Comparative Cost-Effectiveness of Four Supplementary Foods in Treating Moderate Acute Malnutrition in Children 6-59 Months in Sierra Leone
Section 4: Neurocognitive Sub-Study

A Report from the Food Aid Quality Review

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JANUARY 2021

This report was made possible by the generous support of the American people through the support of the United States Agency for International Development's Bureau for Humanitarian Assistance (USAID/BHA) and the legacy Office of Food for Peace (FFP) under the terms of Contract AID-OAA-C-16-00020, managed by Tufts University.

The contents are the responsibility of Tufts University and its partners in the Food Aid Quality Review (FAQR) and do not necessarily reflect the views of USAID or the United States Government.

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ABBREVIATIONS AND ACRONYMS

CSB+ w/oil	Corn-Soy Blend Plus and Fortified Vegetable Oil
CSWB w/oil	Corn-Soy Whey Blend and Fortified Vegetable Oil
MAM	Moderate Acute Malnutrition
MUAC	Mid-Upper Arm Circumference
PHU	Peripheral Health Units
RUSF	Ready-to-Use Supplementary Food
SC+A	Super Cereal Plus Amylase
SRT	Saccadic Reaction Time

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ABSTRACT

Background: Moderate acute malnutrition (MAM) is a potentially life-threatening condition that affects the development and function of multiple organ systems, including the brain. The assessment of functional deficits in MAM has remained difficult given the lack of objective and widely-applicable tests. This study examined the feasibility, measurement properties, and utility of a novel eye-tracking test in the assessment of neurocognitive function in young children in low-resource settings. The study also tested the hypothesis that MAM is associated with impaired neurocognitive functions that are improved after treatment with supplementary food.

Methods: The study used a case-control (4:1) design to compare neurocognitive function in children with MAM and well-nourished controls. The data were collected as a part of a larger intervention study comparing the cost-effectiveness of four supplementary foods in the treatment of MAM in Pujehun District, Sierra Leone. Infants aged 7- to 11-months diagnosed with MAM (N=131) and same-age controls without MAM (N = 60) were enrolled in the study. They were tested with eye tracking and conventional observational tests of visual orienting. The tests were administered upon enrollment to the study/feeding program (i.e., Pretest/Visit 1) and again four weeks later (Post-test/Visit 2). The primary outcome was saccadic reaction time (SRT), reflecting the speed of visual orienting to stimuli on a computer screen. Secondary outcomes were measures reflecting the spatial and temporal characteristics of visual fixations while the infant was exploring a dynamic social scene.

Results: Data on visual orienting were obtained for 76 percent of the infants at the first attempt of eye tracking. Visual orienting responses to stimuli on a computer screen were frequent in MAM and control children (Mean = 95%), yielding sufficient data for reliable estimation of SRTs (test-retest r = .60, P<0.001) and the mean duration of visual fixations (test-retest r = .53, P<0.001). MAM children had marginally slower SRTs than controls in the baseline assessment. SRT improved among the children with MAM after four weeks of supplementary feeding (-6 ms $\pm$ 2, P=0.006), as did fixation duration (+34 ms $\pm$ 6, P<.0001). For control children, there were no significant changes in SRT (+4ms $\pm$ 3, P=0.19) or fixation duration (+8ms $\pm$9, P=0.43). No group or treatment effects were found in the conventional observational tests of visual orienting.

Conclusions: The results demonstrate the promise of eye tracking in the assessment of neurocognitive status in young, vulnerable groups in field settings and show unique evidence for the functional benefits of supplementary feeding of children with MAM.

2. Background

Human brain development is dependent on access to a supportive environment with adequate levels of nutrition, cognitive stimulation, and responsive caregiving (Georgieff, 2007; Nelson et al., 2006). Children who lack access to this optimum due to malnutrition and other forms of adversity are at heightened risk for compromised development of elementary neurocognitive capacities in early childhood, and persistent emotional and social problems in adulthood (Lu et al., 2016; Walker et al., 2011). A timely intervention that supplies the developing brain with adequate nutrition may be effective in preventing such long-term negative consequences (Prado & Dewey, 2014), but studies on the neurocognitive benefits of supplementary feeding programs are scarce given the lack of standardized and widely-applicable measures. It is increasingly recognized, however, that an important next step in the evaluation of the treatment protocols for early childhood malnutrition is to extend the measurement of treatment outcomes from anthropometric indicators to other measures of the child's functional status, including neurocognitive function (Hsieh et al., 2016; Suri & Rosenberg, 2018).

Neurocognitive Development and Nutritional Deficiencies

The human brain undergoes rapid growth and development in the last trimester of pregnancy and the early postnatal period (Georgieff, 2007). This development results in the appearance of a repertoire of elementary neurocognitive capacities that: i) help the child to orient attention to important sources of information in the physical and social environment (e.g., parents' faces); ii) facilitate early learning (e.g., detection of statistical regularities in the environment); and iii) serve as "scaffolds" in the acquisition of more complex cognitive and social skills (Rose et al., 2003).

The development of elementary neurocognitive capacities in infants is based on activity-dependent refinement of connections in distributed neural networks. For example, the appearance of stereopsis (i.e., use of visual input from the two eyes in depth perception, Jando et al., 2012) is based on the formation of distinct columns of neurons in the occipital neocortex that respond selectively to input from one eye (Espinosa & Stryker, 2012). Similarly, age-related changes in attention to faces in infants (Leppänen, 2017) are likely to be related to the appearance of distinct populations of face-sensitive neural cells in the occipital and temporal areas of the brain (Arcaro et al., 2017). In addition to the appearance of new abilities, early neurocognitive development in infants is characterized by rapid age-related improvements in the efficiency of neurocognitive functions, such as the speed of visual orienting (Alahyane et al., 2016). These changes are likely to be related to myelination (i.e., formation of lipid-rich sheaths around neuronal axons) and associated improvements in the neural conduction velocity. In the visual system, myelination first appears in optic radiations (starting around three to four months after birth) and subsequently in occipital and parietal cortices (starting around four to six months after birth [Deoni et al., 2012]).

Nearly all aspects of the early neurodevelopment in infants are vulnerable to nutritional deficiencies (Georgieff, 2007; Prado & Dewey, 2014). While the mechanisms of this vulnerability are poorly understood, the neurodevelopmental effects of malnutrition are hypothesized to be based on: i) specific impairments arising from a direct dependency of

a neural or developmental process on a particular nutrient (e.g., several studies have examined links between visual brain systems and long-chain polyunsaturated fatty acids [Birch et al., 2010; Brenna, 2011; Colombo et al., 2013; 2016; Diau et al., 2005; El-Khayat et al., 2007; Gould et al., 2014; Westerberg et al., 2011]); or ii) a more diffuse effect arising from many neurodevelopmental processes being sensitive to nutritional deficiencies, including protein-energy malnutrition, as well as deficiencies in fatty acids, iron, iodine and thyroid hormones, zinc, choline, and vitamin B (for reviews, see Georgieff, 2007; Prado & Dewey, 2014). The latter may explain the findings of widespread neurocognitive and behavioral problems in individuals with a history of acute malnutrition in early childhood, including increased susceptibility to distraction, frustration, and achievement problems at school age, and intellectual and emotional dysfunction in adulthood (Galler et al, 1983; 1989; Peter et al., 2016).

Given that early neurocognitive-development is highly dependent on activity and relies on the child's ability to interact with the physical and social environment, neurodevelopmental effects in malnourished children may also arise from the fact that this condition is often characterized by reduced interest in the environment, reduced motor activity and reduced exploratory behavior (Prado & Dewey, 2014). If a child is less active, inactivity may inadvertently lead to a negative cycle in which the caregiver becomes less engaged with the child in joint activities that stimulate the child cognitively and offer opportunities for learning (Prado & Dewey, 2014).

