






## RESEARCH ARTICLE

# Parent-mediated intervention in infants with an elevated likelihood for autism reduces dwell time during a gaze-following task

Rachael Bedford<sup>1,2</sup>  | Jonathan Green<sup>3,4</sup>  | Teodora Gliga<sup>5</sup> | Emily H. Jones<sup>6</sup> | Mayada Elsabbagh<sup>7</sup>  | Greg Pasco<sup>8</sup> | Ming Wai Wan<sup>9</sup>  | Vicky Slonims<sup>10</sup> | Tony Charman<sup>8</sup>  | Andrew Pickles<sup>11</sup> | Mark H. Johnson<sup>6,12</sup> | The BASIS Team

<sup>1</sup>Department of Psychology, University of Bath, Bath, UK

<sup>2</sup>Centre for Brain and Behaviour, Department of Psychology, School of Biological and Behavioural Sciences, Queen Mary University of London, London, UK

<sup>3</sup>Social Development Research Group, School of Health Sciences, University of Manchester, Manchester, UK

<sup>4</sup>Royal Manchester Children's Hospital, Manchester, UK

<sup>5</sup>Department of Psychology, University of East Anglia, Norwich, UK

<sup>6</sup>Centre for Brain and Cognitive Development, Birkbeck College, University of London, London, UK

<sup>7</sup>Montreal Neurological Institute, Faculty of Medicine and Health Sciences, McGill University, Montreal, Canada

<sup>8</sup>Psychology Department, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, UK

<sup>9</sup>School of Health Sciences, University of Manchester, Manchester, UK

<sup>10</sup>Evelina London Children's Hospital and King's College London Neurosciences Centre, London, UK

<sup>11</sup>Department of Biostatistics and Health Informatics, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, UK

<sup>12</sup>Department of Psychology, University of Cambridge, Cambridge, UK

## Correspondence

Rachael Bedford, Department of Psychology, Queen Mary University of London, London, UK.

Email: [r.bedford@qmul.ac.uk](mailto:r.bedford@qmul.ac.uk)

Jonathan Green, Social Development Research Group, School of Health Sciences, University of Manchester, Manchester, UK.

Email: [Jonathan.Green@manchester.ac.uk](mailto:Jonathan.Green@manchester.ac.uk)

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## Abstract

Cognitive markers may in theory be more sensitive to the effects of intervention than overt behavioral 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 randomized 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 behavior 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 ( $\beta = -0.32$ ,  $SE = 0.14$ ,  $p = 0.03$ ) 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 toward lower language scores at the treatment endpoint (Green et al. (2015) *The Lancet Psychiatry*, 2(2), 133–140). Future intervention trials should aim to include experimental cognitive measures, alongside behavioral measures, to investigate mechanisms associated with intervention effects.

Rachael Bedford and Jonathan Green are considered as joint first authors.

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### 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 emphasize the need for future trials to include more fine-grained, experimental measures of social interaction, alongside broad assessment measures, and to better understand how the intervention might change behavior.

### KEYWORDS

autism, elevated likelihood for autism, gaze following, infant siblings, intervention, parent-mediated intervention, RCT

## 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 et al., 2023; Johnson et al., 2015; Visser et al., 2016). Neurocognitive markers are intermediate between genes and behavior and are thus potentially closer to the underlying causal mechanism of atypicality, with clinically observable behaviors being a downstream consequence. Such neurocognitive markers may prove to be useful indicators of the effects of early preemptive intervention before they become evident in behavior (Insel, 2007). They may also help indicate the underlying mechanisms of how interventions work, what they change, and how they lead to particular downstream behavioral outcomes; as well as helping to identify any potential harms or adverse events—all important considerations for ethical preemptive intervention (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 (Elsabbagh, 2020; Jones et al., 2014; Wolff & Piven, 2020), as ~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 decades, 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 randomized 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 “preemptive” interventions with infants who have an EL for autism. A recent meta-analysis (Hampton & Rodriguez, 2022)

suggested that across studies, while there were strong effects for changes in parent behaviors there was no evidence for direct alterations in child behaviors. However, Yoder et al. (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 EL 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 with 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 toward reduced autism behavioral 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). 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 behaviors (Johnson et al., 2015). Such early markers are measurable before the onset of overt clinically defining behaviors. Joint attention behaviors, for instance, have been widely studied in infants with an EL for autism, with behavioral studies showing reduced joint attention toward 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 with 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 behavioral 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 behaviors 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 randomized controlled trial (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-randomization 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 h/week of speech and language therapy between the 15- 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 EL 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 randomization 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.

### Randomization and masking

Families were randomly assigned (1:1) to either intervention or no intervention, stratified by the center (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 (see Green et al., 2015 for full details). 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 randomization. All measures analyzed in this article were administered and coded naive to other information, including group allocation.

