EXAMINING THE EFFECTS OF THIAMINE SUPPLEMENTATION ON CAMBODIAN INFANTS' LANGUAGE PROCESSING

by

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A THESIS

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Cambodian infants are at significant risk of malnutrition, and thiamine deficiency, in particular. This can put their survival at stake, but may also imperil the integrity of developing neural systems that support learning and cognitive/linguistic functioning. In this thesis I focused on the extent to which daily thiamine supplementation of Cambodian infants' breast-feeding mothers during early infancy protects infants' language-processing skill when measured at 6 months of age. 335 breast-feeding Cambodian mother/infant pairs were randomly assigned to one of four daily supplementation groups (placebo control, 1.2 mg, 2.4 mg, 10 mg) in a large-scale, double-blind, randomized-control trial. Infants' language-processing skill was measured via a task indexing a previously well-documented tendency for infants to prefer Infant-Directed Speech (IDS) over Adult-Directed Speech (ADS), even when speech is presented in a non-native language. As a whole, the sample of 237 Cambodian 6-month-olds who completed the task displayed a systematic preference for IDS over ADS. Strikingly, however, the level of thiamine supplementation infants received displayed a dose-response relationship with the magnitude of their IDS preference, indicating that thiamine supplementation protects the integrity of language-focused neural systems.

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Introduction

Malnutrition is the consequence of insufficient intake of macro and micronutrients. It can lead to changes in both the structure of the brain and the function of its neurological processes. These outcomes vary widely, as the way in which malnutrition affects the brain depends on the degree of the condition and the specific nutrients that are lacking (Kar, 2008). Such threats are far more severe during early development, especially prenatally and in the first 1000 days after birth. After birth, the extremely fast growth rate and proportionally high nutritional requirements make children more susceptible to negative consequences from malnutrition (Alamy, 2012). This phase during which there is heightened vulnerability to malnutrition-related developmental deficits is often called a critical period (Kar, 2008). Thiamine deficiency is a common contributor to malnutrition in Cambodian babies.

Consequences of Thiamine Deficiency for Infant Development

Thiamine, also called vitamin B1, is a water-soluble B-complex vitamin that helps the body generate energy from nutrients. Thiamine acts as a coenzyme in the processes of carbohydrate and amino acid metabolism (Institute of Medicine, 1998). It is essential in supporting cell growth and development and helps maintain the nervous system functions (Mayo Foundation for Medical Education and Research, 2017). Initially, thiamine is ingested then absorbed in the jejunum and ileum through active diffusion at lower concentrations and passive diffusion at higher concentrations. It is transported throughout the body in erythrocytes and plasma within the blood (Crook, 2018). There are multiple interconvertible forms of thiamine that are found in the body

which vary based on the presence of phosphate groups. It enters the body as free thiamine but mainly exists in the non-phosphorylated version called thiamine pyrophosphate (TPP) which is used in metabolic pathways (Institute of Medicine, 1998). Thiamine can be stored in the liver in very small amounts and excess remains unchanged (free) and is excreted, along with its metabolites, through urine (Crook, 2018).

As thiamine can only be stored in small amounts and has a relatively short half-life, it must be consumed frequently (Whitfield, 2016). There is no known upper limit for thiamine intake (Whitefield, 2019). Humans rely on food or dietary supplements as sources of thiamine. Foods that are naturally rich in thiamine include legumes, seeds, whole grains, and some fish and meats (Thiamine Fact Sheet for Health Professionals). There are also a few foods that contain thiamine antagonists like tea leaves or betel nuts (Allen, 2006) Thiamine is easily destroyed in heat or when cooked in water, and is almost completely removed from grains during the milling process (Guidelines on Food Fortification with Micronutrients). Because of this, thiamine is a popular nutrient used in food fortification in many industrialized countries (Dary, 2006).

In many southeastern Asian countries, including Cambodia, a lack of available dietary variation and high dependency on milled and polished white rice makes it difficult to consume sufficient amounts of thiamine (National Institute of Statistics, 2011; Whitefield, 2016). The average adult requires 1.0-1.2 mg/day of thiamine daily (Bradford, 2015) and this requirement increases to 1.4 - 1.5 mg/day during pregnancy and lactation (Whitfield, 2018). Breastfeeding mothers who are unable to consume sufficient amounts of thiamine in their diet produce milk low in thiamine, which puts

breastfeeding infants at risk for thiamine deficiency. Thus, the 96% of Cambodian babies under six months who are breastfed are at high risk for thiamine deficiency and its negative effects (National Institute of Statistics, 2000).

Early stages of thiamine deficiency include a wide range of symptoms involving the nervous, cardiovascular, and gastrointestinal systems (Office of Dietary Supplements, 2018). More severe cases of thiamine deficiency are known to lead to conditions like beriberi and Wernicke - Korsakov syndrome. There are two categories of beriberi which vary based on symptoms; wet beriberi mainly affects the cardiovascular system causing poor circulation and edema and dry beriberi principally affects the nervous system leading to nerve degeneration. Wernicke - Korsakov syndrome leads to severe neurological damage (Beriberi, 2020).

Thiamine deficiency in infants is more difficult to diagnose because symptoms often mirror other diseases, but it is at least as deadly as thiamine deficiency in adults. Milder cases present with generic symptoms like constipation, vomiting and restlessness and more severe cases like infantile beriberi cause lung, heart, nerve and gastrointestinal disturbances (W., & U., 1999). If left untreated, infantile beriberi can lead to death within hours (Whitfield, 2016). For a long time, the medical community has focused on infantile beriberi as the sole threat to thiamine deficient infants. However, recent evidence suggests that sub-clinical levels of thiamine deficiency -- not severe enough to cause beriberi or other symptoms -- may have adverse effects on cognitive and language development (Fattal-Valevski, et al., 2009), presumably as a result of thiamine’s importance to the integrity of developing neural systems.

Importance of Thiamine for Cognitive and Language Development

In humans, the complex neural circuitry that underlie basic cognitive functions, such as memory, action, and language undergo extensive developmental change over time; patterns of neural activation in these systems typically continue to display noticeable progression through the late teens or early twenties (Barnea, et al., 2005). As previously mentioned, these neural systems experience especially rapid changes during an infant's first 1000 days. The first two years of life appear to comprise a series of time windows that are particularly sensitive for the establishment of foundational cognitive and linguistic abilities that are crucial to subsequent functioning (e.g., Hensch, 2016). To the extent that thiamine deficiency undercuts neural integrity within these sensitive periods of infancy, long-term learning and cognitive/linguistic functioning are likely to be compromised.

A small body of research suggests that language development may be especially vulnerable to the effects of thiamine deficiency during early infancy (Fattal-Valevski, 2005). This research followed a group of Israeli children whose formula-based diet during infancy inadvertently lacked thiamine. When tested at preschool age, these children displayed significant delays in both expressive and receptive language, relative to age-matched peers whose formula had contained adequate thiamine.

Despite these concerning findings, relatively little is yet known about precise ways in which thiamine deficiency may undermine developing language skills. This is in part because it can be challenging to determine the progression of language-development skills in preverbal infants. Techniques are needed that measure infants' developing ability to process linguistic information, and in particular, their ability to

process information that supports subsequent language learning. Measuring infants' preference for infant-directed speech (IDS, aka "motherese") offers a possible way to do so, as I explain below. This thesis research offers the first known investigation of the potential value of measuring infants' IDS preference as an index of the consequences of thiamine deficiency – and potential benefits of thiamine supplementation -- for preverbal infants' developing language-focused neural system.

Infant-Directed Speech Preference as a Window on Early Language Processing

IDS refers to speech patterns that adults often use when speaking to babies; it involves a suite of modifications including higher pitch, exaggerated intonation contours, increased repetition, shorter phrases and longer pauses (Fernald, 1989). Considerable evidence indicates that typically developing infants prefer IDS over adult-directed speech (ADS) (e.g., Fernald, 1989). A large-scale, multi-site replication study recently confirmed a robust and widespread tendency for infants (ranging from 3 to 15 months of age) to prefer IDS over ADS (ManyBabies Consortium, 2020). The IDS preference replicated across three different infant looking-time procedures that were tested. Interestingly, in this large-scale study, infants' preference for IDS was even confirmed when infants were hearing IDS and ADS in a language other than their own native language (see Figure 1).

A now sizable body of research provides additional evidence that infants' preference for IDS over ADS holds functional value, in that IDS facilitates infants' language-learning (e.g., Kuhl, 2004). Among other things, research suggests that a preference for IDS enables infants to more easily segment, discriminate, and recall/recognize words within continuous speech (Frank & Alcock, 2017).