Assessment of Neurocognitive Development
The neurodevelopmental effects of malnutrition may be mitigated by timely interventions that supply the developing brain with required nutrients. However, there is a scarcity of studies on the neurocognitive benefits of supplementary feeding programs in food-insecure environments (Prado & Dewey, 2014), mostly reflecting the difficulties in measuring children's neurocognitive function under field conditions. Traditional observational tests of infant neurocognition, for example, are impractical for repeated use in routine clinical or field settings, rely heavily on user experience and education, and are insensitive to child developmental trajectories before the second year of life (Nishimura et al., 2016).

In recent years, the opportunities to examine neurocognitive function in infants have improved with the advent of technologies that allow for computerized tracking of infant eye movements as well as full automation of procedures that have long been manual, laborious and error-prone (Jones et al., 2014; Leppänen et al., 2015). These technologies have been mostly used in academic research (although see Forssman et al., 2017, Hernik et al., 2018, Pyykkö et al., 2018), but there are growing hopes that some of the new technologies can be developed into practical field-tests for collecting data on specific aspects of human behavior (Itti, 2015; Tseng et al., 2012) and, as such, would also help in creating new, scalable methods for monitoring changes in neurocognitive function in children (Jones et al., 2014; Leppänen et al., 2015).

The technological advancements in the measurement of eye movements are of interest because different metrics of eye movements may offer reliable and widely-applicable

indicators of brain function and its problems across the human lifespan. Eye movement control develops rapidly within the first months of life and gives infants an ability to look at things that are of interest to them, keep their eyes focused on objects and prevent their eyes from moving to things that are distracting (Leppänen, 2017). These abilities are controlled by a distributed network of subcortical and cortical areas (Munoz et al., 2004).

Several studies have further shown that the timing of human eye movements is highly sensitive to changes in a person's neurocognitive status and to individual differences in neurocognitive capacity. Saccadic eye movements (i.e., rapid movements of eyes from one location to another) become slower after a mild traumatic brain injury and subsequently return to the pre-event baseline as the person recovers from the injury (e.g., Pearson et al., 2007). There are also data showing that individual differences in the latency of saccadic eye movements and the mean duration of periods of stationary attentional focus (fixations) in infancy are associated with scores on the conventional measures of cognitive and behavioral capacities in mid childhood (Dougherty & Haith, 1997; Papageorgiou et al., 2014; Rose et al, 2012).

While infant eye movements are easy to measure and correlate with neurocognitive status, a number of questions remain regarding the use of this measure in the assessment of infants and children in low-resource settings. First, the technical feasibility of repeated eye-tracking tests has not been systematically examined in low-resource settings and in children with MAM. Second, the measurement properties of repeated eye-tracking tests are still poorly understood (i.e., variability of test scores across different tests), although existing evidence from high-resource laboratories points to relatively high stability of test results (Leppänen et al., 2015). Limited variability of test scores in populations that are not undergoing changes in neurocognitive status (e.g., well-nourished children without neurological abnormalities) would support the ability of the test to detect changes in neurocognitive status. Further research addressing these questions will be important to determine the utility of eye tracking as an outcome in supplemental feeding programs.

3. Aims and Objectives

The Neurocognitive Sub-study had the following aims and hypotheses:

Aim 1: To conduct a pilot study to assess the feasibility, measurement properties, and utility of eye-tracking tests in monitoring neurocognitive changes in 7 and 18-month-old children over a four-week period (i.e., the typical recovery period from MAM in supplementary feeding programs).

Aim 2: To examine the effects of MAM and of treatment with four supplementary foods on neurocognitive function in children between the ages of 7 to 11-months.

Hypothesis 2a: Compared to well-nourished control children, children with MAM will have slower saccadic reaction time and higher incidence of missing saccades (i.e., reduced speed and accuracy of visual orienting) and shorter periods of fixation/attention

hold on visual stimuli (i.e., reduced oculomotor/attention control) in brief eye-tracking tests.

Hypothesis 2b: Treatment with supplementary food will lead to a recovery of neurocognitive function in MAM. Compared to the assessment at enrollment, children with MAM will exhibit shorter saccadic reaction times and longer fixation durations after four weeks of supplementary feeding.

Hypothesis 2c: There are differences in the effects of the four foods on measures of neurocognitive function in 7 to 11-month-old children with MAM after four weeks of supplementation.

Primary Outcomes: The outcomes measured were: i) child nutritional status (measures of mid-upper arm circumference [MUAC]); ii) neurocognitive function, including counts of saccades to high-contrast patterns (consistency and accuracy of visual orienting), mean saccadic reaction time (speed of visual orienting in different conditions), and mean fixation duration.

4. Methods

4.1 Study Site

Data were collected as a part of a larger intervention study comparing the cost-effectiveness of four supplementary foods in the treatment of MAM in Pujehun District, Sierra Leone. The study was implemented in 29 Peripheral Health Units (PHUs), which were randomized to administer one of four supplementary foods to children 6-59 months of age diagnosed with MAM—defined as MUAC ≥ 11.5 cm and < 12.5 cm without bipedal oedema. Caregivers of children admitted into the feeding program were seen every two weeks until an outcome was reached up to seven rations total and received one of the following foods:

1) Super Cereal Plus with amylase (SC+A): 136 g SC+A/day; 2) Corn-Soy Blend Plus and fortified vegetable oil (CSB+ w/oil): 86 g CSB+/day and 26 g fortified vegetable oil/day; 3) Corn-Soy Whey Blend and fortified vegetable oil (CSWB w/oil): 86 g CSWB/day and 26 g fortified vegetable oil/day; and 4) Ready-to-Use-Supplementary Food (RUSF): 100 g RUSF/day. Depending on recovery (MUAC ≥ 12.5cm), children received the ration for two, four, six, eight, ten or twelve weeks. Children who had not recovered after twelve weeks were referred to the clinic or another health facility for further treatment.

The study was piloted in the study area by assessing children with MAM and well-nourished controls from two age groups (7 months ±14 days and 18 months ±14 days old, targeted sample size N = 32/group). The pilot study showed that the eye-tracking tests were feasible in both age groups, although it was also found that a high proportion of children receiving treatment for MAM in the study area were under 12 months. Given these findings and the hypotheses regarding the effects of malnutrition on early brain development, the main neurocognitive sub-study focused on younger infants and a more narrowly specified developmental window (7- to 11-month-old children). Eligibility

criteria were age between 7 and 11 months and presence of MAM, while exclusion criteria were: a) a known history of visual problems; b) any neurological problem[1]; c) congenital malformation; d) participation in feeding program during the past month; and e) ongoing participation in a supplementary feeding program other than the one in the current study.

Children enrolled in the supplementary feeding program and meeting the age-eligibility were invited for further screening for participation in the sub-study. After a child with MAM was recruited, a control who met the age-eligibility criterion (i.e., 7 to 11 months), had MUAC ≥ 12.5 cm, and resided in the area of the same PHU was screened and recruited for the study. The same exclusion as those used with the MAM group were applied for the control group.

Children were tested at enrollment into the supplementary feeding program and again four weeks later. The four-week time period was chosen because all MAM children received four weeks of rations, even if they achieved recovery after two weeks.

The study received ethical approval from the Tufts University Health Sciences Institutional Review Board, the Washington University in St. Louis School of Medicine Institutional Review Board and the Sierra Leone Ethics and Scientific Review Committee. Beneficiary caregivers signed or thumb-printed the consent form on behalf of their infants.

4.2 Sample Size

Of the 202 infants enrolled in the sub-study, 191 participated in the eye-tracking assessments at Visit 1 (baseline) and Visit 2 (four weeks post-enrollment). Of these, three infants (2 percent) were excluded after prescreening due to non-eligibility (neurological history), and 44 infants (23 percent) for insufficient number of valid eye tracking test trials from Visits 1 or 2 (<10 trials/visit, **Table 1**). Demographic and anthropometric data on the sample children (cases and controls) are provided in **Table 1**.

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[1] Known neurological problems, visual problems or congenital malformation were screened on the basis of caregiver report.

Table 1. Sample Demographic and Anthropometric Data by Control and Study Arm.

