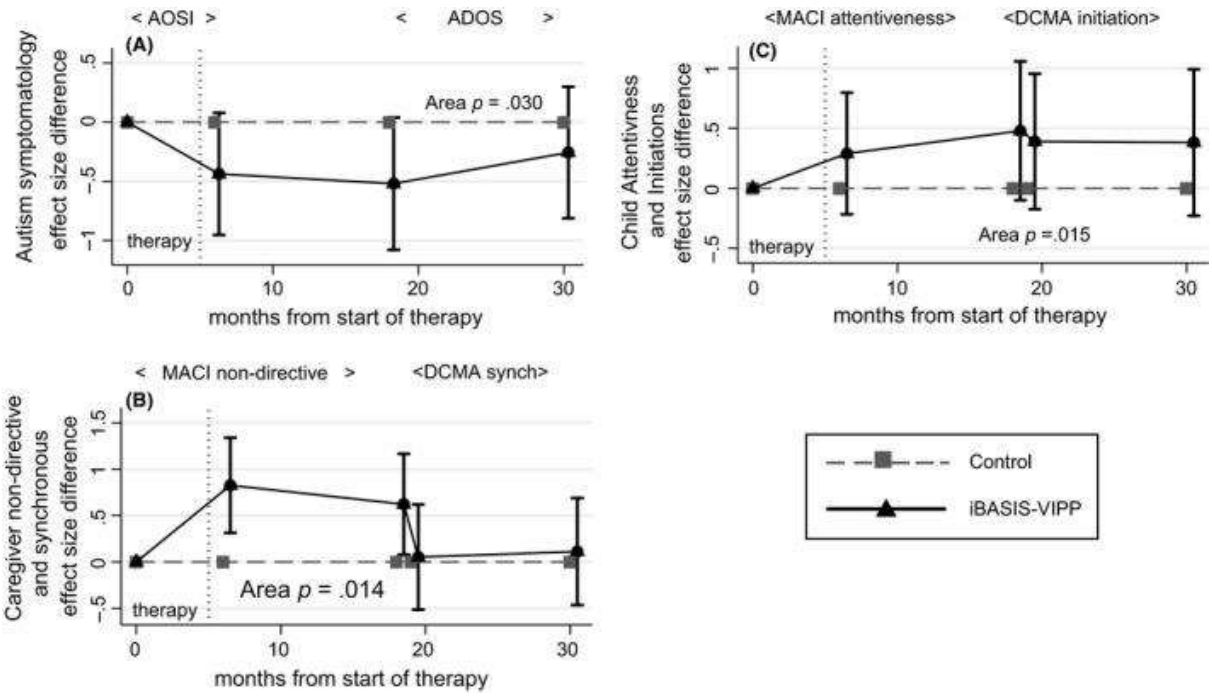
	No Intervention				**Intervention**			
	Baseline	15 months	27 months	39 months	Baseline	15 months	27 months	39 months
	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)
AOSI Baseline raw score	9.08 (5.32) N = 26	7.31 (5.83) N = 26	-	-	10.04 (4.60) N = 28	5.93 (4.05) N = 27	-	-
ADOS-2 Total score	-	-	6.32 (6.79) N = 25	5.13 (5.03) N = 24	-	-	4.13 (3.61) N = 23	3.96 (3.68) N = 27
MACI Infant attentiveness*	3.65 (1.29) N = 26	4.19 (1.13) N = 26	4.21 (1.44) N = 24	-	3.39 (1.26) N = 28	4.22 (1.05) N = 27	4.74 (1.63) N = 23	-
MACI Caregiver non-directiveness*	3.73 (1.43) N = 26	3.92 (1.32) N = 26	4.29 (1.73) N = 24	-	3.50 (1.48) N = 28	4.67 (1.24) N = 27	5.00 (1.65) N = 23	-
DCMA Proportion Child Initiations	-	-	0.47 (0.20) N = 24	0.44 (0.14) N = 23	-	-	0.57 (0.23) N = 23	0.50 (0.18) N = 25
DCMA Proportion Parent Synchrony	-	-	0.46 (0.19) N = 24	0.45 (0.10) N = 23	-	-	0.48 (0.18) N = 23	0.43 (0.14) N = 25
MSEL Receptive raw score	10.81 (1.86) N = 26	15.46 (3.25) N = 26	25.48 (6.44) N = 25	34.17 (7.53) N = 24	10.43 (1.67) N = 28	13.81 (1.75) N = 27	26.43 (4.41) N = 23	34.07 (5.33) N = 27
MSEL Receptive T-score	50.38 (9.30) N = 26	43.04 (12.11) N = 26	48.92 (13.68) N = 25	50.75 (13.59) N = 24	49.89 (9.03) N = 28	36.89 (7.13) N = 27	50.57 (12.64) N = 23	50.30 (12.61) N = 27
MSEL Expressive raw score	10.73 (1.73) N = 26	15.42 (2.93) N = 26	24.00 (6.17) N = 25	34.54 (7.48) N = 24	10.21 (2.17) N = 28	14.41 (2.00) N = 27	24.87 (4.86) N = 23	34.22 (5.58) N = 27