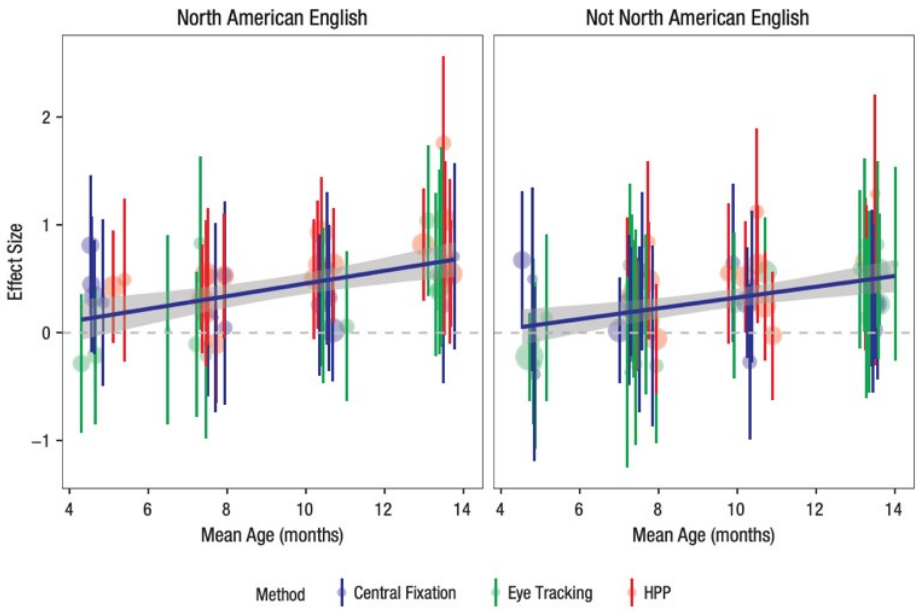

Figure 1: Report of effect sizes from ManyBabies Consortium's large-scale replication of infants' preference for North-American English IDS over ADS when babies were hearing their native language (left panel) versus when babies were hearing a non-native language (right panel).

In addition to holding functional value for language learning, infants' IDS preference also is indicative of underlying skill at processing linguistic information. Displaying a preference for IDS over ADS implies that infants can discriminate between these two speech registers. To an adult ear, making such a discrimination may seem blatantly easy. However, doing so actually requires impressive perceptual skill for analyzing the differences between complex and dynamically-evolving auditory streams as they are produced across time. The ability to make such a discrimination for IDS versus ADS in an unfamiliar, non-native language implies even more skill given the novelty of the perceptual sequences over which differences must be detected. Together, these observations raise the possibility that measuring infants' IDS preference – and

perhaps, as well, IDS preference in a non-native language – may provide a sensitive index of the integrity of the neural systems that support early language-processing skill.

If this is correct, one wonders what the significance may be when infants fail to show an IDS preference, or even display an IDS "dispreference" (i.e., a preference for ADS over IDS). One possibility is that such unusual patterns may be an indication of developmental disruption in language-focused neural systems. A handful of studies provide initial support for this hypothesis. For example, Kuhl and colleagues found that children later diagnosed with autism spectrum disorder tended to display a dispreference for IDS relative to ADS earlier on. As well, the extent to which they dispreferred IDS predicted the degree of disruption they displayed in their social and linguistic functioning (e.g., Kuhl, 2004).

The present thesis research offers another and different test of the possibility that unusual patterns in infants' response to IDS may indicate disruption in neural systems supporting language learning. As described earlier, Cambodian infants are not only at risk for malnutrition; they are at risk for thiamine deficiency, as well. If thiamine deficiency disrupts the development of neural systems important for language processing, Cambodian infants' language-processing skill may be negatively affected. Such negative effects may be measurable in terms of a reduced ability to discriminate, and thus prefer, IDS relative to ADS, especially when IDS and ADS are presented in a non-native language. Based on this hypothesis, I predicted that Cambodian infants' access to thiamine supplementation during early infancy would be associated with stronger non-native IDS preference at 6 months (24 weeks) of age.

To investigate this prediction, I coded and analyzed findings from videotaped data collected from 6 month-old, exclusively breast-fed, Khmer-learning infants in Cambodia. The videotapes were recordings of infants participating in the IDS Preference Task (IDSPT), in which they watched a video that presented one and the same visual stimulus (a rainbow checkerboard pattern) accompanied by either IDS or ADS speech in North-American English. Of interest was whether infants looked longer at the checkerboard when accompanied by non-native IDS relative to ADS, and the extent to which levels of thiamine supplementation were associated with the magnitude of infants' preference for non-native IDS over ADS

It is important to note that in everyday use, IDS and ADS vary on many dimensions that may make comparison of the two difficult. To grapple with this, we utilized speech stimuli for the IDSPT that had previously been carefully formulated by the Many Babies Consortium to vary on dimensions that naturally distinguish IDS from ADS, while being equivalent on factors that introduce unnecessary, or possibly confounding, variation. In particular, the IDS and ADS stimuli were carefully selected to be similar in length, volume, the number of objects mentioned per audiotrack and the number of mothers speaking per audiotrack (ManyBabies Consortium, 2020).

My thesis research was embedded within a larger research enterprise. The Cambodia Project is an interdisciplinary and international research project exploring the physical and neurological consequences of malnutrition, and thiamine deficiency in particular, in Cambodia children. This project ventured into the research gap that is a lack of existing data on the effects of sub-clinical levels of thiamine deficiency. It is also one of the first projects to attempt to measure preverbal infant language processing

in the field. Again, this thesis specifically analyzed the data collected from the larger longitudinal study to investigate the degree to which thiamine supplementation is related to non-native IDS preference in 6-month-old Cambodian infants. This research has potential implications for public health policies and medical awareness. Specifically, this research holds promise to further clarify individual and societal costs of thiamine deficiency, which in turn will help to shape efforts to relieve these problems.

Research Questions

Research Questions

The overarching goal of this research was to explore how infants' nutritional status affects neurological, cognitive and social development. Three experimental questions were the specific focus of this thesis:

1. To what extent do 6-month-old Cambodian infants display a preference for IDS over ADS in non-native speech, replicating previous findings (e.g., ManyBabies, 2020)?
2. To what extent is access to thiamine supplementation during early infancy associated with increases in non-native IDS preference in Cambodian 6-month-olds?
3. To what degree does thiamine supplementation in early infancy display a dose-response relationship to the magnitude of infants' non-native IDS preference at 6 months of age?

Hypothesis and Predictions

I hypothesized that sub-clinical levels of thiamine deficiency may undercut neurological development in ways that negatively impact infants' processing of the speech stream, thereby reducing the likelihood that they will display a preference for IDS over ADS in non-native speech. Likewise, I hypothesized that access to thiamine supplementation from early infancy would protect the integrity of these neural systems, and thereby be associated with stronger IDS preference. I predicted that, on the whole, 6-month-old Cambodian infants would display a non-native IDS preference, replicating previous findings reported by the recent, large-scale documentation of this phenomenon in 69 research laboratories across the world (ManyBabies Consortium, 2020). I also predicted, however, that infants whose breastfeeding mothers received thiamine supplementation would display stronger non-native IDS preference at 6 months of age. Likewise, I predicted that higher levels of thiamine supplementation in early infancy would be associated with a greater magnitude in non-native IDS preference in 6-month-old Cambodian infants.

Methods

Prior to my involvement in the larger project, video-recorded data for this research was collected by the Cambodian staff, employed by the organization Helen Keller International, who are part of the larger study described in a recent registered report (Whitfield, et al., 2019). Thus, this thesis focused on coding these video data as well as analyzing and interpreting the results.

Participants

This study initially included 335 Cambodian mother/ baby pair participants. This sample was Khmer speaking and relatively socio-economically disadvantaged. All mothers were exclusively breastfeeding their babies. Testing occurred when infants were 2 weeks, 12 weeks and 24 weeks of age. See table 1 for further demographic information on this study's sample.

Characteristic	Dose = 0 mg n = 83	Dose = 1.2 mg n = 86	Dose = 2.4 mg n = 81	Dose = 10 mg n = 86	Total n = 335
Mean age of mother (years): Mean (SD)	28.3 (6.1)	27.9 (6.7)	28.1 (6.1)	28.1 (5.9)	28.1 (6.2)
Mother's whose highest level of education attended was primary school: N(%)	43 (51.8 %)	37 (43.0 %)	40 (49.4 %)	41 (48.2 %)	161 (48.1%)
Income for the entire household in the past 12 months in US dollars: Median (IQ range)	1800.0 (950.0-3000.0)	2050.0 (962.5-3500.0)	1600.0 (1000.0- 3000.0)	2000.0 (1200.0-3500.0)	2000.0 (1000.0-3000.0)
Mother's household does not have electricity: N(%)	44 (53.0%)	33 (38.4%)	40 (49.4%)	40 (47.1%)	157 (46.9%)
Mother's household does not have a refrigerator: N(%)	82 (98.8)	82 (95.3)	81 (100.0)	85 (100.0)	390 (98.5)
No member of the Mother's household has a bank account: N(%)	76 (91.6)	75 (87.2)	76 (93.8)	76 (89.4)	303 (90.4)

Table 1: Demographic information gathered in a survey administered to participating mothers prior to testing.

