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A Typical Feeding Enhances Memory for Spoken Words in Healthy 2- to 3-Day-Old Newborns

A. Grace Valiante, MSc[a], Ronald G. Barr, MDCM[b], Philip R. Zelazo, PhD[c], Apostolos N. Papageorgiou, MDCM[d], Simon N. Young, PhD[e]

[a]Department of Developmental Pediatrics, Montreal Children's Hospital–McGill University Health Centre and Department of Neurology and Neurosurgery, McGill University, Montreal, Quebec, Canada; [b]Child and Family Research Institute, University of British Columbia Faculty of Medicine, Vancouver, British Columbia, Canada; [c]Department of Psychology, McGill University and Center for Research in Human Development, Concordia University, Montreal, Quebec, Canada; [d]Department of Neonatology, Sir Mortimer B. Davis Jewish General Hospital, Montreal, Quebec, Canada; [e]Department of Psychiatry, McGill University, Montreal, Quebec, Canada

The authors have indicated they have no financial relationships relevant to this article to disclose.

ABSTRACT

OBJECTIVE. The objective of this study was to determine whether healthy 2- to 3-day-old newborns have better memory of a spoken word after a typical feeding (breast milk or formula) than before a feeding and, if so, whether memory is related to blood glucose.

METHODS. A naturalistic study was conducted in which delayed recognition memory of a spoken word was examined in 60 healthy 2- to 3-day-old newborns either 120 minutes after their previous feeding (preprandial) or 30 minutes after their last feeding (postprandial). In this procedure, infants initially turn their head toward a novel word (orientation) and with repeated presentations cease turning toward it (habituation). Mean number of trials to reach orientation and habituation criteria provides measures of attention and rate of learning, respectively. After a 100-second delay, the word is presented again. Infants either turn toward it, indicating that they have forgotten it, or remain habituated, indicating that they remembered the word. Percentage of trials with head turns toward the word after the delay is the principal dependent measure.

RESULTS. The postprandial group was split at the median for blood glucose to define high- and low-glucose groups. All 3 groups showed similar rates of orientation and habituation. On reexposure to the word during postdelay trials, the preprandial group displayed less retention than the postprandial high and low groups. No correlation was found between memory and blood glucose levels. The postprandial high blood glucose level differed statistically from the preprandial level, whereas the postprandial low level did not.

CONCLUSIONS. Memory for spoken words in newborns is better after a typical milk feeding than before a feeding. This feeding effect is specific to memory and does not include attention or rate of learning. Also, it is not necessarily associated with increased blood glucose. It remains to be seen whether feeding enhances memory for other types of stimuli and what implications this may have for development.

THE INTAKE OF food affects memory in both well-nourished human and non-human animals across different ages. In adult and preweanling infant rats, subcutaneous injections of the carbohydrate glucose (versus saline) enhance memory storage and retrieval.[1–3] In humans, ingestion of a glucose drink, compared with placebo, improves declarative verbal memory as well as storage and retrieval processes in healthy young adults,[4] the elderly,[5,6] and populations that are known to exhibit memory deficits, such as patients with mild Alzheimer's disease.[7,8] This may explain why eating breakfast as opposed to missing breakfast leads to improved performance on memory and learning tasks in well-nourished school-aged children and university students.[9] Altogether, these data suggest an important role of nutrient intake on memory across different ages and raise the question of whether fluctuations in memory with acute nutritional intake are present from birth.

We recently assessed whether ingestion of a glucose solution, as opposed to water, affects delayed recognition memory for spoken words in healthy 2- to 3-day-old human newborns.[10] Using head-turning to sound in an information-processing paradigm,[11] we found that infants who were fed glucose before the test were able to remember a spoken word better than infants who were fed water. The glucose effects on memory were not attributable to differences in level of attention to or rate of learning the word.