N	Control	CSB+	CSWB	RUSF	SC+A
Enrolled and tested	60	35	20	39	37
Not eligible	0 (0%)	2 (11%)	0 (0%)	1 (5%)	0 (0%)
Insufficient eye-tracking data	14 (23%)	3 (9%)	8 (40%)	8 (21%)	11 (30%)
Final N	46 (77%)	30 (86%)	12 (60%)	30 (77%)	26 (70%)
Mean Age in Days (SD)	274.4 (41.6)	266.6 (44.6)	259.3 (45.2)	259.4 (37.5)	271.5 (42.1)
Gender (Female/Male)	22/24	15/15	8/4	20/10	21/5
Birth weight (kg)	3.2	2.9	3.0	3.0	3.1
Beneficiary caregiver Illiterate	40 (87%)	27 (90%)	12 100%)	24 (80%)	22 (85%)
Visit 1 MUAC (cm)	13.7	11.9	11.9	11.9	12.0
Visit 2 MUAC (cm)	13.9	12.3	12.3	12.2	12.4
Visit 1 Height (cm)	67.6	64.1	64.3	63.8	64.6
Visit 2 Height (cm)	68.3	65.1	65.6	65.0	66.0
Visit 1 Weight (kg)	7.6	6.0	6.1	6.0	6.1
Visit 2 Weight (kg)	7.8	6.5	6.5	6.4	6.6
Visit 1 Head C (cm)	43.5	42.2	42.0	42.1	41.8
Visit 2 Head C (cm)	43.8	42.6	42.9	42.6	42.4

4.3 Data Collection and Management

All participants enrolled in the study were assessed by conventional observational tests and novel eye-tracking-based tests of visual orienting (i.e., saccadic reaction time and fixation measures). The primary outcome was the speed of visual orienting (i.e., saccadic reaction time) as assessed by eye tracking. Secondary outcomes were eye-tracking measures reflecting the spatial and temporal characteristics of visual fixations while the infant was exploring a dynamic social scene.

4.4 Anthropometric Assessment

Infant length was assessed to the nearest 1 mm by using a length board (Harpenden Infantometer, Holtain Limited, Crosswell, Crymych, UK), weights by using an electronic scale (SECA 735, Seca GmbH & Co., Hamburg, Germany) and MUAC and head circumference to the nearest 1 mm with insertion tapes (ShorrTape, Weigh and Measure, LLC, Olney, MD). More detail on the anthropometric measures may be found in the main study section of this report.

Figure 1. Eye Tracking Assessment
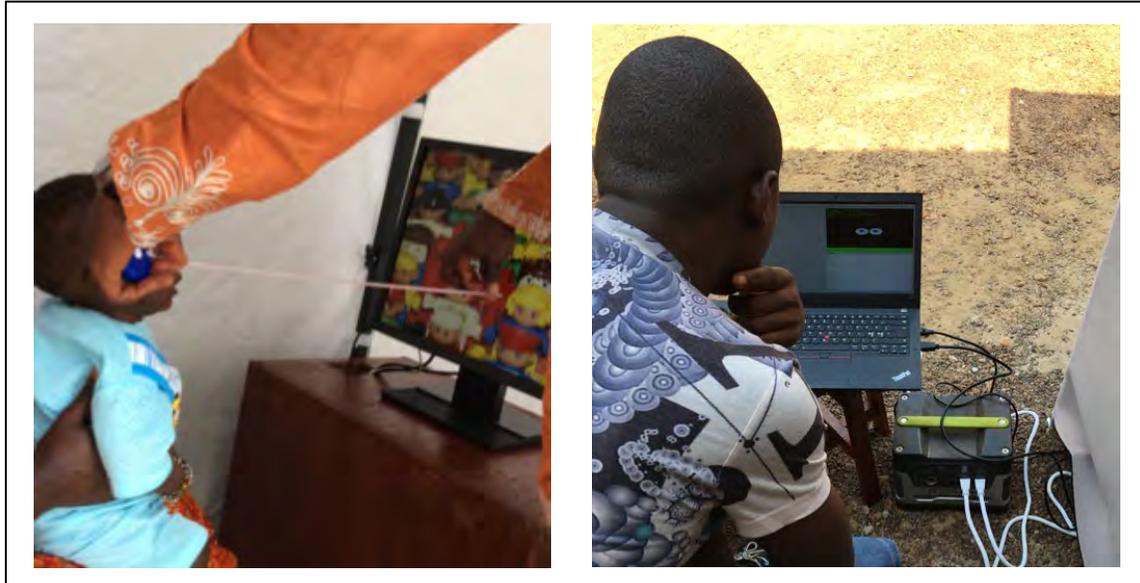
A child positioned for eye tracking assessment in a field laboratory tent (the child in the picture is not related to the study). During the assessment, infants viewed short sequences of visual stimuli on the screen (colorful cartoon animations of common objects.) Data collector monitored the assessment outside the laboratory via real-time visualization of eye tracking. The devices used in the testing were powered by a solar-chargeable battery.

4.5 Eye-tracking Testing

Infants were assessed in a 1.5 m (width) x 1.5 m length x 2 m (height) canopy tent with custom-made walls of monochromatic dimout fabric (**Figure 1**). The tent was mounted in the vicinity of a PHU, typically on a covered outdoor porch area. The caregiver held the infant in a baby carrier so that the infant's eyes were facing forward and positioned at approximately 60 cm viewing distance from a 19-Inch monitor (Acer V196L LCD monitor, Resolution: 1280 x 1024, Refresh rate: 60 Hz, Response time: 5 ms) and a screen-based Tobii X3-120 eye tracker (Tobii Technology, Stockholm, Sweden). The monitor and the eye tracker were placed on a wooden desk that was custom-made to be at suitable height for the participants in the sample age range. Infant status during testing was monitored via a video recorder and a baby monitor. The video recorder (Sony HDR-CX240E) was mounted on top of the monitor. The baby monitor (Summer) was placed next to the monitor on the desk.

A Sierra Leonian, Mende-speaking data collector was trained to perform the eye tracking assessments. The data collector instructed the caregiver to look away from the screen and positioned the caregiver, holding the infant in a forward-facing baby carrier, so that the infant's eyes were at an optimal distance from the eye tracker. The data collector then moved outside the tent laboratory to start the tests while constantly monitoring the caregiver and the infant through two monitors. One monitor showed an

overall view of the caregiver and the infant. The other monitor showed a visualization of infant gaze position on the screen.

During the assessment, infants viewed short sequences of visual stimuli on the screen (colorful cartoon animations of common objects). A detailed description of the stimuli is given in **Appendix 1**. While the infants were viewing the stimuli on the screen, their pupil diameter, point of gaze in the display area and position of the eye in a three-dimensional user coordinate system were recorded (120 samples/sec). The testing consisted of two parts, each lasting three to four minutes. If the infant became restless, inattentive or fussy during the procedure or if the eye tracking system lost contact of the eyes, the experimenter paused the test and entered the laboratory to administer a break and/or to perform required adjustments (e.g., adjusted the infant's position).

The presentation of the stimuli on the screen and the synchronization of the data regarding stimulus onset with the eye-tracking data stream was controlled by an open-source software written in Python programming language (https://github.com/infant-cognition-tampere/drop) together with Psychopy functions (Peirce, 2007) and a Tobii SDK plug-in. The software includes a graphical user interface that allowed the data collector to follow real-time visualizations of the stimulus presentation and eye tracking data streams throughout the testing (**Figure 1**). The eye-tracking software was run on Linux operating system (Mint 17) and a Lenovo X260 laptop computer (Lenovo Group Ltd.) and were connected to the stimulus display via a HDMI-DVI cable and to the eye tracker via an Ethernet cable and a TRENDnet 4-Port Broadband Router.

The devices used in the testing were powered by a solar-chargeable battery (GoalZero Yeti 400, NRG Energy, Houston, Texas, USA). A fully-charged battery supplied power for a full day of testing.