Part 1: IDS Preference Task Data Collection in Cambodia

The larger experiment of which the thesis was a part is a double-blind, randomized controlled trial. 335 breastfeeding mother- baby pairs were recruited in Kampong Thom province in Cambodia and randomly assigned to one of four groups to consume a thiamine supplement capsule of 0, 1.2, 2.4 or 10 mg of thiamine

hydrochloride daily between 2 and 24 weeks postnatal. At 2, 12 and 24 weeks researchers collected nutrition, health, sociodemographic, and neurological measurements from babies and mothers. Blood and breast milk samples were included in collection. Another component of the larger project was to discover whether, in the future, it will be possible to supplement Cambodians' diet with thiamine via salt intake. Researchers thus were also measuring each family's salt intake in order to calculate the concentration of thiamine needed in future salt supplementation products. As my project focused on the neurological measurements specific to IDS preference, I will go into further detail about this data collection

Unlike the other physical and neurological measurements taken more frequently throughout the larger study, the task measuring IDS preference, called the IDS Preference Task was only administered to 24-week olds. North American researchers visited Cambodia and trained the field team on how to carry out the IDS Preference Task infant looking-time procedures. This training emphasized the necessity of careful timekeeping and ensuring infants be in a quiet alert state before beginning procedures. IDS Preference Task data collection for the entire sample took place over multiple months, and each data collection session followed the same methodology.

A research team pair traveled to the home of a participating mother/baby pair and set up in an area with as little distraction as possible. A Samsung tablet displaying the IDS Preference Task visual/auditory stimulus was placed on a tripod approximately three feet in front of the mother/baby pair; the mother sat with the infant on her lap and facing the tablet displaying the stimulus video. The mother was instructed to physically stabilize the infant if needed but to not intervene in directing the infant's attention. A

camera was set up on the ground directly below the tablet and angled up at the baby's face in order to make it possible to later code infants' looking time to each trial as the video stimulus unfolded. The angle of the camera allowed the recording to capture the baby's eye movements from below the eyelids. To initiate each trial, the researcher turned on the camera and began calibration of the baby's gaze. To calibrate, the researcher shook a rattle just behind the center of the tablet, then above, below, left, right and center again while correspondingly dictating the direction of the toy out loud. This gaze calibration served to provide a frame of reference for the "center" field which the later video coders could use to identify when the baby was directing attention to the screen. Shortly after calibration was completed, the researcher turned on the IDS Preference Task stimulus which began with a chime.

Figure 2: A mother/baby pair during the IDS Preference Task data collection

After the initial chime the rest of the IDS Preference Task video alternated trials of IDS versus ADS speech samples, accompanied by a colorful checkerboard for infants to look at. Each trial was preceded by a few seconds of a laughing baby depiction, which was used as a technique for reorienting infants' attention to the tablet screen in case their attention had wandered. Throughout the video the researcher avoided intervening unless absolutely necessary to remove background distraction, such as an animal (dog, chicken, etc.) or other person walking through the room. The mother continued to sit behind the baby offering physical support but avoiding influencing the baby's attention. The stimulus ended with a final chime and shortly after the researcher turned off the camera to end the data collection.

Part 2: Data Coding

2.1 Coding Development

Coding infant looking time as an index of their preference for IDS over ADS has a long and well-established history (e.g., Frank & Alcock, 2017). However, this task has not previously been carried out in a field setting of the kind involved in the Cambodia Project. Thus, it was necessary to modify details of existing coding systems to respond to the unique aspects of the field setting. There was a need for a system that would identify when and how long each baby looked at the tablet throughout a given trial of the stimulus video. Team members constructed a coding template using Datavyu, a software package that provides a platform for establishing looking times via marking onsets and offsets of each look. A coding template was solidified and circulated to team members. The established coding template included three columns. Column one was a

hidden column (it was not be edited during coding) titled “stim” and included a time frame script of the auditory and visual components of the IDS Preference Task stimulus (black screen, chime, checkered screen, laughter, etc.). The second column was titled “gaze” and was for documenting the onset/ offset of a baby’s looks. And, the third column was titled “length” and served to distinguish what parts of the recording were within the beginning and end chimes of the IDS Preference Task stimulus. Additionally, the audio editing software Audacity was incorporated into the coding system in order to allow more accurate temporal location of chimes that marked the onset and offset of the experimental session.

2.2 Coding Data

Once the coding system had been created, 270 codable videos were identified out of the full sample of 335 infants. Coding was shared between two trained coders who worked independently regarding coding judgments. Reliability was established through 15% of the sample being double coded.

The goal of coding each video was to identify when a baby was giving attention to the screen during the IDS and ADS trials and thus to identify if he/she showed any language preference. The more than 300 IDS Preference Task videos were available to coders on One Drive and Google Drive storage. Prior to coding each video, a coder downloaded an IDS Preference Task video onto a secure computer and uploaded it into the Datavyu template and the Audacity software. In Audacity the coder listened for the first chime. Once the general location of this chime had been located the coder pressed zoom in, then zoom normal and zoom normal again to increase and unify the precision of the seconds to which chime onsets were identified. The coder did the same with the

end chime of the video and recorded those times in the first cell of the “trial length” column in Datavyu.

After establishing the beginning and end of the experimental session of the video in Audacity, the coder began to record the baby’s looks in Datavyu. The calibration in the beginning of the video specified where the infant’s gaze was considered a look and where it was not. Using the Datavyu controllers the coder went through the entirety of the video marking the onset and offset of each look. Further, more specific details were listed in the coding manual and were available for coders to reference at any time. Once completed, the Datavyu file was saved to the lab’s Google Drive and One Drive account.

Figure 3 provides a visualization of one infant’s IDS Preference Task session. Each rectangle on the graph represents a checkerboard stimulus trial that is either accompanied by IDS or ADS auditory stimuli. The varying colors represent when the infant was focused on the visual stimuli. This visualization displays the order of trials each infant experienced and captures general information about an individual infant’s looking patterns throughout the IDS Preference Task.

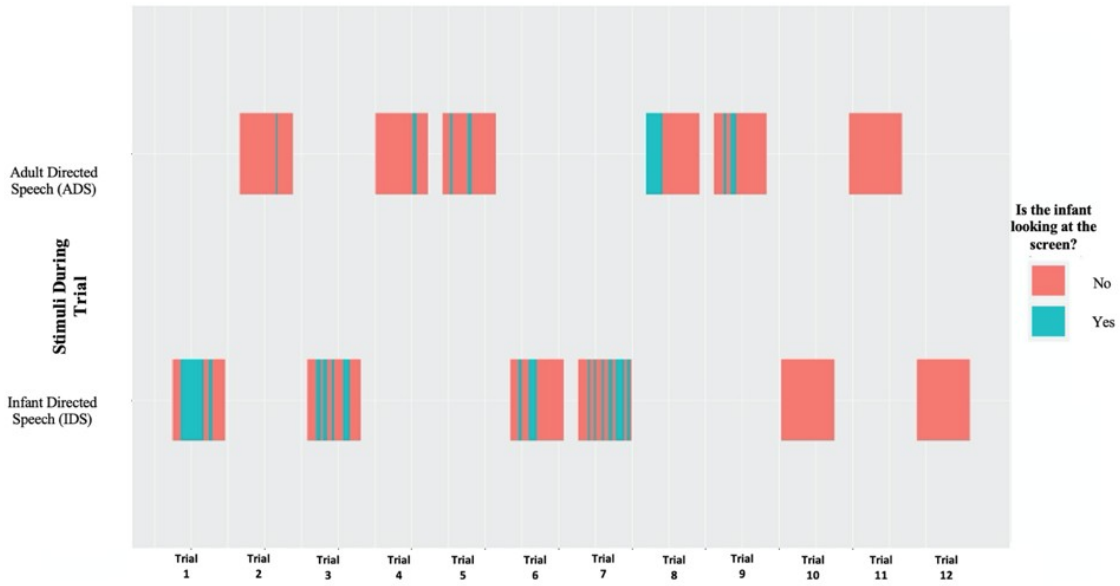

Figure 3: A visual representation of the looking patterns and looking times demonstrated by an infant during the IDS Preference Task (participant D004).

Part 3: Data Analysis

Looking-time data was analyzed separately from the Cambodia Project as a whole for the purpose of this thesis. There were several things I was looking for. First, I analyzed the data to see if there was a tendency across the whole sample for infants to prefer IDS over ADS. If confirmed, this finding would replicate other research on infant language preference (Frank & Alcock, 2017). Next, I was interested in testing for possible individual differences in IDS preference among babies in relation to their thiamine supplementation group. My analytic approach focused on use of analysis of variance and multiple regression, testing for the extent to which thiamine supplementation group predicted IDS preference. I predicted that infants whose breastfeeding mothers received thiamine supplementation at any level would display increased IDS preference, and a dose-response relationship between level of thiamine supplementation and the magnitude of infants' IDS preference.

Results:

In all analyses below, I report results with respect to the looking-time measure utilized in the large-scale multi-site replication study conducted by the ManyBabies consortium (ManyBabies, 2020) documenting infants' tendency to prefer IDS over ADS. This variable represents infants' total duration of looking for each checkerboard stimulus. As looking times tend to be positively skewed, they were log-transformed prior to all data processing. For data analysis, a difference score (time spent looking at the IDS-accompanied checkerboard minus time spent looking at the ADS-accompanied checkerboard) was computed for each adjacent pair of IDS/ADS speech trials. Positive difference scores indicate a tendency to prefer IDS over ADS, whereas negative difference scores indicate an IDS dispreference. The resulting difference scores, calculated from log-transformed looking times, were generally normally distributed (see Figure 3 below). As per the ManyBabies (2020) protocol, trials in which an infant looked for less than two seconds were eliminated from analysis. This criterion resulted in a final sample for analysis of 237 infants. Additionally, effect size was calculated using d_z, the version of Cohen's standard d statistic that was used in the ManyBabies study (computed as infants' average IDS preference score divided by the standard deviation of those scores).