In our recent study, postprandial blood glucose levels after the memory-enhancing dose of glucose overlapped those reported after a normal meal.[12–15] The aim of this study was to determine whether delayed recognition memory for spoken words is better after a typical feeding than before and whether blood glucose levels are associated with memory. Healthy 2- to 3-day-old infants were studied under naturalistic conditions; that is, memory was compared before and after a routine breast or formula feeding. Blood glucose was obtained after the memory test. The main hypothesis was that memory for words would be better after a feeding than before a feeding. The secondary hypothesis was that enhancement of memory after a feeding would occur only in infants with higher blood glucose levels, that is, levels that overlap those found after the glucose feeding in our previous study.[10]

METHODS

This was a naturalistic study in which memory was assessed in 60 newborns before or after a routine breast or formula feeding (preprandial versus postprandial). One third of the infants were tested before a feeding, and two thirds were tested after a feeding. Blood glucose measures were obtained after the memory test. The postprandial group then was split at the median for blood glucose to define 2 groups: low and high blood glucose.

Study Infants

Sixty healthy, term newborn infants (mean age ± SD: 58.1 ± 20.5 hours; range: 34.0–104.5 hours) were recruited from the well-infant nursery at the Sir Mortimer B. Davis Jewish General Hospital (Montreal, Quebec, Canada). Criteria for eligibility included birth weights between 2800 and 4100 g, Apgar scores of 7 or greater at 5 minutes, uneventful deliveries and perinatal histories, no jaundice or surgery (eg, circumcision), no maternal diabetes (gestational, type 1, or type 2), no illegal drug use, and, if a smoker, smoking ≤10 cigarettes per day during pregnancy. In maternal diabetes, fluctuations in blood glucose level during fetal development are likely to affect the newborn's responses to elevations in blood glucose after a meal[16]; maternal substance abuse and heavy cigarette smoking during pregnancy have negative effects on neonatal auditory information-processing ability.[17,18]

The study was approved by the Research Ethics Boards of the Sir Mortimer B. Davis Jewish General Hospital and of the Montreal Children's Hospital. Mothers who were on the postpartum ward were approached 24 hours after delivery. The purpose of the study and the procedure were explained to them, and permission was sought for the participation of their infant. Signed informed consent was obtained for each infant.

Design

Postprandial infants were tested 30 to 90 minutes after their last feeding (mean ± SD: 51.9 ± 16.2), and preprandial infants were tested at least 120 minutes after their previous feeding (mean ± SD: 181.1 ± 41.2). Newborn blood glucose levels after a feeding tend to be highest at 30 to 90 minutes and decline steadily to baseline values after 90 to 120 minutes.[12–15] Because previous studies suggested that only some infants have postprandial blood glucose levels that increase up to levels that are found after a memory enhancing dose of glucose (2 g/kg), twice as many infants were tested after a feeding as before (two thirds versus one third). Blood glucose was measured in all infants after the memory test (mean ± SD: 16.4 ± 8.8 minutes). Before the analysis, the postprandial group was split at the median for blood glucose to define high- and low-glucose groups.

Assignment of Prandial Groups

Infants were not randomly allocated to preprandial or postprandial groups but were tested on the basis of availability during the period 8 AM to 12 PM, as soon as they met 1 of the prandial criteria and testing was convenient for the parents. This "restricted-randomization"[19] process was used so that blood glucose measurements after the

memory test could be obtained during the legally required heel-prick phenylketonuria test, which generally was done before noon, when an extra drop of blood was collected. Recruiting infants on the basis of availability accommodated the nurses' scheduling of phenylketonuria testing and allowed us to measure blood glucose in all infants.

After the first 57 infants were restricted-randomized to 1 of the 2 prandial conditions, the preprandial group was completed ($n = 20$). The last 3 infants then were restricted-randomized to the postprandial group. In this study, the experimenters were not blind to the prandial condition, but the memory procedure was designed to ensure that the experimenters could not introduce a systematic bias (see below).