4.6 Conventional Eye Movement Testing

Conventional eye testing included tests of saccades, smooth pursuit and fixation (Olsson et al., 2015). In the saccade and smooth pursuit tests, the first target (a colorful rattle) was presented in the child's field of vision at eye level, centered with respect to the child's line of gaze, and at approximately 50 cm from the child's eyes. When the child fixated the target, a second similar target was presented to the child's lateral field, at the same level as the first target and approximately 50 cm to the left or right of the first target. After the child shifted gaze from the first (central) to the second (lateral) target, the lateral target was moved toward the central target. The procedure was repeated twice for both directions. Saccades from the central to the lateral target and smooth pursuit eye movements following the moving target were scored by using a 3-point scale, where 0 indicated absence of saccade or smooth pursuit, 1 partial, and 2 complete saccade or smooth pursuit.

In the tests of visual fixation, the data collector presented a target (toy) for four seconds in an alternating sequence in the child's frontal, lower left, upper left, lower right and

upper right visual field. The child's response (fixation) was scored by using a 3-point scale where 0 indicated no fixation, 1 partial, and 2 complete fixation of the target.

4.7 Data Analysis

Raw data from the eye tracking tests of visual function were analyzed by using a library of computer scripts and functions (Leppänen et al., 2015). Key indicators of data quality were first extracted from the data, including measures of infant movement during testing, accuracy of recorded gaze positions, amount of data available for the estimation of the outcome variables and eye tracking noise (i.e., sample-to-sample variation in recorded gaze position). The main outcome variable from the eye tracking test, Saccadic Reaction Time (SRT), was defined as the time interval from the onset of the saccade target to the first entry of the gaze in the area of the saccade target ($\pm 1.4°$ margin). Secondary eye tracking outcomes were measures reflecting the spatial and temporal characteristics of visual fixations (i.e., periods when the eyes were stationary and fixated at a particular location of the image). For further detailed about the extraction of these variables from the raw eye tracking data, see **Appendix I**.

In statistical analysis of eye-tracking data, consistency of the eye-tracking outcomes within test sessions was assessed by calculating correlations between means extracted from odd and even-numbered test items (Pearson r) and across time (test-retest) by comparing means from Visit 1 and Visit 2. Odd-even split-half correlations have varied from .38 to .88 for measures of infant attention (Ahtola et al., 2014; Rose et al., 2012; Gillespie-Smith et al., 2016), and test-retest correlations from .53 to .76 over one to two-week interval and from .40 to .76 over a two-month interval in previous studies in high-resource settings (Cousijn et al., 2017; Leppänen et al., 2015).

The hypothesis that MAM is associated with neurocognitive slowing (i.e., longer SRTs) was tested by examining the effects of Group (MAM vs. Control) on mean log-transformed SRTs by using a linear mixed model (R & lme4 package). The Model included group, test block, trial number as fixed effects, child age and child gender as fixed effects, and a random intercept for each child as a random effect. To test the hypothesis that neurocognitive slowing in MAM resolves by supplementary feeding, the same model was fitted to the data with visit (pre vs. post) and Group x Visit as additional fixed effects. Corresponding models were fitted to the secondary indices of eye-tracking data (i.e., the coverage and duration of fixations while observing a social scene).

Data from the conventional tests of visual function were transformed into a binary outcome variable indicating the absence (0) or presence of the observed behavior (Partial/Complete, coded as 1) for each individual trial in each task, and the effects of Group (MAM vs. Control), Time (pre vs post), and test trial (1-4/5) on outcome behaviors (saccades, smooth pursuit and fixations) were modeled by using mixed effects logistic regression models, with random intercept for each child, as implemented in R and the lme4 package (R Core Team, 2014, Bates et al., 2015).

Figure 2. Children's Eye Positions (Upper) and Accuracy of Eye Tracking (Lower)

Upper: Visualization of the children's eye positions during the eye tracking assessment in the MAM (left) and Control (right) groups. The mean distance of the eyes from the optimal tracking position was similar in the MAM (Mean 4.80 cm) and control (Mean 5.02 cm) groups. **Lower:** Visualization of the accuracy of eye tracking in the MAM and control group. The scatterplot shows the recorded position of the eyes on the screen from all children while they were looking at a target stimulus. The size of the target stimulus is shown by the grey circle. The targets were presented at randomly chosen locations one at a time so that the distance between two successive targets was always 10° (the location of the first off-center target ('T1') from one subtest is shown)

5. Results
5.1 Eye Tracking Data Quality

Given that the current study used eye tracking in a novel setting, several variables were extracted to examine the quality of the measurements and the precision of the key outcome metrics (i.e., SRTs, fixation coverage and duration). Eye movements were recorded by remote cameras that allow for some degree of head movement during testing without data loss (**Figure 2**). Variability in head movement, calculated as root mean square of the distance from the eyes to the optimal position (x = 0 cm, y = 20 cm, and z = 56.4 cm) was 4.80 cm in the MAM group and 5.02 cm among controls, $p > .10$.

SRT Measures

For SRT analysis, the key indicators of data quality were error in the estimates of point of gaze, precision of the mean SRTs which is dependent on the number of valid trials and the within-subject consistency (reliability) of SRTs.

Mean error in the estimates of the point of gaze (i.e., distance from the returned value to the actual location of a calibration target) ranged from 0.68° to 1.14° (**Figure 2**). Given the focus on "object-level" attention shifts in the current analyses (i.e., detection of gaze shifts between two spatially-separate objects), the effect of this error (as well as the entire range of errors in the study) can be evaluated by contrasting the size of the error with the size of the saccade targets as well as the eccentricity of two successive targets. (This analysis, showing that all observed errors were within the boundaries of a single target object, is presented in **Figure 2.**)

Precision (standard error) in the estimates of the mean SRT values, as obtained from SD/SQRT(n), was near optimal in the current analyses given that: i) SRTs based on <10 valid trials were not included in the analysis; ii) the mean number of valid trials ranged from 20 to 23; and iii) further increase in the number of valid trials would have led to negligible improvements in precision. The odd-even split-half reliability of the mean SRTs ranged from $r = .65$ to $r = .68$, and, the test-retest correlation (v1-v2) of mean SRT was $r = .59$ (**Figure 3**). None of these data quality indicators differed significantly between MAM and Controls, $ps > .10$.

Fixations

Spatiotemporal analyses of gaze fixations during visual exploration can be sensitive to noise, which is typically assessed by calculating the sample-to-sample change in xy position of the eyes during periods of stable fixations. Median noise levels was similar for MAM (V1 mean = 1.13, V2 mean = 1.19) and Control groups (V1 mean = 1.18, V2 mean = 1.10), $ps > 10$). Approximately 80 percent or more of the noise estimates were in the range that is considered optimal for the detection of the fixations with the algorithm used in the current study (<2°). Similar analyses were performed for the amount of valid data (in sec). The mean duration of valid data per scene did not differ significantly between MAM and Controls in the first visit (MAM 10.32 sec, Controls 10.25 sec), but MAM had more valid data in the second visit (MAM 11.31 sec, Controls 10.91 sec), $t(93.95) = 2.08$, $p = 0.04$. The odd-even split-half correlations were .26 (Visit

1) and .47 (Visit 2) for measures of the spatial coverage of fixations, and .41 and .46 for the mean duration of fixations. Test-retest correlations were .31 for spatial coverage and .44 for the mean duration of fixations (**Figure 3**).