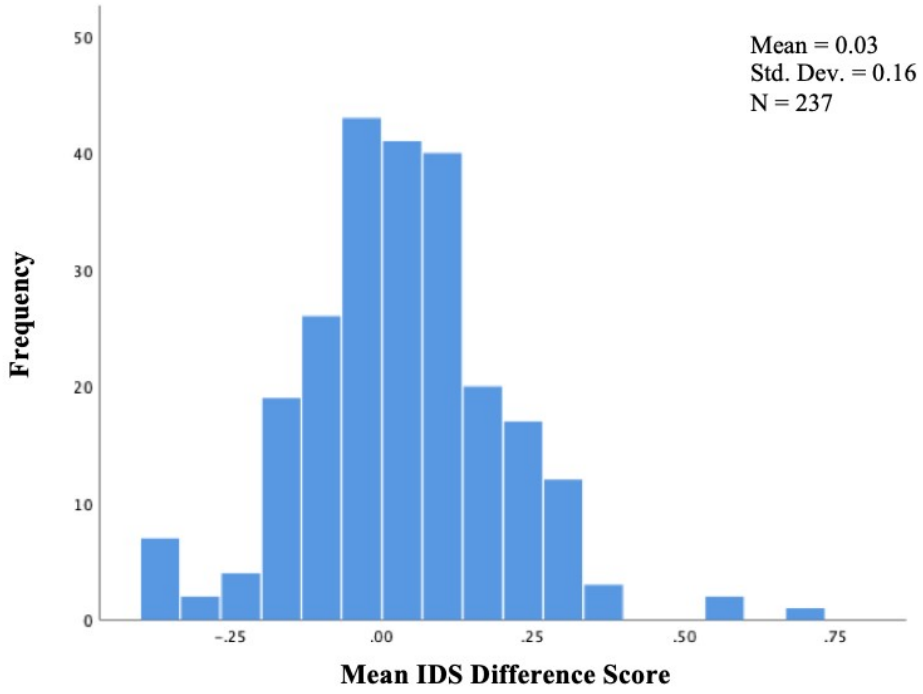

Figure 4: Histogram demonstrating the normality of the distribution of the difference scores calculated from log-transformed looking times.

Replication Results

Our first research question was one of replication in relation to findings reported by the ManyBabies Consortium (2020): to what degree did Cambodian infants, as a whole, display a preference for IDS over ADS, despite the fact that they were hearing IDS in a non-native language? We predicted that infants would display a difference score significantly greater than chance levels (chance = 0), indicating a preference for IDS. Infants' overall mean difference score of log- transformed looking times (M = 0.03, SD = 0.16) indeed revealed a significant preference for IDS, t (236) = .03, p = 0.002, 95% confidence interval 0.01 - 0.05, Cohen's d_z = 0.20, indicating an IDS preference in our Cambodian sample as a whole and therefore replicating the ManyBabies findings. Of the 237 infants in our final sample (remaining after exclusions

due to eliminating trials with <2 seconds looking), 136 (=57.38%) displayed a numerical preference for IDS (statistically significant by a binomial test, p = .01).

Overall Supplementation and IDS Preference Results

A second research question concerned the degree to which thiamine supplementation, at any level, was associated with increased preference for IDS compared to infants who were not supplemented. There were 182 infants who received supplementation on some level, and 55 infants who were in the control group and thus received no supplementation. I predicted that infants who received thiamine supplementation would display significantly higher IDS difference scores relative to infants who were not supplemented for thiamine. A one-way between subjects ANOVA with condition (control group vs. all thiamine supplementation groups) failed to clearly confirm this prediction: infants given thiamine supplementation (mean = 0.04, SD = 0.16) demonstrated only a marginal increase in IDS difference scores compared to the control group (Mean = 0.01, SD = 0.17), [f(1,235) = 2.09, p = 0.15)], partial eta squared = .01.

A series of planned independent-samples t-tests compared infants' IDS difference scores in each of the four conditions. These tests revealed that IDS difference scores were significantly higher in infants who received 10 mg thiamine supplementation relative to infants who received either a placebo control (t(115) = -2.21, p = 0.029) or 1.2 mg (t(117) = -0.894, p = 0.041), but did not differ relative to infants who received 2.4 mg supplementation. No significant differences emerged in the

magnitude of IDS preference among any of the other supplementation groups (t's $\leq$ -0.353, p's $\geq$ 0.300).

Dose Response Results

The third research question concerned the degree to which Cambodian infants' preference for IDS over ADS displayed a dose-response relation to thiamine supplementation level. I predicted that infants would display larger-magnitude IDS preference in relation to increased thiamine supplementation level. Using the difference score of the log transformed looking times, a linear regression was carried out to test the extent to which thiamine supplementation level (0 mg, 1.2 mg, 2.4 mg, 10.0 mg) predicted infants' IDS difference scores. A significant regression equation emerged $f(1,236) = 4.81$, $p = 0.029$), confirming that infants' tendency to prefer IDS over ADS was higher in relation to the thiamine supplementation dosage they received. The beta coefficient for the supplementation group variable was 0.124. Figure 4 displays the relationship between condition and IDS difference score; for interpretability, raw mean differences between IDS and ADS for each of the groups are displayed.

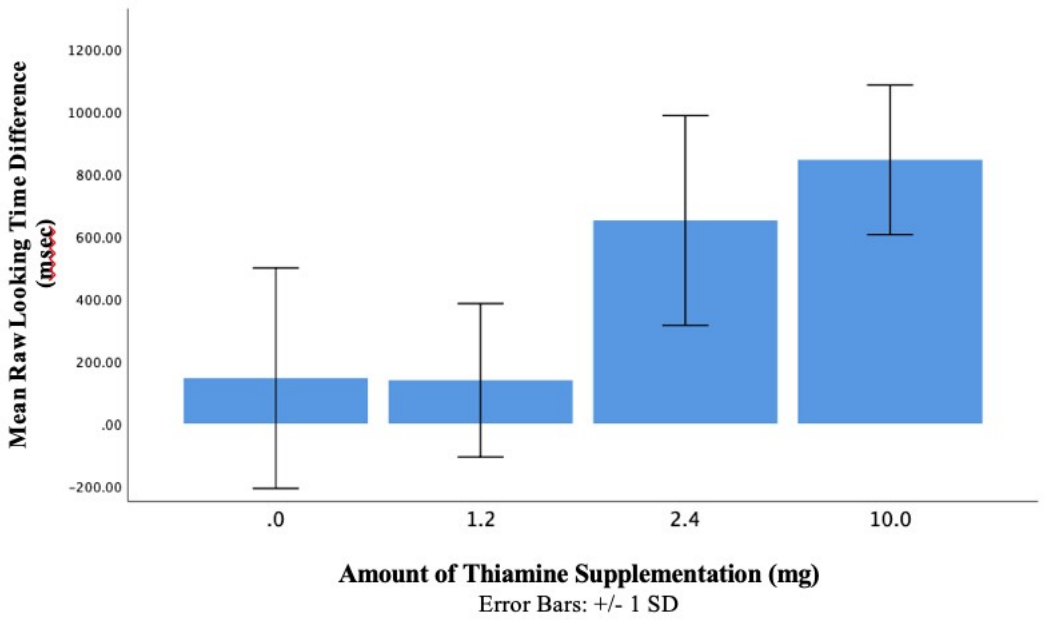

Figure 4: Infants' mean raw looking time difference scores (IDS – ADS) Control = 0 vs. thiamine supplementation of 1.2, 2.4 and 10 mg. Standard errors are also depicted.

To discover which groups of infants, when considered alone, displayed systematic IDS preferences, we undertook one-sample t-tests comparing individual supplementation group IDS difference scores to the level predicted by chance (0). These comparisons revealed that only infants in the 10.0mg supplementation group displayed a systematic IDS preference, $t(61) = 3.88$, $p = 0.000$, 95% confidence interval .03 to .10, Cohen's $d_z = .49$. Trends toward IDS preference in all other groups were non-significant, t's ≤ 1.66, p's ≥ 0.115.

Discussion

In this thesis I investigated the extent to which thiamine deficiency predicts the degree to which infants show a preference for IDS speech as an index of the integrity of their neural systems for language processing. I examined this question by means of the

IDS Preference Task, which measures infants' looking time at a neutral visual stimulus while they heard audio-tracks of either IDS or ADS. I then examined the extent to which the displayed preference for motherese was related to the level of thiamine supplementation that infants' breast-feeding mothers had received over the previous 6 months.

Replication

The first specific point of interest in this study was a replication of the preference for IDS over ADS in non-native language as documented by the ManyBabies Consortium; our results confirmed the replication with a resulting effect size of 0.20. Across the entire sample, 57.58% of infants displayed a numerical preference for IDS, which is roughly comparable to the 58.95% who did so in the ManyBabies Consortium's study. The ManyBabies study found an effect size of 0.35 for overall IDS preference and 0.29 for IDS preference among infants tested in a non-native language.