Attrition

A total of 208 mothers gave consent to have their infants participate in the study (Fig 1). Restricted randomization allocated 119 infants to the postprandial group and 66 to the preprandial group. In 23 infants, postfeeding time was either <30 minutes or between 90 and 120 minutes. This latter group failed to meet the predefined prandial criteria and consequently were not included in the final analysis. Of the 185 infants who met prandial criteria and were tested on the memory procedure, 33 (21 postprandial and 12 preprandial) were excluded as a result of external factors (infant did not fit inclusion criteria, experimental error, parent withdrew infant from study, or testing was interrupted by hospital staff or parent) and 92 (58 postprandial and 34 preprandial) were excluded as a result of infant-related factors (infant failed to reach criteria during familiarization or novelty phases or poor testing state with infant with eyes closed or fretting for ≥15 seconds on 3 consecutive trials). Overall, the restricted-randomization process resulted in the recruitment of twice as many postprandial as preprandial infants, possibly because 2- to 3-day-old infants are more likely to be in a quiet awake state soon after a feeding than just before a feeding and so a greater number of infants were available for testing at that time. However, prandial condition did not influence attrition rates that resulted from infant-related factors during testing (poor state or poor performance; $\chi^2 = 0.20$, degrees of freedom = 3; $P > .05$), suggesting that failure to complete the test successfully was not affected by whether the infant was tested before or after a feeding.
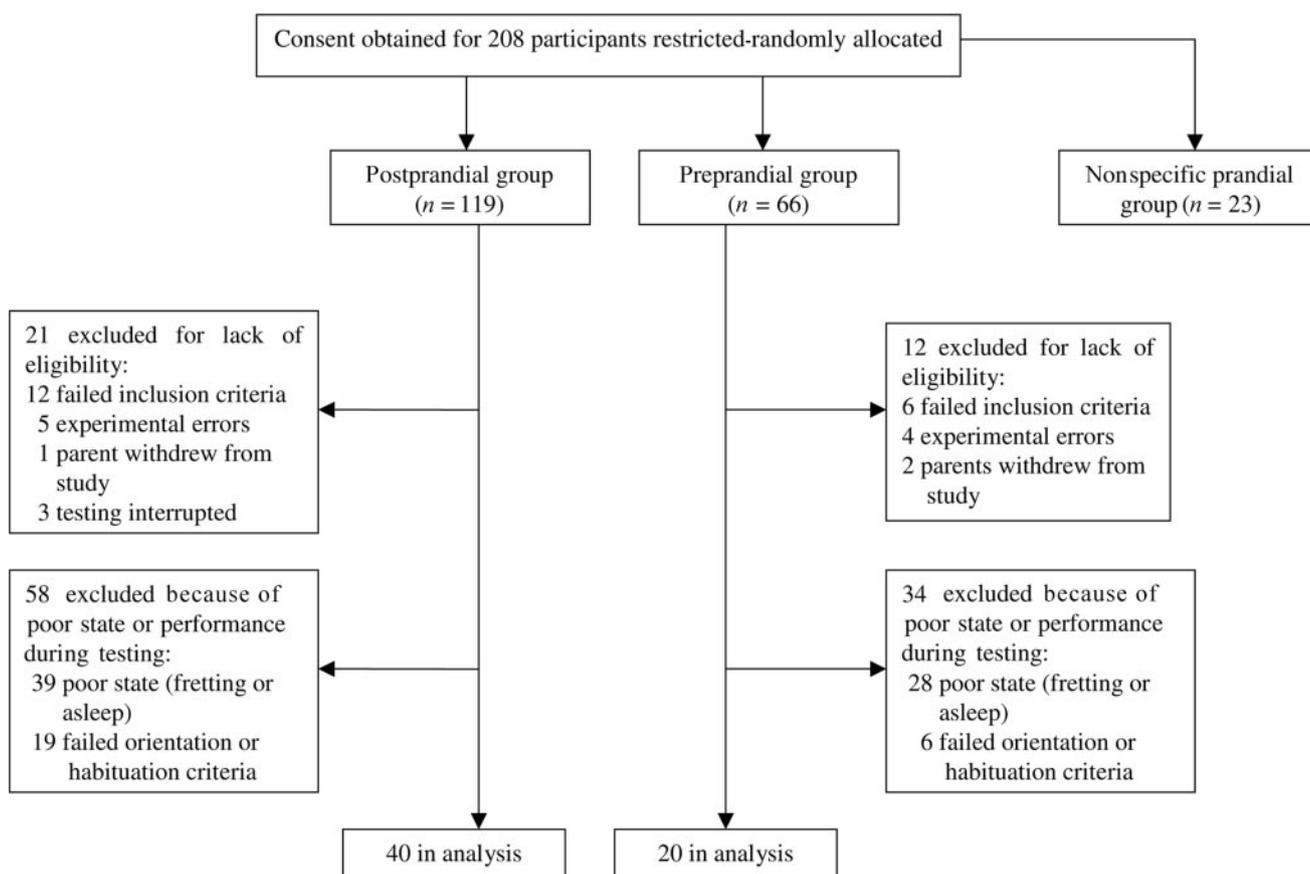

FIGURE 1
Study infant flow diagram.