Figure 3. Reliability of Saccadic Reaction Time (Upper) and Fixation Duration (Lower)

Reliability of Saccadic Reaction Time (upper) and Fixation Duration (lower) estimates in the baseline and post-treatment assessment. The reliability (or consistency) of the measurements within a testing session was estimated by examining the similarity of the means obtained when using data from odd (x-axis) and even-numbered (y-axis) test items in each assessment.
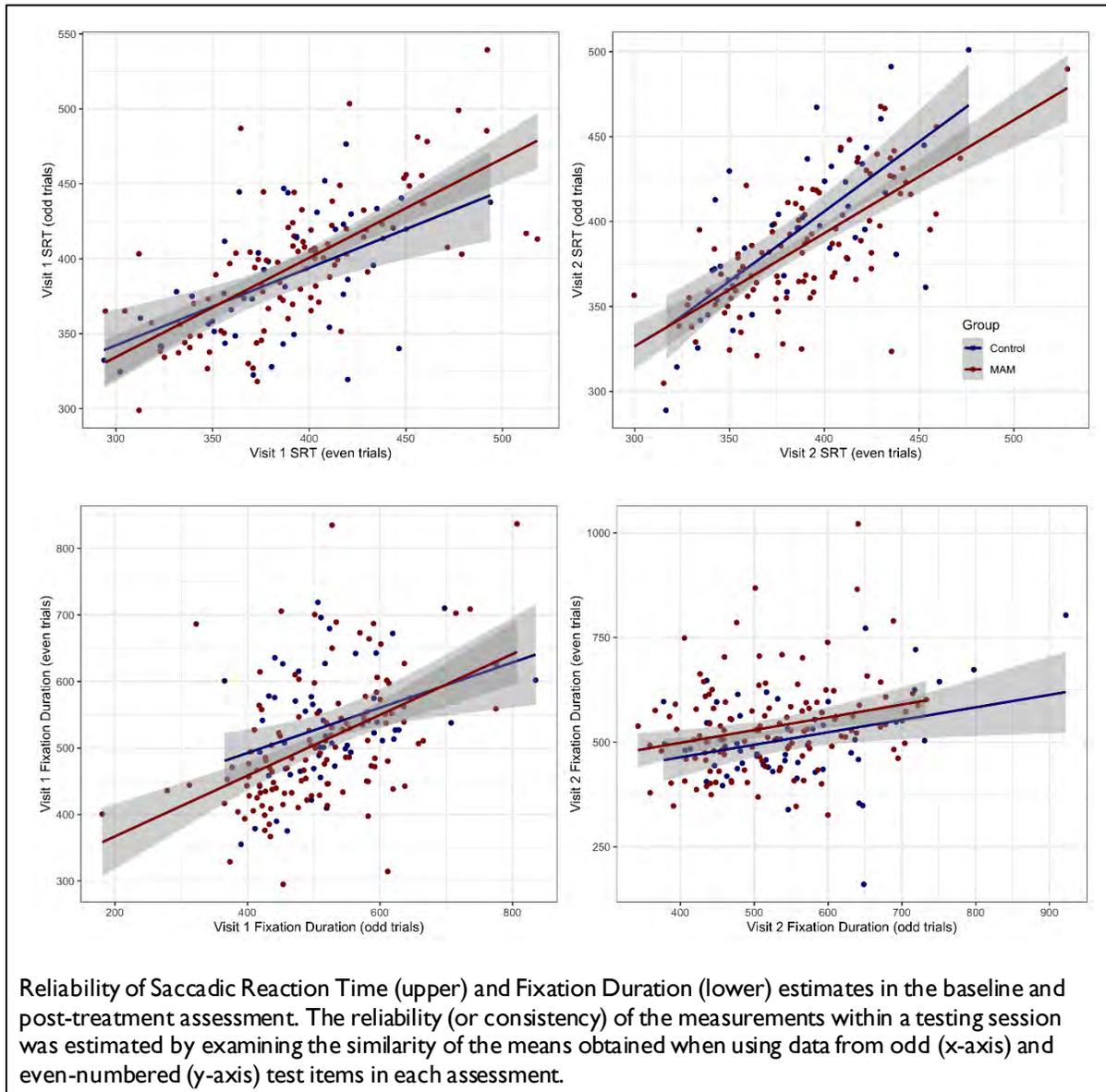
5.2 Effects of Supplementary Foods on Measures of Neurocognitive Function
Although the original aim of the study was to compare the four supplementary foods, the sample sizes were limited in some of the subgroups and for this reason, all statistical analyses were conducted by combining the MAM subgroups receiving different foods into a single MAM group.

SRTs

Response rates to the saccade targets on the computer screen were high for both
groups, and there were no significant group differences in the rate of responding to the
stimuli (Mean MAM_{visit1} = 95%, MAM_{visit2} = 94%, $Control_{visit1}$ = 94%, $Control_{visit2}$ = 95%). This
result supports the feasibility of conducting the assessments in the two groups.

Figure 4. Mean Saccadic Reaction Times for Infants with MAM and Controls by Visit

Mean saccadic reaction times (SRTs) for infants with MAM and Controls by visit. Data points are raw
means for individual subtests with 5 saccade targets. Lines represent predicted effects of group and
subtest number. Error bars represent 95% confidence intervals of the estimates.
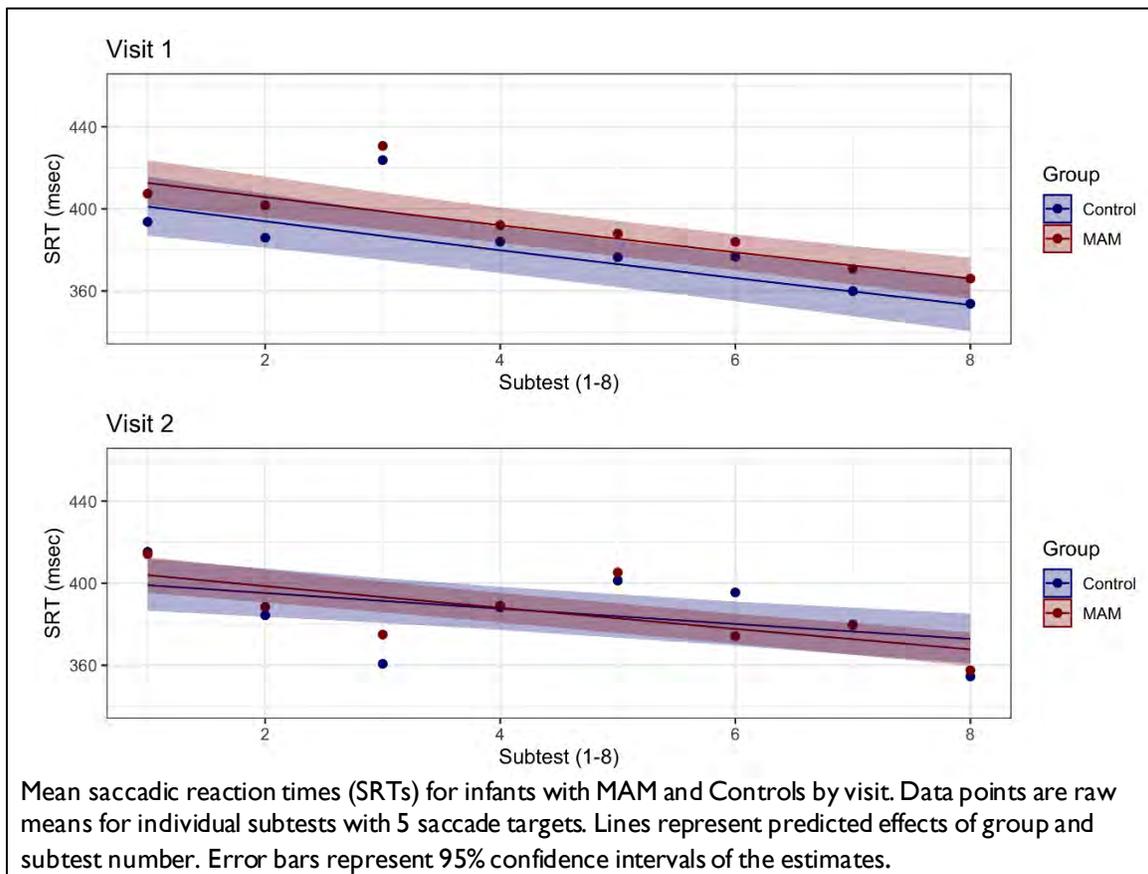
The effects of Group (MAM vs. Control) on SRTs was examined by using data from the
baseline assessment (i.e., before the supplementary feeding for MAM was started). MAM
children had marginally slower SRTs than Controls in the baseline assessment (**Figure
3**), (χ^2 (1) = 2.93, p = .086). This difference was consistent across the subtests (blocks)
in Visit 1 and independent of the general effect showing that the SRTs shortened over
the course of the assessment, (χ^2 (1) = 194.45, p < .001 [**Figure 4**]). To examine
neurocognitive recovery after supplementary feeding in MAM children, the MAM and
the control groups were compared for the pattern of change in SRTs over time (pre vs.
post). The Group by Time Interaction was significant, (χ^2 (1) = 7.14, p = .008). Further
analyses of the change within each group showed that SRTs shortened 7 ms ±2 between

the first and the second visit in infants with MAM, (χ^2 (1) = 9.69, p = 0.002 [**Figure 5**]). No significant change in the mean SRT between the first and second visit was seen in the control group, p = .23 (**Figure 5**).