## Intervention

The “intervention arm” received the iBASIS-VIPP, which was based on VIPP (Juffer et al., 2008) and modified for the early autism prodrome (see Green et al., 2015, 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 (Green et al., 2013). During the therapy sessions, which took place in participants’ homes, the therapist used video excerpts of parent–child interactions as a basis for increasing parents’ ability to identify and interpret infant behavior, 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 (Figure 1) was run as part of a battery of eye-tracking tasks at the endpoint only (15 months). Infants were seated on their mother’s lap, at ~60 cm 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 behavior 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

The gaze-following component of this task was embedded within a word-learning paradigm (Parsons et al., 2019). 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 a direct gaze from the actress accompanied by a greeting (e.g., “hello”) the actress then exclaimed “look” and shifted her gaze toward one of two objects (the referent), labeled it (e.g., “kobe”) and then returned to central direct gaze. There were then two further gaze shifts, in which the same object was labeled 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 labeled and then immediately followed by a test trial (one-word test trial). For the other object pair, both objects were labeled before being followed by the corresponding test trials (two-word test trials). Two-word test trials were harder because the infant could only succeed if they associated the words and the objects. When only one object in the pair was labeled, infants could perform correctly during testing (i.e., look longer at the referent of the label) by simply remembering which object had been labeled, 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 analyzed for the current study as the task was unsuccessful in measuring word learning (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 >60 ms 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 200 ms 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 analyzed in the current study is the proportion of dwell time to the referent compared with 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 Data S1 for the proportion of dwell time across all regions (Table S3).

## Mullen scales of early learning (MSEL)

The MSEL is a standardized developmental assessment, which examines early motor and cognitive development (Mullen, 1995). 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 Section 2.5.4).

## Statistical analysis

Statistical analysis using intention-to-treat (ITT) was run in Stata (StataCorp, 2017). Standardized 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 an 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 the 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 (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).

### Dwell time to the referent in the gaze-following task

A regression adjusting for age at outcome showed a significant effect of the treatment group,  $\beta = -0.32$ ,

$SE = 0.14$ ,  $p = 0.03$ , with lower dwell time to the referent at endpoint in the intervention arm compared with the non-intervention arm (Figure 3; intervention arm: mean proportion = 0.11,  $SD = 0.07$ ; non-intervention arm: mean proportion = 0.18 and  $SD = 0.11$ ).

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):  $\beta = -0.32$ ,  $SE = 0.14$ ,  $p = 0.03$ . 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:  $\beta = -0.26$ ,  $SE = 0.14$ ,  $p = 0.08$ .