Procedure

Apparatus and Stimuli

Auditory stimuli consisted of 2 words, "tinder" and "beagle," that were digitally recorded and played on a Pentium computer and amplified through 1 of 2 Fisher stereo speakers, placed on either side of the infant's head at a distance of ~30 cm. These words were chosen as test stimuli because of their equally low frequency of occurrence,[20] comparable length, phonetic content, and discriminability by neonates[21] and older infants.[22] The words were presented at a sound pressure level of 72 ± 2 dB by depressing a foot pedal connected to the computer. Each word was ~1 second in duration and repeated at a consistent volume and intonation at a rate of 1 word every 2 seconds in 30-second trials.

Spontaneous-Recovery or "Memory" Paradigm

Memory was assessed using the head-turning response in the spontaneous-recovery procedure.[11,23] Infants initially turn toward a word that is presented randomly on either side, representing orientation. With continued presentations, they stop turning toward it, indicating habituation. When the word is presented again after a pause, turning toward indicates that the infant is treating it as a new word and has forgotten it, whereas not turning or turning away indicates that the word is being treated as a familiar stimulus and is remembered. Last, for ensuring that lack of turning toward the word after the pause is not attributable to lack of alertness, a novel word is presented. Infants must turn toward the novel word, or their data are discarded regardless of whether they turned toward the original word after the pause. The principal measure of memory is the percentage of trials with turns toward the initial word after the pause: low levels of turns toward the word indicate retention, whereas high levels indicate that the infant has forgotten the word.

A partial infant-controlled (as opposed to fixed-trial) paradigm was used in which the infant's responses determined the length of trials as well as the duration of the phases. Each infant was tested across 4 phases[23]: (1) familiarization: the initial auditory stimulus (the word "beagle" or "tinder") was presented in repeated trials until criteria for orientation and habituation (see below) were attained (maximum of 16 trials); (2) delay: a 100-second pause during which time no stimuli were presented; (3) recovery: the initial word was reintroduced until the orientation criterion was reached (maximum of 6 trials); and (4) novelty: a novel word was presented until the infant reached orientation criterion or produced at least 2 consecutive turns toward (maximum of 9 trials). Orientation in the familiarization phase was defined as 3 turns toward the word within 4 consecutive trials, whereas habituation was defined as turns away from the word or no turns on 3 successive trials. When

an infant began to reach orientation or habituation criteria in the last trials of phases 1, 3, and 4, up to 2 extra trials were added to provide a final opportunity to meet criterion. Responses during the recovery period were the primary outcome measure.

Infant Testing

Infants were taken from the nursery or mother's room and brought to a dimly lit quiet room across from the main nursery. Before testing, all infants were engaged in a subset of behaviors that included face-to-face looking and Babinski, Moro, Palmer, and tonic-neck reflexes over a 5- to 10-minute period to encourage an awake, nonagitated state. When an awake quiet state was not achieved, the infant was returned to the mother and rescheduled for a later time. During testing, the infant was held by 1 experimenter at a 45° angle between vertical and supine, with the infant's head and shoulders supported in the experimenter's right hand and lower back and buttocks in the left hand, allowing the head to move freely from side to side.[24] The infant was held over a mattress that was placed on a table to allow the holder to lean against it while resting her elbows. Two stereo speakers through which the sound was presented were located on each side of the table. A second experimenter coded the infant's responses and behavioral state by pressing a hand-held silent 4-button box recorder that was connected to a computer: (1) head turn to the right, (2) head turn to the left, (3) fretting (ie, grimacing with vocalization, and (4) eyes closed. As a control for experimenter bias, the holder and the coder wore headphones that delivered the stimuli simultaneously to both ears.