Figure 5. Change in Saccadic Reaction Times Between Visits at Baseline and Posttreatment

Change in saccadic reaction times (SRTs) between visits 1 (baseline) and 2 (posttreatment) in MAM and control children. Mean SRTs in are predicted values from a linear mixed effects model with group, visit, subtest number (1-8), saccade target (1-5), child age, and child gender as fixed factors. Error bars represent 95% confidence intervals of the point estimates.
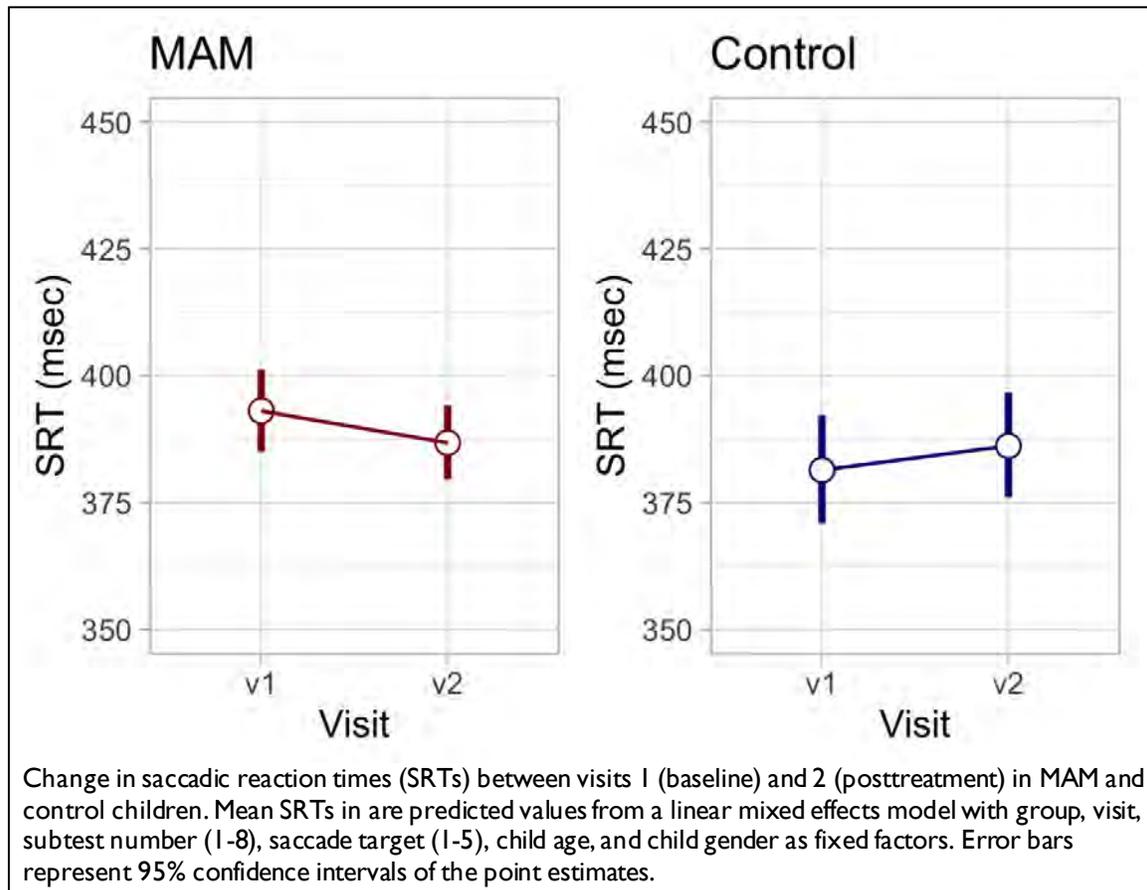
Fixations

Spatial and temporal characteristics of fixations were examined by using data collected while the infants were viewing dyadic social scenes (four 10- to 15-second scenes per visit). This analysis showed that the local maxima of fixations correspond to the approximate location of the face in the stimulus videos (**Figure 6**), consistent with infants at this age typically exhibiting a strong perceptual predilection for faces[2]. There was no indication of group differences in the distribution of fixation at baseline or a differential pattern of changes in the distribution across time, p = .37, suggesting similar areal coverage of fixations for MAM and control children while viewing social scenes.

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[2] As this study was not designed to examine the bias for face per se (e.g., faces were located in the same area of the display across the scenes), our data do not allow us to make a clear distinction between a face bias and other biases that may affect infant looking behavior (e.g., center bias), even though we consider the former as the most likely interpretation of the observed pattern.

Figure 6. Social Scenes Excerpts (Upper) and Distribution of all Visual Fixations (Lower)
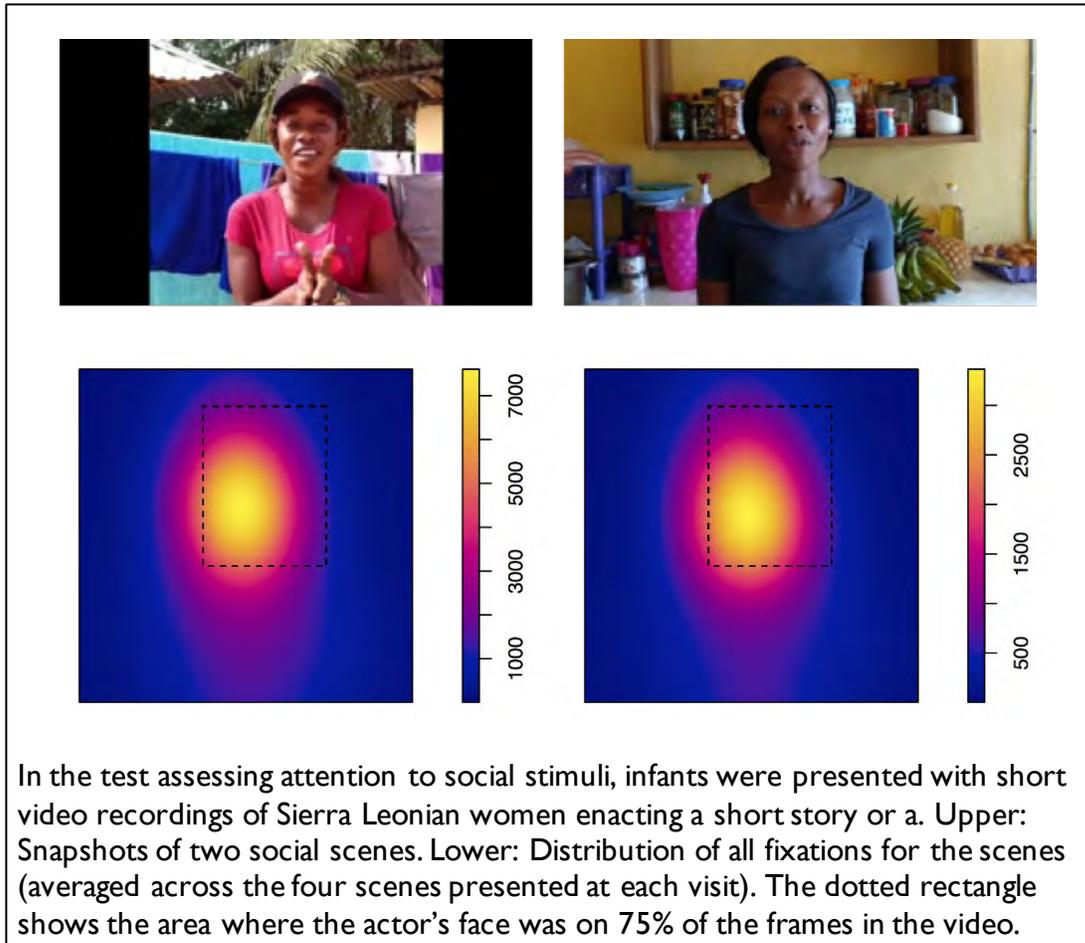
In the test assessing attention to social stimuli, infants were presented with short video recordings of Sierra Leonian women enacting a short story or a. Upper: Snapshots of two social scenes. Lower: Distribution of all fixations for the scenes (averaged across the four scenes presented at each visit). The dotted rectangle shows the area where the actor's face was on 75% of the frames in the video.