There are several reasons why it is unsurprising that our effect size of 0.20 was smaller than the effect sizes documented in the large-scale ManyBabies' study. First, infant participants in the present thesis tended to be socio-economically disadvantaged relative to the ManyBabies sample and were likely to be malnourished or thiamine deficient. As discussed in the introduction of this thesis, malnutrition and thiamine deficiency likely undercut language-processing skill, thus reducing the effect size. Additionally, the ManyBabies sample was averaged across a broad age range (3 to 15 months), with infants showing substantially larger IDS difference scores as their age increased across that range. Cambodian infants included in the thesis sample were on

the younger end of the ManyBabies age range, as they were all 6 months of age at the time they participated in the IDS Preference Task. Another factor was that the ManyBabies effects sizes were averaged across findings from several different methods for measuring infants' IDS preference (central fixation, eye-tracking, head-turn preference procedure). The central fixation method (utilized in this thesis) was intermediate in terms of effect size relative to the other two methods. Lastly, we conducted the IDS Preference Task in a field setting – Cambodian infants' village homes – whereas the ManyBabies data collection was completed in lab settings. Lab settings are likely to be more amendable to sensitive recording of looking-time data and therefore hold potential to provide a more sensitive test of IDS preference, which might result in a larger effect size.

Taking all these factors into account, the findings reported here provide robust replication of the previously observed non-native IDS preference. Moreover, these findings extend the scope of the current evidential base regarding IDS preference to a new culture/language group, in a field setting, and within a population of infants who were at risk for socio-economic disadvantage, malnutrition, and thiamine deficiency.

IDS Preference and Thiamine Deficiency

The other major topic of interest in the thesis research concerned whether, and to what degree, thiamine supplementation predicted an increase in the magnitude of infants' IDS preference. A comparison of IDS preference in infants from all supplementation groups relative to the control group revealed only a marginal trend toward increased IDS in the supplemented groups. However, the more sensitive

regression analysis testing for a dose-response relationship confirmed a statistically significant increase in the magnitude of IDS preference with increasing levels of thiamine supplementation. It is noteworthy that only the group of infants whose breast-feeding mothers received the highest level of thiamine supplementation – 10 mg – displayed a systematic IDS preference when considered alone. All other groups displayed unsystematic looking-time patterns.

These findings collectively point to two important conclusions regarding thiamine deficiency and its relation to infants' language processing. First, given that Cambodian infants are at risk for thiamine deficiency, the fact that infants who received low levels (or no) thiamine supplementation failed to show the predicted IDS preference strongly suggests that thiamine deficiency undercuts infants' developing language-processing skills. This finding provides additional support for previous findings that a history of thiamine deficiency in infancy is associated with later delays in language development (Fattal-Valevski, 2005), and provides the first evidence to date for a link between thiamine deficiency and reduced language processing facility in preverbal infants.

Second, the fact that the predicted IDS preference emerged only in infants receiving 10mg thiamine supplementation suggests guidelines for future supplementation dosage: 10mg per day supplementation for breast-feeding mothers may possibly be the minimally efficacious dosage level in providing infants with adequate thiamine necessary to protect development of language-focused neural systems.

Broader Implications

Robustness of IDS Preference

The first important implication of this study was one of replication. Participating infants as a whole displayed a preference for IDS over ADS while hearing language in a non-native language, thus replicating the pattern found in the ManyBabies study. The ManyBabies study included a diverse range of infants from non-English speaking countries including Turkey, Italy, Germany, Japan, Norway, Hungary, France, Mexico, Switzerland, Singapore, Netherlands and Korea. Thus, the IDS preference found in this study with Cambodian infants, whose native language was Khmer, further contributes to the range of regions and native languages across which infants' preference for non-native IDS has been demonstrated.

Unlike the ManyBabies study, the infants and mothers included in the present thesis were overall socially and economically disadvantaged. The majority of the participating Cambodian mothers' highest level of education was primary school and almost half of their households did not have electricity or generators (see study analysis report in the Appendix). The replication information this study provided is thus additionally important as this was among the few studies investigating IDS preference in an economically disadvantaged sample. Children born into disadvantaged families are more likely to face challenges, such as malnutrition, that may undercut their cognitive and language development. Therefore, the demonstrated replication of an overall IDS preference points to the robustness of the phenomenon in which infants show preference for IDS over ADS.

Additionally, to our knowledge, this is the first time that assessment of IDS preference has been carried out in the field. The IDS Preference Task and other cognitive testing took place in participants' village homes, whereas the data in the ManyBabies study was collected in lab settings. This field setting inevitably included more distractions and variables that are otherwise controlled for in a research lab. As this study still successfully replicated the IDS preference, the usefulness of cognitive measures like testing for IDS preference in the field is further validated. Overall, the unique setting and sample of this study expands the scope of the previously documented motherese preference.

IDS Preference: Indexing the Neural Integrity of Infant's Language Processing Systems

As I have described, prior research documents significant preference for IDS as early as 4-6 months of age, even when infants are hearing a non-native language (ManyBabies, 2020). In the context of field-wide ongoing questions about the reproducibility of scientific findings, this is perhaps the single most-strongly documented phenomenon regarding infant language development. Further, a handful of previous studies suggest that individual differences in IDS preference may carry clinical significance. For example, a dispreference for IDS has been found to predict autism symptomatology in some studies (e.g., Kuhl, 2004). Additionally, language development is significantly impaired in children with autism (e.g., Mody, 2013). These findings, taken together, suggested the possibility of harnessing IDS preference as an index of the integrity of neural systems supporting language acquisition. Moreover, given previous findings of significant delays in language development among children who experienced thiamine-deficiency as infants (e.g., Fattal-Valevski, 2005), measuring

IDS preference would plausibly be of particular value for indexing effects of thiamine deficiency on the integrity of developing language-oriented neural circuits.

The present findings offer strong initial support for these hypotheses. In general, infants growing up in Cambodia are at risk for thiamine deficiency as a result of a high level of cultural dependence on polished rice in the everyday diet, putting development of neural circuits for language processing likewise at risk. If IDS preference indexes the integrity of neural circuits for language processing, then thiamine supplementation in a group at risk for thiamine deficiency should be associated with gains in IDS preference. As predicted, we found that infants' IDS preference increased in magnitude as the level of thiamine supplementation increased. Indeed, only infants receiving a minimum of 10mg supplementation displayed a systematic preference for IDS over ADS, potentially pointing to the efficacy of supplementation at that level as adequate for protecting infants' neural integrity. All in all, the present findings offer the first evidence to date that measuring IDS preference holds value as a clinical tool for indexing, and potentially for ensuring, the integrity of infants' developing brains.

IDS Preference and Scaffolding the Scaffold

As described earlier, considerable evidence in the available literature documents that infants' preference for motherese serves a functional purpose for language development (e.g., Fernald, 1989; Kuhl, 2004). IDS has unique structural and acoustic patterns that elicit enhanced interest from infants. This increased orientation in turn gives infants more access to speech that is particularly informative for language learning, and thus scaffolds language development (e.g., Kuhl, 2004).

The results of the present thesis study have shown that infants who are a) at risk for thiamine deficiency, and b) are receiving little or no thiamine supplementation fail to demonstrate a beneficial preference for IDS over ADS. Without this preference, infants do not orient to linguistically beneficial IDS, and thus are not able to take full advantage of the scaffolding it provides for their language development. In this way, the absence of IDS preference may itself further undercut subsequent development of language-focused neural pathways.

Additionally, children who are unable to show a preference for IDS may further lag in subsequent language development because they fail to provide caregivers (or other language-proficient speakers) with positive feedback that encourages continued production of IDS. That is, when a child is less responsive to IDS, a caregiver may be less incentivized to continue using IDS in the context of their interactions. If infants fail to respond positively to IDS for an extended period of time, it is possible caregivers may phase it out altogether from their interactions with infants. If so, this occurrence would further decrease the availability of IDS to infants, likewise reducing the availability of quality language input to promote infants' language development. Overall, infants who preferentially orient to IDS may "scaffold the scaffold," thereby propelling their own language development. Infants lacking an IDS preference may miss out on this positive feedback loop, slowing the course of language learning.

If these speculations are correct, thiamine deficiency may put language development at risk in several ways simultaneously: by undercutting neural developments crucial to language processing, reducing infants' access to linguistically-

rich IDS, and disabling the positive feedback loop for language learning – "scaffolding the scaffold" – that IDS preference may support.

Limitation and Future Directions

As with any study, this thesis was presented with challenges and limitations throughout the research process. One initial challenge facing the Cambodian researchers working to collect this data was the difficulty of performing the IDS Preference Task in the field. In an ever-changing field setting, it was difficult at times to sufficiently coordinate the tablet screen presenting the visual stimuli, the speaker playing the auditory stimuli, and the video camera recording the infant. Additionally, this research used a laborious method of human-coded recording of infant looking times from videotaped data, which is a slow and labor-intensive process. For future research utilizing the IDS Preference Task, it would be extremely beneficial to combine these aspects into a single platform that presents visual and auditory stimuli while computational algorithms simultaneously record and process eye tracking data. Technological advances may soon afford these valuable improvements to field-measurement of infant looking-time measures such as IDS preference.