Presentation of the Word Stimuli

When an awake quiet state was achieved, the holder centered the infant's head and signaled the coder to begin stimulus presentation by depressing the foot pedal. One-word stimulus (either "beagle" or "tinder") was presented to the infant repeatedly in 30-second trials. The trial ended before 30 seconds when the infant produced a 3-second sustained head turn of 45° to either side. The 45° criterion was chosen over previously used criteria of 6°[25] and 15°[24] to reduce the probability of spurious head turns.[23] The coder began each new trial by depressing a foot pedal. The side of word presentation across the trials was in a right-left-left-right order with the initial side of presentation counterbalanced within subjects.

Infant Head-Turning Response and Behavioral State

For each trial, 1 of 3 head-turning responses could be registered by the computer: infant turning (1) toward or (2) away from the sound source or (3) no turn at all. The duration of each head-turning response, negative state (fret or eyes closed), and trial and intertrial delay was recorded. The intertrial delay allowed the holder to re-

center the infant's head before the start of each new trial or to regain an alert quiet state if the infant began fretting or falling asleep. Intertrial delays generally lasted 10 seconds. During a sustained turn, when 1 or both negative states occurred for >2.1 consecutive seconds, the computer canceled the turn because at that point the infant no longer seemed attentive to the sound. Moreover, infants who completed the memory paradigm but displayed negative state for 15 seconds or longer on 3 consecutive trials were not included in the final sample (ie, disqualified). Although the experimenters were not blind to the prandial condition, they were blind to whether the word was presented on the infant's right or left side, making it impossible to know whether there was a head turn toward or away from the word.

Blood Glucose

Blood glucose levels were measured with a Glucometer Elite (Bayer Healthcare, Ontario, Canada) glucose meter after the memory test. Blood glucose levels in the postprandial group ($n = 40$) were split at the median to define 2 groups: high and low blood glucose. The median glucose value that was obtained after the median split was 4.4 mmol/L. Infants with glucose levels of 4.4 mmol/L ($n = 3$) were included in the postprandial low blood glucose group. The number of participants in each group was 20 (preprandial), 22 (postprandial low), and 18 (postprandial high). Mean blood glucose level in the postprandial high group was expected to differ significantly from that in the preprandial group.

Dependent Variables

Measures of Information Processing

Four measures of information processing were assessed: (1) attention; (2) rate of learning; (3) memory; and (4) alertness. Attention and rate of learning were defined as the number of trials to reach orientation and habituation criteria, respectively, during the familiarization phase. Memory was defined as the percentage of turns toward the sound during the first 6 trials of the recovery phase. Alertness was defined as the percentage of turns toward the sound during the first 6 trials of the novelty phase. The 3 phases of the information-processing procedure were analyzed separately as each phase contributed differentially to the assessment.

Measures of Infant State and Responsiveness

Positive state was derived by subtracting the total time that the infant spent in a negative state (ie, fretting or with eyes closed) from the total trial length and summing over trials in each phase. Responsiveness was defined as the percentage of trials that ended with a head turn, either toward or away.

Characteristics of Groups

Two separate analyses were conducted to determine whether the groups differed on demographic characteristics. Before the median split for blood glucose, preprandial infants ($n = 20$) and all postprandial infants combined ($n = 40$) were compared on maternal and infant characteristics (Table 1) using unpaired t tests or χ^2 tests to ascertain whether the restricted-randomization process that was used to allocate infants generated similar prandial groups. The 2 groups did not differ on any of the variables.

After the postprandial median split for blood glucose, the 3 prandial groups were compared on infant and maternal demographic characteristics (Table 1) and testing parameters (Table 2). A 3 (group) analysis of variance (ANOVA) yielded significant main effects for age and birth length, with follow-up posthoc pairwise comparisons (Tukey's) indicating that postprandial high-glucose infants were older and shorter than both preprandial and postprandial low-glucose infants. Independent χ^2 tests also revealed that the prandial groups differed on method of delivery, intrapartum analgesia, and type of daily feeding. Confirmatory follow-up χ^2 tests between prandial group pairs indicated that infants with high glucose after a feeding, relative to both preprandial and postprandial low-glucose infants, were more likely to be born by cesarean section (with more mothers receiving spinal analgesia as opposed to epidural analgesia) and receive a mixed feeding (ie, combination of breast milk and <250 mL of formula per day).