An established measure of the temporal characteristics of fixations in infants is the mean duration of fixations. The mean duration of fixations was calculated by averaging the duration of all fixations recorded while viewing the scenes (Mean number of fixations contributing to the average was 61.34 for Visit 1 and 66.55 for Visit 2). Relatively longer duration of fixations during free viewing in infancy has been associated with relatively better cognitive and behavioral control in mid childhood (Papageorgiou et al., 2014). The MAM and Control children exhibited a differential pattern of change in fixation duration over time, $\chi^2 (1) = 6.20$, $p = 0.01275$ (corrected $p = 0.032$). Further analysis of the pattern of change within each group showed that the MAM group had marginally shorter fixations in the pre-test, $\chi^2 (1) = 3.95$, $p = 0.04680$ (corrected $p = 0.078$), but the mean duration increased reliably for the MAM children in the post-treatment assessment, ($\chi^2 (1) = 33.31$, $p < .0001$ (corrected $p < .0001$ [**Figure 7-8**]). No difference between visits was found in the control group, $p = .43$. The corrected p-values are corrected for false discovery rate by taking into account all the tests performed in the exploratory analysis of the fixation data.

Figure 7. Change in Fixation Duration Between Baseline and Posttreatment Visits in MAM and Control Children

Mean durations are predicted values from a linear mixed effects model with group, visit, scene (1-4), child age, and child gender as fixed factors. Error bars represent 95% confidence intervals for the point estimates.
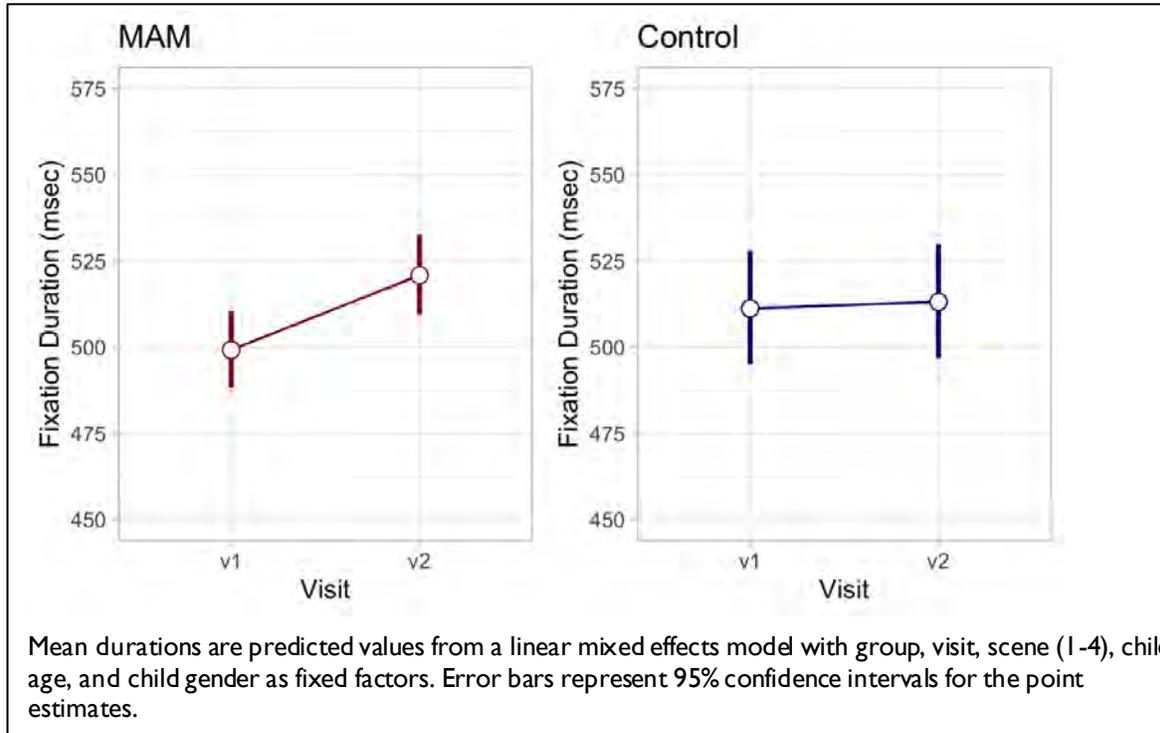
Figure 8. Distribution Density Plots for Raw Fixation Durations for First and Second Visits by Group
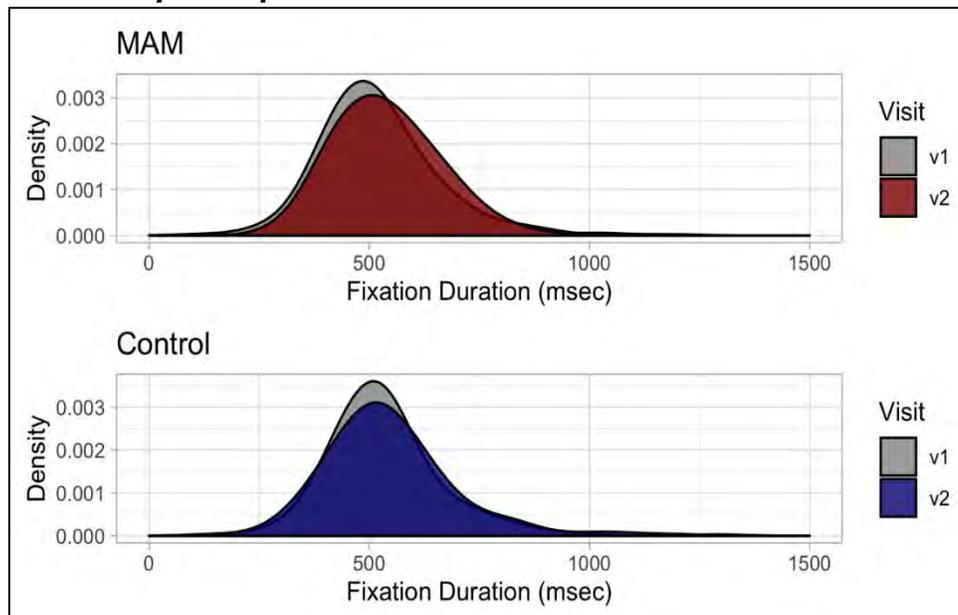
Conventional Eye Movement Testing

The MAM and Control children did not differ in observational tests of eye movement control and these behaviors did not change in response to treatment, $ps > .10$. There was a significant effect of trial on saccades (χ^2 (1)=3.71, $p = .05$), smooth pursuit (χ^2 (1)=17.4, $p < .001$), and fixation (χ^2 (1) =70.51, $p < .001$), reflecting a general decline in the expression of the measured behaviors over the course of the test in both groups. This pattern did not vary by group, $ps > .10$. As a further analysis to verify the presence of the studied functions in each of the groups (i.e., saccades, fixation, and smooth pursuit), the number of infants in each group that showed no evidence for the targeted capacity were counted. This analysis was limited to data from Visit 1 (pretest) given the general decline in the targeted behaviors between the visits. There were no infants

without any partial/full saccades, smooth pursuit, or fixations in the MAM group and There were no infants without any partial/full saccades, smooth pursuit, or fixations in the MAM group and only one infant in the control group did show any response that would have been counted as a partial/complete response in the fixation condition.