Another limitation in this research is the possibility of confounding variables that may have acted antagonistically to thiamine supplementation's benefits. Specifically, betel leaf chewing and maternal depression. Betel leaf chewing is common in many Asian countries and is known to have many negative consequences. When chewed, it releases thiamine antagonists into the body that react with ingested thiamine and render it un-digestible and therefore useless (WHO, 1999). Consequently, mothers in any of the supplementation groups who chewed betel leaf may have reduced the

amount of thiamine they absorbed, thus in turn reducing the amount of thiamine available to their breastfeeding infants. If so, benefits of thiamine supplementation, including IDS preference, would have been negatively affected. Data regarding mothers' betel-leaf-chewing rates were collected in the larger study, but have not yet been circulated for analysis. Future analyses that control for betel-leaf chewing rates will be needed in order to provide a more controlled, and sensitive, test of the effects of thiamine supplementation on infants' IDS preference.

Like betel leaf chewing, maternal depression was a potential confounding variable that may have masked thiamine supplementation's effects. Maternal depression is known to be a risk factor for infant's social, emotional and cognitive development (Kaplan, 2014). In general, research suggests this is due to disruptions in a depressed caregiver's abilities to support their infant's behavior or productively scaffold their infant's neurological development (Kaplan, 2014). Some research specifically documents that depressed mothers often fail to effectively use motherese (Bettes, 1998). Both decreased scaffolding, and lower production of motherese in particular, would likely have resulted in infants displaying reduced IDS preference in this study. It is noteworthy that mothers in the 10 mg supplementation group answered affirmatively to questions that screened for depression at somewhat higher levels than mothers in the other groups (see summary findings reported in Appendix), which may have reduced the effect size of analyses testing for a dose-response relationship between thiamine supplementation and the magnitude of infants' IDS preference. Again, once the full data set including individual mothers' responses to depression questions is circulated to all

researchers, it will be important to control for maternal depression in analyses examining relationships between thiamine supplementation and IDS preference.

The same overarching point can be made regarding the possible impact of general malnutrition on the findings in this thesis in relation the impact of thiamine supplementation. That is, our Cambodian sample was at risk for malnutrition generally, as well as being at risk for thiamine deficiency more specifically. Benefits of thiamine supplementation may have been either masked, or amplified, to the extent that infants' malnutrition levels differed substantially across supplementation groups. Although random assignment to supplementation groups is expected to have mitigated this concern, it will ultimately be important to conduct analyses relating thiamine supplementation to IDS preference that control for blood-markers of malnutrition. These measures were collected as part of the larger study, but also are not as yet available to researchers for analysis.

Among the additional cognitive and language measures that were collected with the infants participating in this thesis was The Mullen Scales of Early Learning (MSEL). The MSEL is a field standard, widely used test that comprehensively assesses children's motor, language and perceptual-cognitive abilities. Measurements are taken on five scales: visual reception, receptive language, expressive language, fine motor abilities and gross motor abilities. In future analysis, it will be of great interest to investigate the extent to which infants' scores on the MSEL tests converge with their scores on the IDS Preference Test.

Conclusion

Infants' preference for IDS over ADS has previously been well documented. This phenomenon was replicated in the present thesis. Participating Cambodian infants, who were at risk for malnutrition and thiamine deficiency, displayed an IDS preference in the context of non-native speech. While the results showed an IDS preference across the sample as a whole, it was nevertheless clear that thiamine deficiency had an effect on the extent of this preference. In particular, when each group of infants (0 mg, 1.2 mg, 2.4 mg, or 10mg of thiamine supplementation) was considered separately, only infants whose breastfeeding mothers received 10 mg of daily thiamine supplementation displayed a significant IDS preference. These findings suggest three important conclusions. First, they point to the potential efficacy of the IDS preference task as a valuable measure of neural integrity that is sensitive to thiamine-related differences in children's developmental progress. Second, they confirm previous findings regarding thiamine deficiency's negative consequences for infant's language development. Lastly, the findings suggest that, in the at-risk Cambodian context, 10 mg of thiamine supplementation per day for breastfeeding mothers may be minimally necessary to protect infants' developing language- focused neural systems.

Thesis Index

Thiamine Cambodia Study Analysis Report: Baseline Characteristics

Baseline characteristics (2 weeks postnatal questionnaire)

Characteristic	Dose=0 (n=83)	Dose=1.2 (n=86)	Dose=2.4 (n=81)	Dose=10 (n=85)	Total (n=335)
Age of woman (years): Mean (SD)	28.3 (6.1)	27.9 (6.7)	28.1 (6.1)	28.1 (5.9)	28.1 (6.2)
3. What is your marital status?: N(%)					
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
1. Married	79 (95.2)	86 (100.0)	81 (100.0)	84 (98.8)	330 (98.5)
2. Divorced/Separated	4 (4.8)	0 (0.0)	0 (0.0)	0 (0.0)	4 (1.2)
3. Widowed	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)	1 (0.3)
4. What is your ethnicity?: N(%)					
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
1. Khmer	83 (100.0)	86 (100.0)	81 (100.0)	85 (100.0)	335 (100.0)
5. How many pregnancies have you had?: Mean (SD)	2.6 (1.5)	2.3 (1.4)	2.4 (1.2)	2.6 (1.4)	2.5 (1.4)
6. How many live births have you had?: Mean (SD)	2.1 (1.1)	2.0 (1.2)	2.1 (0.9)	2.4 (1.2)	2.2 (1.1)
9. Have you attended school?: N(%)					
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
No	10 (12.0)	8 (9.3)	13 (16.0)	9 (10.6)	40 (11.9)
Yes	73 (88.0)	78 (90.7)	68 (84.0)	76 (89.4)	295 (88.1)
10. What is the highest level of school you attended?: N(%)					
Not applicable	10 (12.0)	8 (9.3)	13 (16.0)	9 (10.6)	40 (11.9)
1. Primary school	43 (51.8)	37 (43.0)	40 (49.4)	41 (48.2)	161 (48.1)
2. Lower Secondary school	16 (19.3)	29 (33.7)	19 (23.5)	19 (22.4)	83 (24.8)
3. Upper Secondary school	12 (14.5)	9 (10.5)	8 (9.9)	14 (16.5)	43 (12.8)
4. Higher education	2 (2.4)	3 (3.5)	1 (1.2)	2 (2.4)	8 (2.4)
11. Has your husband/partner attended school?: N(%)					
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
No	10 (12.0)	9 (10.5)	9 (11.1)	10 (11.8)	38 (11.3)
Yes	73 (88.0)	77 (89.5)	72 (88.9)	75 (88.2)	297 (88.7)
12. What is the highest level of schooling your husband/partner attended?: N(%)					
Not applicable	10 (12.0)	9 (10.5)	9 (11.1)	10 (11.8)	38 (11.3)
1. Primary school	42 (50.6)	37 (43.0)	39 (48.1)	33 (38.8)	151 (45.1)
2. Lower Secondary school	21 (25.3)	24 (27.9)	23 (28.4)	29 (34.1)	97 (29.0)
3. Upper Secondary school	5 (6.0)	13 (15.1)	8 (9.9)	8 (9.4)	34 (10.1)
4. Higher education	5 (6.0)	3 (3.5)	2 (2.5)	5 (5.9)	15 (4.5)
13. What is your Usual occupation?: N(%)					
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
1. Homemaker	42 (50.6)	41 (47.7)	40 (49.4)	40 (47.1)	163 (48.7)
2. Unemployed	6 (7.2)	3 (3.5)	8 (9.9)	6 (7.1)	23 (6.9)
3. Seller	4 (4.8)	9 (10.5)	4 (4.9)	5 (5.9)	22 (6.6)
4. Garment Factory	1 (1.2)	1 (1.2)	0 (0.0)	2 (2.4)	4 (1.2)
5. Farmer	19 (22.9)	27 (31.4)	23 (28.4)	25 (29.4)	94 (28.1)
6. other	11 (13.3)	5 (5.8)	6 (7.4)	7 (8.2)	29 (8.7)