A series of linear regression analyses then were conducted to determine whether any of the demographic variables that were found to discriminate the groups were correlated. Results revealed the following: (1) age was highly correlated with type of delivery ($r = 0.85$; $P < .001$) and intrapartum medication ($r = 0.88$; $P < .001$) but not with type of daily feeding ($r = 0.32$; $P = .001$) and birth length ($r = 0.12$; $P = .14$); (2) type of daily feeding was not highly correlated with type of delivery ($r = 0.30$; $P = .07$), birth length ($r = 0.33$; $P = .01$), or intrapartum medication ($r = 0.22$; $P = .24$); and (3) birth length was not highly correlated with type of delivery ($r = 0.33$; $P = .01$) or intrapartum medication ($r = 0.33$; $P = .04$). Consequently, to adjust for any confounding effects of these variables on dependent measures of information processing and infant state/responsiveness, we performed analysis of covariance tests using the nonrelated variables as covariates (age, birth length, and type of daily feeding). Results indicated that the demographic variables did not account for any group difference on the dependent measures.

Statistical Analysis

The 3 prandial groups were compared on levels of blood glucose and measures of information processing with one-way ANOVAs followed by Tukey's posthoc test. To

TABLE 1 Infant and Maternal Demographics for Preprandial, Postprandial Combined, Postprandial Low Blood Glucose, and Postprandial High Blood Glucose Groups

Categories	Preprandial[1] (N = 20)	Postprandial Combined[2] (N = 40)	Postprandial Low Blood Glucose[3] (N = 22)	Postprandial High Blood Glucose[4] (N = 18)	P[a]
Infant					
Age at testing, h	53.0 (17.3)	60.6 (21.7)	50.7 (16.1)	72.7 (21.9)	.15[1,2]
					1.00[1,3]
					.01[1,4]
					.001[3,4]
Type of daily feeding					
Breast only	10	10	10	0	.22[1,2]
Formula only	2	8	3	5	.44[1,3]
Mix (<250 mL of formula)	6	19	9	10	.01[1,4]
Mix (>250 mL of formula)	2	3	0	3	.004[3,4]
No. of feedings per day	9.0 (1.5)	9.0 (1.5)	9.1 (1.4)	8.6 (1.6)	.81[1,2]
					.64[1,3,4]
Infant medications					
None	20	35	21	14	.26[1,2]
Antibiotics	0	2	1	1	.07[1,3,4]
Other	0	3	0	3	
Method of delivery					
Vaginal	16	25	18	7	.24[1,2]
Cesarean section	4	15	4	11	1.00[1,3]
					.02[1,4]
					.01[3,4]
Birth length, cm	51.1 (1.3)	50.7_{37} (2.5)	51.4 (1.8)	49.7_{15} (3.0)	.53[1,2]
					1.00[1,3]
					.16[1,4]
					.05[3,4]
Head circumference, cm	34.6 (1.1)	34.7_{39} (1.0)	34.8 (0.9)	34.6_{17} (1.1)	.85[1,2]
					.87[1,3,4]
Mother					
Age	30.8 (5.4)	30.1 (5.3)	29.6 (6.3)	30.4 (3.8)	.63[1,2]
					.77[1,3,4]
Marital status					
Married	18	36	18	18	.30[1,2]
Living together	1	4	4	0	.15[1,3,4]
Single	1	0	0	0	
Hollingshead	46.5_{17} (9.8)	48.0_{32} (12.0)	50.2_{17} (12.5)	45.5_{15} (11.4)	.67[1,2]
					.46[1,3,4]
Mother smoked during pregnancy (<10 cigarettes per day)					
No	19	37	19	18	1.00[1,2]
Yes	1	3	3	0	.21[1,3,4]
Intrapartum analgesia					
None	2	2	1	1	.35[1,2]
Epidural	14	23	17	6	.04[1,4]
Spinal	4	15	4	11	.76[1,3]
					.02[3,4]
Postpartum medication if breastfeeding					
None	2	3	2	1	.70[1,2]
Analgesic	3	8	6	2	.89[1,3,4]
Antibiotic	1	2	1	1	
Other	1	0	0	0	
≥2	11	19	10	9	

Values are mean (±SD) for numerical variables or counts for categorical variables. Change in sample size as a result of missing values is indicated by subscript numbers.