MSEL Expressive T-score	55.04 (9.99) N = 26	49.77 (11.13) N = 26	47.36 (13.96) N = 25	50.88 (12.35) N = 24	53.54 (11.27) N = 28	46.52 (8.69) N = 27	49.96 (12.23) N = 23	50.33 (12.37) N = 27
Vineland Communication standard score	92.68 (16.18) N = 25	98.76 (14.74) N = 25	99.76 (16.29) N = 25	95.92 (16.47) N = 24	91.78 (18.54) N = 27	93.42 (11.05) N = 26	100.48 (11.97) N = 23	98.27 (12.33) N = 26
Vineland Socialization standard score	99.92 (10.33) N = 25	97.76 (13.11) N = 25	98.28 (15.78) N = 25	94.54 (13.73) N = 24	94.93(16.26) N = 27	99.27 (12.04) N = 26	98.04 (10.94) N = 23	95.27 (13.80) N = 26
Attention Disengagement ms	182.79 (81.59) N = 25	171.62 (100.39) N = 24	163.99 (129.67) N = 20	-	209.74 (76.49) N = 28	160.84 (81.75) N = 26	158.03 (84.90) N = 20	-
Diagnostic Outcome				N (%)				N (%)
HR No ASD				N = 16 (62%)				N = 16 (59%)
HR Atypical				N = 8 (31%)				N = 7 (26%)
HR ASD				N = 2 (8%)				N = 4 (15%)

* 1 (low) to 7 (high) scoring scale; AOSI: Autism Observational Schedule for Infants; ADOS-2: Autism Diagnostic Observation Schedule – 2nd Edition; DCMA: Dyadic Communication Measure for Autism; MACI: Manchester Assessment of Caregiver-infant Interaction; MSEL: Mullen Scale of Early Learning); Vineland: Vineland Adaptive Behavior Scale standard scores.

Figure S1 Time profile of treatment effects on autism symptoms and caregiver–child interaction showing cumulative area under the curve effect of the intervention for autism symptoms, attentiveness/initiation and parent non-directiveness/synchrony.

Reproduced from Green et al. (2017)



The effect size difference is shown by holding TAU as zero. (A) Primary Outcome, Autism Prodromal Symptoms. (The negative effect size reflects a reduction in symptom severity in iBASIS-VIPP relative to TAU). (B) Parental Dyadic Social Interaction. (C) Child Dyadic Social Interaction. For AUC: the multiple point estimates are combined into an area between the curves (sum of trapeziums). A Wald test for this estimated area was calculated from the individual effect estimates and their parameter covariance using the lincom procedure. Confidence intervals for area effect sizes were obtained by bootstrap, resampling participants with replacement.

Follow-up analyses: Dwell time across regions

Looking behaviour to different areas of interest is mutually dependent and so proportionally less dwell time to the referent means proportionally more looking to other parts of the screen. Table S3 shows the proportion of dwell time to each region of the screen for the two arms.

Table S3 Proportion of dwell time to regions of interest during the Gaze Following task.

	Referent	Distractor	Face	Other
Intervention N=26				
M (SD)	.108 (.070)	.052 (.048)	.669 (.243)	.171 (.196)
No intervention N=25				
M (SD)	.178 (.109)	.070 (.053)	.628 (.117)	. 124 (.105)

While descriptively, reduced dwell time to referred-object in the intervention arm occurs with concomitant increased dwell time to the face and to other parts of the screen, follow-up analysis showed that there were no significant effects of treatment on dwell time to other regions. Regression models adjusting for age at outcome showed no significant effect of treatment group for dwell time to Distractor: beta=-.07, SE=.14, p=.63, Face: beta=.03, SE=.15, p=.84, or Other regions of the screen: beta=.18, SE=.15, p=.25.

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