Characteristic	Dose=0 (n=83)	Dose=1.2 (n=86)	Dose=2.4 (n=81)	Dose=10 (n=85)	Total (n=335)
14. What was the income for your whole household last month?in US: Median (IQ range)	150.0 (82.5-250.0)	155.0 (81.2-300.0)	150.0 (97.5-250.0)	150.0 (100.0-260.0)	150.0 (86.2-250.0)
15. What was the income for your whole household in the past 12 months??in US: Median (IQ range)	1800.0 (950.0-3000.0)	2050.0 (962.5-3500.0)	1600.0 (1000.0-3000.0)	2000.0 (1200.0-3500.0)	2000.0 (1000.0-3000.0)
16. How many cigarettes do you smoke per week?: N(%)					
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
None	83 (100.0)	86 (100.0)	81 (100.0)	84 (98.8)	334 (99.7)
≥1	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)	1 (0.3)
17. How often do you chew betel nut/betel leaf?: N(%)					
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
1. Daily	4 (4.8)	1 (1.2)	1 (1.2)	1 (1.2)	7 (2.1)
2. Several times per week	1 (1.2)	0 (0.0)	2 (2.5)	2 (2.4)	5 (1.5)
3. Once per week	1 (1.2)	3 (3.5)	3 (3.7)	3 (3.5)	10 (3.0)
4. Several times per month	1 (1.2)	0 (0.0)	2 (2.5)	1 (1.2)	4 (1.2)
5. Once per month	4 (4.8)	0 (0.0)	2 (2.5)	4 (4.7)	10 (3.0)
6. Less than once per month	9 (10.8)	4 (4.7)	6 (7.4)	5 (5.9)	24 (7.2)
7. Never	63 (75.9)	78 (90.7)	65 (80.2)	69 (81.2)	275 (82.1)
18. How often do you drink alcohol, including traditional postpartum?: N(%)					
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
1. Daily	11 (13.3)	10 (11.6)	19 (23.5)	19 (22.4)	59 (17.6)
2. Several times per week	8 (9.6)	7 (8.1)	4 (4.9)	7 (8.2)	26 (7.8)
3. Once per week	4 (4.8)	6 (7.0)	4 (4.9)	6 (7.1)	20 (6.0)
4. Several times per month	3 (3.6)	2 (2.3)	3 (3.7)	2 (2.4)	10 (3.0)
5. Once per month	2 (2.4)	2 (2.3)	0 (0.0)	1 (1.2)	5 (1.5)
6. Less than once per month	4 (4.8)	6 (7.0)	3 (3.7)	4 (4.7)	17 (5.1)
7. Never	51 (61.4)	53 (61.6)	48 (59.3)	46 (54.1)	198 (59.1)
19. How many episodes of diarrhea did you experience in the last week?: Mean (SD)	0.7 (2.4)	0.7 (3.5)	0.6 (1.7)	0.5 (1.3)	0.6 (2.4)
20. Do you typically experience diarrhea?: N(%)					
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
No	81 (97.6)	83 (96.5)	78 (96.3)	84 (98.8)	326 (97.3)
Yes	2 (2.4)	3 (3.5)	3 (3.7)	1 (1.2)	9 (2.7)
21. Over the last 2 weeks, how often have you been bothered by having little interest or pleasure in doing things?: N(%)					
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
0. never	51 (61.4)	53 (61.6)	50 (61.7)	41 (48.2)	195 (58.2)
1. several days	30 (36.1)	28 (32.6)	29 (35.8)	41 (48.2)	128 (38.2)
2. more than half the days	1 (1.2)	3 (3.5)	1 (1.2)	1 (1.2)	6 (1.8)
3. nearly every day	1 (1.2)	2 (2.3)	1 (1.2)	2 (2.4)	6 (1.8)
22. Over the last 2 weeks, how often have you been bothered by feeling down, depressed, or hopeless?: N(%)					

Characteristic	Dose=0 (n=83)	Dose=1.2 (n=86)	Dose=2.4 (n=81)	Dose=10 (n=85)	Total (n=335)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
0. never	71 (85.5)	73 (84.9)	63 (77.8)	59 (69.4)	266 (79.4)
1. several days	10 (12.0)	11 (12.8)	14 (17.3)	25 (29.4)	60 (17.9)
2. more than half the days	1 (1.2)	1 (1.2)	3 (3.7)	0 (0.0)	5 (1.5)
3. nearly every day	1 (1.2)	1 (1.2)	1 (1.2)	1 (1.2)	4 (1.2)
23. Does your household have electricity?: N(%)					
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
No	44 (53.0)	33 (38.4)	40 (49.4)	40 (47.1)	157 (46.9)
Yes	39 (47.0)	53 (61.6)	41 (50.6)	45 (52.9)	178 (53.1)
24. Does your household have a television?: N(%)					
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
No	48 (57.8)	30 (34.9)	40 (49.4)	43 (50.6)	161 (48.1)
Yes	35 (42.2)	56 (65.1)	41 (50.6)	42 (49.4)	174 (51.9)
25. Does your household have a refrigerator?: N(%)					
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
No	82 (98.8)	82 (95.3)	81 (100.0)	85 (100.0)	330 (98.5)
Yes	1 (1.2)	4 (4.7)	0 (0.0)	0 (0.0)	5 (1.5)
26. Does your household have a CD / DVD player?: N(%)					
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
No	69 (83.1)	68 (79.1)	68 (84.0)	73 (85.9)	278 (83.0)
Yes	14 (16.9)	18 (20.9)	13 (16.0)	12 (14.1)	57 (17.0)
27. Does your household have a wardrobe?: N(%)					
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
No	54 (65.1)	48 (55.8)	57 (70.4)	60 (70.6)	219 (65.4)
Yes	29 (34.9)	38 (44.2)	24 (29.6)	25 (29.4)	116 (34.6)
28. Does your household have a generator / battery / solar panel?: N(%)					
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
No	32 (38.6)	42 (48.8)	31 (38.3)	36 (42.4)	141 (42.1)
Yes	51 (61.4)	44 (51.2)	50 (61.7)	49 (57.6)	194 (57.9)
29. Does any member of your household own a motorcycle / scooter?: N(%)					
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
No	21 (25.3)	11 (12.8)	17 (21.0)	17 (20.0)	66 (19.7)
Yes	62 (74.7)	75 (87.2)	64 (79.0)	68 (80.0)	269 (80.3)
30. Does any member of your household own a watch?: N(%)					
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
No	71 (85.5)	74 (86.0)	66 (81.5)	71 (83.5)	282 (84.2)
Yes	12 (14.5)	12 (14.0)	15 (18.5)	14 (16.5)	53 (15.8)
31. Does any member of this household have a bank account?: N(%)					
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

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Characteristic	Dose=0 (n=83)	Dose=1.2 (n=86)	Dose=2.4 (n=81)	Dose=10 (n=85)	Total (n=335)
36. What kind of toilet facility do members of your household usually use? : N(%)					
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
0. No facility - bush, field	13 (15.7)	15 (17.4)	21 (25.9)	19 (22.4)	68 (20.3)
1. Flush to piped sewer system (not shared with other households)	7 (8.4)	2 (2.3)	6 (7.4)	4 (4.7)	19 (5.7)
2. Flush to septic tank (not shared with other households)	39 (47.0)	41 (47.7)	41 (50.6)	39 (45.9)	160 (47.8)
3. Flush or pour toilet piped sewer system (shared with other households)	1 (1.2)	4 (4.7)	2 (2.5)	2 (2.4)	9 (2.7)
4. Flush or pour toilet to septic tank (shared with other households)	21 (25.3)	22 (25.6)	10 (12.3)	18 (21.2)	71 (21.2)
5. Traditional pit latrine	1 (1.2)	2 (2.3)	1 (1.2)	2 (2.4)	6 (1.8)
6. Ventilated Improved Pit (VIP) latrine	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)	1 (0.3)
7. Pit latrine without slab	1 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
37. Do you share this toilet facility with other households?: N(%)					
Not applicable	13 (15.7)	15 (17.4)	21 (25.9)	19 (22.4)	68 (20.3)
No	47 (56.6)	47 (54.7)	44 (54.3)	45 (52.9)	183 (54.6)
Yes	23 (27.7)	24 (27.9)	16 (19.8)	21 (24.7)	84 (25.1)
45. Did you avoid eating certain foods/drinks in pregnancy?: N(%)					
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
No	65 (78.3)	65 (75.6)	70 (86.4)	76 (89.4)	276 (82.4)
Yes	18 (21.7)	21 (24.4)	11 (13.6)	9 (10.6)	59 (17.6)
47. Did you avoid eating/drinking certain foods/drinks in the postpartum period?: N(%)					
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
No	26 (31.3)	37 (43.0)	29 (35.8)	22 (25.9)	114 (34.0)
Yes	57 (68.7)	49 (57.0)	52 (64.2)	63 (74.1)	221 (66.0)
49. Were there foods/drinks you specifically chose to eat/drink during pregnancy?: N(%)					
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
No	49 (59.0)	56 (65.1)	52 (64.2)	52 (61.2)	209 (62.4)
Yes	34 (41.0)	30 (34.9)	29 (35.8)	33 (38.8)	126 (37.6)
51. Were there foods/drinks you specifically chose to eat/drink during the postpartum period?: N(%)					
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
No	57 (68.7)	52 (60.5)	49 (60.5)	54 (63.5)	212 (63.3)
Yes	26 (31.3)	34 (39.5)	32 (39.5)	31 (36.5)	123 (36.7)
53. How would you rate the current quality of your own sleep?: N(%)					
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
1. Not at all rested by morning	4 (4.8)	10 (11.6)	3 (3.7)	7 (8.2)	24 (7.2)
2	13 (15.7)	10 (11.6)	13 (16.0)	10 (11.8)	46 (13.7)
3. Somewhat rest by morning	30 (36.1)	25 (29.1)	37 (45.7)	34 (40.0)	126 (37.6)
4	27 (32.5)	33 (38.4)	19 (23.5)	29 (34.1)	108 (32.2)
5. Definitely rested by morning	9 (10.8)	8 (9.3)	9 (11.1)	5 (5.9)	31 (9.3)