[a] P values are based on 1-way ANOVA for means followed by Tukey's posthoc tests (if applicable) and independent α^2 tests for counts followed by confirmatory analysis (if applicable). Superscript numbers specify the group comparison.

ensure that the groups did not differ on degree of positive state and overall responsiveness (head-turning in either direction, as opposed to no turn), we used repeated measures to assess between group differences on these measures across each phase (within-subjects factor). Also, to explore associations between blood glucose levels and memory as defined by percentage of turns toward during the spontaneous recovery phase, we computed correlational (Pearson's) analyses for (1) each group separately and (2) postprandial groups combined.

TABLE 2 Testing Parameters for Preprandial, Postprandial Combined, Postprandial Low Blood Glucose, and Postprandial High Blood Glucose Groups

Testing Parameters	Preprandial[1] (N = 20)	Postprandial Combined[2] (N = 40)	Postprandial Low Blood Glucose[3] (N = 22)	Postprandial High Blood Glucose[4] (N = 18)	P[a]
Time since last feeding, min	181.1 (41.2)	51.9 (16.2)	53.8 (16.3)	49.5 (16.2)	$<.001^{1,2}$ $<.001^{1,3}$ $<.001^{1,4}$ $1.00^{3,4}$
Duration of feeding, min	37.9_{17} (19.4)	35.1 (16.5)	37.2 (17.6)	32.5 (15.2)	$.56^{1,2}$ $.60^{1,3,4}$
Duration of memory test, min	11.5 (3.7)	12.7 (2.7)	12.5 (3.0)	12.9 (2.4)	$.16^{1,2}$ $.34^{1,3,4}$
Time from start of feeding to glucose measurement, min	206.8 (38.9)	77.0 (24.4)	79.0 (23.3)	74.5 (26.2)	$<.001^{1,2}$ $<.001^{1,3}$ $<.001^{1,4}$ $1.00^{3,4}$
Time from end of test to glucose measurement, min	17.0 (9.9)	16.1 (8.3)	15.4 (6.0)	16.9 (10.6)	$.70^{1,2}$ $.81^{1,3,4}$
Type of feeding before or after test					
Breast only	14	23	15	8	$.31^{1,2}$
Formula only	6	13	4	9	$.12^{1,3,4}$
Mix	0	4	3	1	
Amount fed					
Breast milk, min	37.5_{14} (14.9)	33.5_{23} (10.7)	33.3_{15} (11.6)	33.8_{8} (9.5)	$.35^{1,2}$ $.64^{1,3,4}$
Formula, mL	35.0_{6} (20.7)	44.6_{13} (21.9)	41.3_{4} (21.8)	46.1_{9} (23.2)	$.38^{1,2}$ $.64^{1,3,4}$
Mix feeding: breast milk, min		26.3_{4} (11.1)	25.0_{3} (13.2)	30.0_{1}	$.78^{3,4}$
Mix feeding: formula, mL		30.0_{4} (19.2)	21.7_{3} (11.6)	55.0_{1}	$.13^{3,4}$
Time between mother's last medications and breastfeeding, h	4.1_{6} (4.2)	2.9_{16} (2.7)	3.3_{9} (3.2)	2.4_{7} (2.2)	$.44^{1,2}$ $.65^{1,3,4}$

Values are mean ($\pm$SD) for numerical variables or counts for categorical variables. Change in sample size as a result of missing values is indicated by subscript numbers.

[a] P values are based on 1-way ANOVA for means followed by Tukey's posthoc tests (if applicable) and independent α^2 tests for counts followed by confirmatory analysis (if applicable). Superscript numbers specify the group comparison.

RESULTS

Blood Glucose Levels

As expected, postprandial high blood glucose level differed statistically from the preprandial level ($P < .001$), whereas the postprandial low blood glucose level did not ($P = .39$; Fig 2). Range and group values (mean mmol/L $\pm$ SD) were 3.6 to 5.0 and 4.2 $\pm$ 0.4 (preprandial), 3.2 to 4.4 and 4.1 $\pm$ 0.3 (postprandial low glucose), and 4.5 to 5.9 and 5.0 $\pm$ 0.4 (postprandial high glucose).