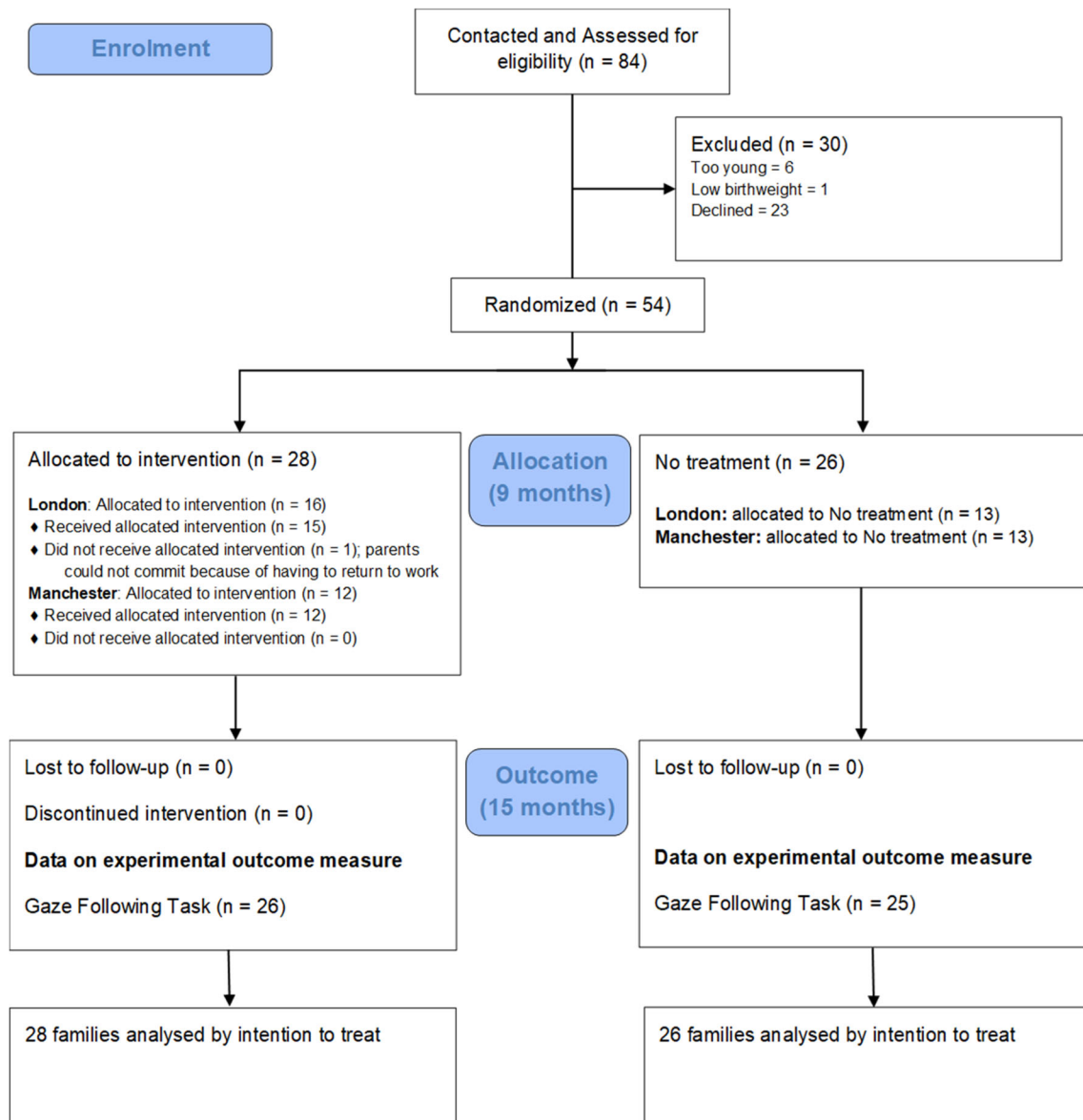
## Follow-up correlations

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:  $r = 0.130$ ,  $p = 0.364$ ; expressive language:  $r = 0.161$ ,  $p = 0.258$ ) or longitudinally at 24 months (receptive language:  $r = 0.241$ ,  $p = 0.103$ ; expressive language:  $r = 0.173$ ,  $p = 0.245$ ) or 36 months (receptive language:  $r = 0.241$ ,  $p = 0.096$ ; expressive language:  $r = 0.181$ ,  $p = 0.213$ ). There was no significant correlation between dwell time and parental directiveness ( $r = -0.04$ ,  $p = 0.787$ ).

## 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. Generalization 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, 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 with 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 behaviors 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



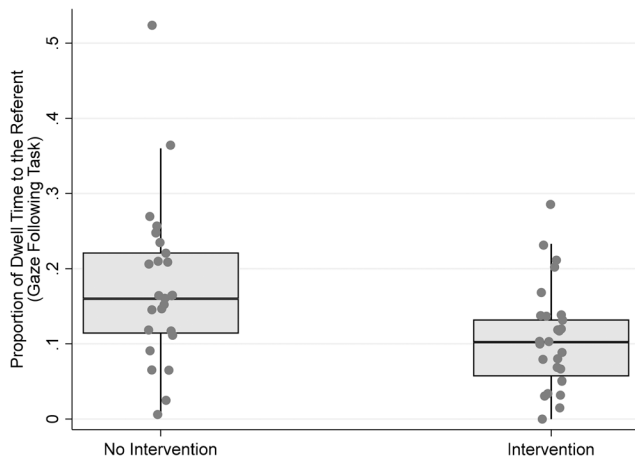
**FIGURE 2** CONSORT participant flow diagram.

adverse effect of increasing child initiation but with less referential cues to follow. In other words, it could 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 (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 (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 allocations 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 et al., 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



**FIGURE 3** The effect of an intervention on the proportion of dwell time to the referent during a gaze-following task.

scores in the intervention sample were in the same direction but did not reach significance ( $r$  values between 0.13 and 0.24). 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: 0.17, through to moderate–large: 0.62). 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 socialization/language trade-off. Modulating attention to different facial features during peek-a-boo is predictive of increased language ability longitudinally in cohort studies of neurotypical 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 et al., 2021). In this regard it is reassuring that the iBASIS trial follow-up through to 3 years-of-age showed a reversal of these trends, toward 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 with “indicated” in Whitehouse et al. (2021) with community ascertained early markers for autism.

The results should be considered with respect to the 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 toward 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 generalized 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 randomization. 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 toward 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 toward 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.

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## CONFLICT OF INTEREST STATEMENT

Authors have no conflict of interest to declare.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

## ETHICS 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.

## ORCID

Rachael Bedford  <https://orcid.org/0000-0002-8581-055X>

Jonathan Green  <https://orcid.org/0000-0002-0143-181X>

Mayada Elsabbagh  <https://orcid.org/0000-0002-7311-9059>

Ming Wai Wan  <https://orcid.org/0000-0002-5353-786X>

Tony Charman  <https://orcid.org/0000-0003-1993-6549>

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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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