Characteristic	Dose=0 (n=83)	Dose=1.2 (n=86)	Dose=2.4 (n=81)	Dose=10 (n=85)	Total (n=335)
54. How would you rate the current quality of your baby's sleep?: N(%)					
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
2	1 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
3. Somewhat rest by morning	18 (21.7)	25 (29.1)	11 (13.6)	27 (31.8)	81 (24.2)
4	37 (44.6)	35 (40.7)	32 (39.5)	32 (37.6)	136 (40.6)
5. Definitely rested by morning	27 (32.5)	26 (30.2)	38 (46.9)	26 (30.6)	117 (34.9)
1. Height of Mother (cm) : Mean (SD)	153.1 (5.5)	154.0 (4.6)	152.8 (5.0)	153.6 (4.6)	153.4 (4.9)
2. Weight of Mother (kg): Mean (SD)	53.1 (8.6)	52.9 (6.4)	52.7 (7.1)	53.5 (7.6)	53.0 (7.4)
3. Length of Infant (cm): Mean (SD)	50.9 (1.9)	50.7 (2.1)	50.7 (2.0)	50.7 (1.9)	50.8 (2.0)
4. Weight of Infant (kg): Mean (SD)	3.5 (0.5)	3.4 (0.5)	3.4 (0.4)	3.4 (0.5)	3.4 (0.5)
5. Head circumference of Infant (cm): Mean (SD)	35.0 (1.2)	34.7 (1.1)	34.6 (1.4)	34.7 (1.1)	34.7 (1.2)

7.3.9 Mullen (composite and 5 subscales)

Descriptive characteristics by treatment group and timepoint

Characteristic	Timepoint	n	0 (n=83)	n	1.2 (n=86)	n	2.4 (n=81)	n	10 (n=85)	Total (n=335)
Mullen composite score: Mean (SD)	Baseline	83	127.4 (10.5)	86	126.7 (10.2)	81	125.2 (10.9)	85	127.2 (11.9)	126.6 (10.9)
Raw gross motor: Median (IQ range)	Baseline	83	1.0 (1.0-2.0)	86	1.0 (1.0-2.0)	81	1.0 (1.0-2.0)	85	1.0 (1.0-2.0)	1.0 (1.0-2.0)
Raw visual: Median (IQ range)	Baseline	83	0.0 (0.0-0.0)	86	0.0 (0.0-0.0)	81	0.0 (0.0-0.0)	85	0.0 (0.0-0.0)	0.0 (0.0-0.0)
Raw fine motor: Median (IQ range)	Baseline	83	1.0 (0.0-1.0)	86	1.0 (0.0-1.0)	81	1.0 (0.0-1.0)	85	1.0 (0.0-2.0)	1.0 (0.0-1.0)
Raw receptive language: Median (IQ range)	Baseline	83	1.0 (0.0-1.0)	86	1.0 (0.0-1.0)	81	1.0 (0.0-1.0)	85	1.0 (0.0-1.0)	1.0 (0.0-1.0)
Raw expressive language: Median (IQ range)	Baseline	83	1.0 (1.0-1.0)	86	1.0 (1.0-1.0)	81	1.0 (1.0-1.0)	85	1.0 (1.0-1.0)	1.0 (1.0-1.0)
Mullen composite score: Mean (SD)	24 weeks	73	183.8 (23.8)	79	180.8 (23.0)	72	181.5 (25.5)	74	188.0 (23.1)	183.5 (23.9)
Raw gross motor: Median (IQ range)	24 weeks	73	10.0 (10.0-10.0)	79	10.0 (9.0-10.0)	72	10.0 (9.0-10.0)	74	10.0 (9.2-10.0)	10.0 (9.0-10.0)
Raw visual: Median (IQ range)	24 weeks	73	8.0 (7.0-9.0)	79	8.0 (7.0-9.0)	72	8.0 (7.0-9.0)	74	8.0 (7.2-8.0)	8.0 (7.0-9.0)
Raw fine motor: Median (IQ range)	24 weeks	73	7.0 (7.0-8.0)	79	7.0 (7.0-8.0)	72	7.0 (7.0-8.0)	74	7.0 (7.0-8.0)	7.0 (7.0-8.0)
Raw receptive language: Median (IQ range)	24 weeks	73	8.0 (7.0-9.0)	79	8.0 (7.0-9.0)	72	8.0 (7.0-9.0)	74	8.0 (7.0-10.0)	8.0 (7.0-9.0)
Raw expressive language: Median (IQ range)	24 weeks	73	7.0 (6.0-7.0)	79	6.0 (6.0-7.0)	72	6.0 (6.0-7.0)	74	7.0 (6.0-7.0)	7.0 (6.0-7.0)

Results from linear regression comparing treatment groups

Mullen scales	Contrast	Unadjusted Mean difference (95% CI)	P*	Adjusted Mean difference (95% CI)#	P*
Composite score	1.2 - 0	-2.97 (-12.98, 7.04)	0.87	-2.71 (-11.01, 5.59)	0.83
	2.4 - 0	-2.27 (-12.51, 7.97)	0.94	-2.51 (-11.05, 6.02)	0.87
	2.4 - 1.2	0.70 (-9.34, 10.75)	1.00	0.20 (-8.14, 8.54)	1.00
	10 - 0	4.22 (-5.95, 14.39)	0.71	4.22 (-4.19, 12.63)	0.57
	10 - 1.2	7.19 (-2.78, 17.17)	0.25	6.93 (-1.33, 15.19)	0.13
	10 - 2.4	6.49 (-3.72, 16.69)	0.36	6.73 (-1.76, 15.22)	0.17
	Overall		0.25		0.12
Raw gross motor	1.2 - 0	-0.21 (-0.70, 0.27)	0.67	-0.20 (-0.66, 0.25)	0.65
	2.4 - 0	-0.18 (-0.68, 0.31)	0.77	-0.19 (-0.65, 0.28)	0.72
	2.4 - 1.2	0.03 (-0.46, 0.51)	1.00	0.02 (-0.44, 0.47)	1.00

Mullen scales	Contrast	Unadjusted Mean difference (95% CI)	P*	Adjusted Mean difference (95% CI)#	P*
	10 - 0	-0.08 (-0.57, 0.41)	0.98	-0.10 (-0.56, 0.36)	0.94
	10 - 1.2	0.13 (-0.35, 0.62)	0.89	0.10 (-0.35, 0.56)	0.93
	10 - 2.4	0.11 (-0.39, 0.60)	0.95	0.09 (-0.37, 0.55)	0.96
	Overall		0.66		0.64
Raw visual	1.2 - 0	-0.14 (-0.59, 0.31)	0.85	-0.11 (-0.55, 0.33)	0.91
	2.4 - 0	-0.15 (-0.61, 0.31)	0.83	-0.14 (-0.59, 0.31)	0.86
	2.4 - 1.2	-0.01 (-0.46, 0.44)	1.00	-0.02 (-0.46, 0.41)	1.00
	10 - 0	-0.19 (-0.65, 0.26)	0.70	-0.19 (-0.63, 0.26)	0.70
	10 - 1.2	-0.05 (-0.50, 0.40)	0.99	-0.07 (-0.51, 0.36)	0.97
	10 - 2.4	-0.04 (-0.50, 0.42)	1.00	-0.05 (-0.49, 0.40)	0.99
	Overall		0.72		0.74
Raw fine motor	1.2 - 0	-0.07 (-0.51, 0.36)	0.97	-0.06 (-0.45, 0.33)	0.98
	2.4 - 0	-0.07 (-0.51, 0.38)	0.98	-0.06 (-0.46, 0.34)	0.98
	2.4 - 1.2	0.01 (-0.42, 0.44)	1.00	0.00 (-0.39, 0.39)	1.00
	10 - 0	0.14 (-0.29, 0.58)	0.83	0.15 (-0.24, 0.55)	0.74
	10 - 1.2	0.22 (-0.21, 0.65)	0.55	0.21 (-0.17, 0.60)	0.48
	10 - 2.4	0.21 (-0.23, 0.65)	0.61	0.21 (-0.18, 0.61)	0.50
	Overall		0.54		0.45
Raw receptive language	1.2 - 0	-0.26 (-0.98, 0.47)	0.80	-0.25 (-0.86, 0.37)	0.73
	2.4 - 0	-0.03 (-0.77, 0.72)	1.00	-0.05 (-0.68, 0.58)	1.00
	2.4 - 1.2	0.23 (-0.50, 0.96)	0.85	0.20 (-0.42, 0.82)	0.85
	10 - 0	0.44 (-0.30, 1.18)	0.41	0.44 (-0.19, 1.06)	0.27
	10 - 1.2	0.70 (-0.03, 1.42)	0.06	0.68 (0.07, 1.30)	0.02
	10 - 2.4	0.47 (-0.27, 1.21)	0.36	0.49 (-0.14, 1.12)	0.19
	Overall		0.10		0.03
Raw expressive language	1.2 - 0	-0.01 (-0.46, 0.45)	1.00	-0.00 (-0.40, 0.39)	1.00
	2.4 - 0	-0.11 (-0.57, 0.36)	0.94	-0.14 (-0.55, 0.27)	0.82
	2.4 - 1.2	-0.10 (-0.56, 0.36)	0.94	-0.14 (-0.54, 0.27)	0.82

Mullen scales	Contrast	Unadjusted Mean difference (95% CI)	P*	Adjusted Mean difference (95% CI)#	P*
	10 - 0	0.24 (-0.22, 0.70)	0.54	0.25 (-0.16, 0.65)	0.40
	10 - 1.2	0.24 (-0.21, 0.70)	0.51	0.25 (-0.15, 0.65)	0.37
	10 - 2.4	0.34 (-0.12, 0.81)	0.22	0.38 (-0.02, 0.79)	0.07
	Overall		0.26		0.10

* Post-hoc (Tukey) adjusted p-values for multiple comparisons
# adjusted for corresponding baseline scale at 2 weeks and health center

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