6. Challenges and Limitations

The current study showed no major barriers for wider use of eye tracking in the field and in the assessment of short-term changes in neurocognitive function in groups of infants.

Supporting the technical feasibility of the methodology in this novel context, the key metrics of visual orienting and holding were obtained for most infants for two separate time points, showed expected levels of precision and within observer consistency. Completion rates for the tests were slightly lower than expected (76 percent, expected 81 percent for two successful tests). The team has made changes to the assessment technology that have helped to improve completion rates, and they are currently at the expected level. Some other aspects of the methodology can be further improved (e.g., spatial precision).

7. Conclusions

This report documents a novel use of eye tracking in the assessment of short-term changes in neurocognitive function in malnourished infants in settings that have very few facilities. However, they represent the circumstances of many resource-poor communities in sub-Saharan Africa.

Consistent with the predicted effect of malnutrition on neurocognitive function, infants with MAM had marginally slower saccadic reaction times and shorter fixations than Controls did. The small size of these differences may reflect the fact that while the two groups differed in nutritional status, the participants were all children from environments that are disadvantaged by many measures. When compared to values reported in the literature, the mean SRTs in the current study were clearly slower than the mean SRTs typically found for infants in this age range. Direct comparisons are

complicated by procedural differences between studies, but the mean SRTs were 400 ms for MAM and 390 for Controls in the current study. The corresponding values in previous studies in Western populations have been consistently shorter, ranging from 270 to 375 msec (Caudill et al., 2017, Cousijn et al., 2017; Rose et al., 2002; Wass & Smith , 2014). Thus, our findings are consistent with the hypothesis that MAM has neurocognitive effects, but they also raise the possibility that the effects of MAM on neurocognition may not stand out as a strong effect in resource-poor settings, possibly reflecting the fact that most children are affected by various poverty-related risk factors in these environments (McCoy et al., 2016).

As a first direct demonstration of neurocognitive benefits of supplementary feeding, our results showed a significant change towards improved visual orienting (saccadic reaction time) and attentional focusing (mean duration of fixations) in the MAM group after four weeks of supplementary feeding. The interpretation of these changes as genuine improvements in neurocognitive function is supported by the consistency of the observed pattern across the two measures, by previous data showing that specific nutritional supplements result in similar changes in saccadic reaction time in high-resource settings in the U.S. (Caudill et al., 2017), by the established status of faster orienting and longer holding as markers of cognitive function (Dougherty & Haith, 1997; Papageourgiou et al., 2014), and, lastly, by the apparent functional benefits that come from faster orienting and longer durations of stable fixations during visual exploration. There were also no indications in the data that the differential change in the MAM and control group in either of the two measures reflected secondary effects arising from the test administration becoming more feasible between the two visits. The possibility remains, however, that the size of the improvements in the MAM group may change by supplement type.

To conclude, the results of this study demonstrate the promise of eye tracking in the assessment of neurocognitive status in malnourished children in low-resource field settings. The results also show novel evidence for the functional benefits of supplementary feeding of children with MAM.

In the future, this approach could be used to assess the effectiveness of different food compositions in the treatment of undernutrition in food-insecure environments. First, the current method can be optimized for larger scale use as a standardized, widely-applicable marker of neurocognitive outcomes in children in different environments and of varying age. Second, future studies will be needed to examine whether the treatment effects that were visible within a relatively short time scale in the current study (i.e., after four weeks of treatment) are maintained or increased over a longer period of time, and whether they transfer to more complex cognitive skills later in childhood.

Given the hierarchical nature of brain development and skill formation, even small improvements in elementary sensory and attentional functions in the early stages of development may result in large secondary effects on more advanced neurocognitive processes and, thereby, have a long-term, accumulating impact on skill formation. Finally,

the sample size in the current sub-study was limited for reliable analysis of differences among the four foods, but future studies with larger samples can use the current technology as an automated, standardized, and scalable method to compare neurocognitive outcomes across different food compositions and interventions. Together, these steps will be significant in finding the most effective interventions for early childhood malnutrition, and in helping the field to move beyond anthropometric outcomes to other outcomes that are important in the development of human capacity and well-being.

Acknowledgements

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Appendix I: Procedure and Stimuli in the Eye-Tracking Test

The eye tracking test consisted of two sessions that lasted three to four minutes. In each session, the infant saw alternating blocks of dynamic stimuli, including: a) 3-9 calibration targets; b) 4x5 saccade targets; c) 2 videos depicting a dyadic social scene; and d) 2 filler videos. The order of the blocks was always the same: 1) calibration targets; 2) social scene 1; 3) saccade targets 1-5; 4) filler 1; 5) saccade targets 6-10; 6) social scene 2; 7) saccade targets 11-15 ;8) filler 2; and 9) saccade targets 16-20. Infants completing both test sessions saw a total of six to eighteen calibration targets, eight blocks of five saccade targets (forty saccade targets in total), and four social scenes on each visit.

Calibration Targets

Calibration targets were short sequences of stimuli, consisting of an audiovisual animation (5.7° x 5.7°, duration: 1000-3000 msec), an isoluminant white disc (1.3°x 1.3°, 1000 ms), and reappearance of the animation (5.7° x 5.7°, 1000 msec). The sequences were presented in the screen center (0°,0°), bottom-left (-11.4°, -11.4°) and top right (11.4°, 11.4°). The targets were presented up to two times if less than 75 percent of the recorded point of gaze samples were valid for more than one of the targets. Samples recorded during the white discs that fell in a 9°x 9° rectangle surrounding the disc and a similarity transformation estimator (https://pypi.org/project/nudged/) were used to calibrate the raw point of gaze estimates from the eye tracker. The accuracy of the calibrated point-of-gaze estimates was verified by calculating the Euclidean distance of the corrected estimates from the location of the targets at the start of the experiment and in half-way of the experiment. Similar comparisons were performed for the raw uncalibrated point of gaze estimates. The method that provided the lowest error was used. Corrected values were superior for 88 percent of infants for Visit 1 data and 83 percent for Visit 2 data.

Saccade Targets

Saccade targets were colorful cartoon animations of common objects (e.g., fish, bird, pig, rabbit or a human face), subtending a 5.7° x 5.7° visual angle. The targets were presented one at a time without onset delay so that the first target was always presented in the center of the screen (0°,0°) and each subsequent target was presented in a new, randomly-chosen on-screen location 10° away. After presented on screen, the animations remained paused at the first frame until the infant looked at the animation (i.e., the first gaze point overlapping with the target area was recorded) or a 1000-msec wait period elapsed. The animation was subsequently played for 2500 msec. After the initial stimulus in the center of the screen (not used in the analysis given that the starting position for the first saccade was unknown), Infants saw a total of five saccade targets in one block and total of eight blocks on each visit. The decision to use clearly discernible colorful animations, randomly-chosen target locations and novel targets for each presentation instead of more uniform visual stimuli and fixed locations (Bargary et al., 2017) was based on infants' known proclivity for novelty and on evidence showing

superior response rates to colorful, pictorial stimuli in young children (Irving et al.,
2011)

Filler Items

To reduce monotony, filler items were presented in between the blocks of saccade
targets. The items were short (five second) video recordings of two Sierra Leonian,
Mende-speaking female models who greeted the child with a friendly tone of voice. The
videos were taken in various environments (i.e., in an outdoor yard or in a living room
area) and depicted two of the same models used in the dynamic social scene stimuli
(described below).

Social Scenes

Similar to previous studies (Constantino et al., 2017; Jones & Klin, 2013) social scenes
were 9.5 to 15-sec video recordings of Sierra Leonian female models who greeted the
child and continued by enacting a short story or a song appropriate for the participants'
age range. The videos were taken in various environments (i.e., in a kitchen, in a yard, in
a living room area). Infants saw a total of four scenes on each visit.