Information-Processing Ability

The 3 groups displayed similar levels of attention to and rate of learning the word (Fig 3). Separate 3 (group) ANOVAs revealed no significant effect of group for number of trials to orientation ($F_{2,57} = 1.9$; $P = .16$; effect size = .06, posthoc power = .38) and number of trials to habituation ($F_{2,57} = 0.1$; $P = .95$; effect size $< .002$, posthoc power = .06). Mean ($\pm$SD) number of trials to reach criteria for orientation and habituation, respectively, in the familiarization phase were 4.8 $\pm$ 2.2 and 12.4 $\pm$ 3.9 (preprandial), 5.0 $\pm$ 3.0 and 12.7 $\pm$ 3.1 (postprandial low glucose), and 3.7 $\pm$ 1.1 and 12.7 $\pm$ 4.0 (postprandial high glucose).
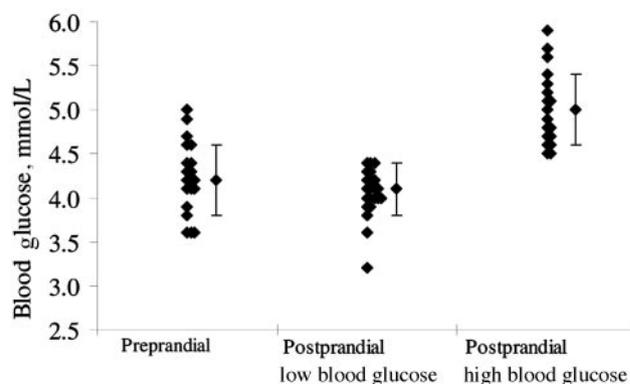
FIGURE 2
Mean blood glucose levels observed after the memory test. The data points represent individual ($\blacklozenge$) and group mean ($\pm$SD) blood glucose levels.

As shown in Fig 4, infants who were tested after a feeding remembered the word better than infants who were tested before a feeding ($F_{2,57} = 6.4$; $P < .003$; effect size = .18). Preprandial infants displayed more turns toward the word than did infants in the postprandial high-glucose group ($P = .003$) and low-glucose group (P
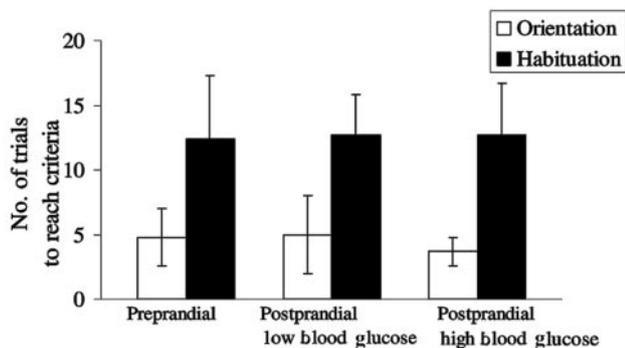
FIGURE 3
Measures of attention to and rate of learning the initial word during the familiarization phase.

= .05), which did not differ significantly on head turns toward (P = .72). Mean (±SD) percentage of trials with turns toward on reexposure to the familiar word during recovery were 70.8 ± 27.1 (preprandial), 51.2 ± 27.4 (postprandial low glucose), and 41.4 ± 22.9 (postprandial high glucose). All of the infants who completed the test successfully remained similarly aroused during novelty testing ($F_{2,57}$ = 0.3; P = .78; effect size = .009, posthoc power = .09). Mean (±SD) percentage of trials with head turns toward the novel word were 68.0 ± 23.6 (preprandial), 63.6 ± 32.6 (postprandial low glucose), and 62.2 ± 21.2 (postprandial high glucose).

Measures of Infant State and Responsiveness

The 3 groups were compared on responsiveness (head-turning in either direction, as opposed to no turn) and degree of positive state (duration of time not spent crying or with eyes closed) to determine whether differences in memory performance may have resulted from differences in head-turning response or state. As might be expected, all infants spent more time fretting or with eyes closed toward the end of the procedure, but there were no significant group difference in state during any of the 3 phases. Across all groups, infants remained in a testable state for 95.3%, 91.3%, and 90.0% of the time during the familiarization, recovery, and novelty phases,
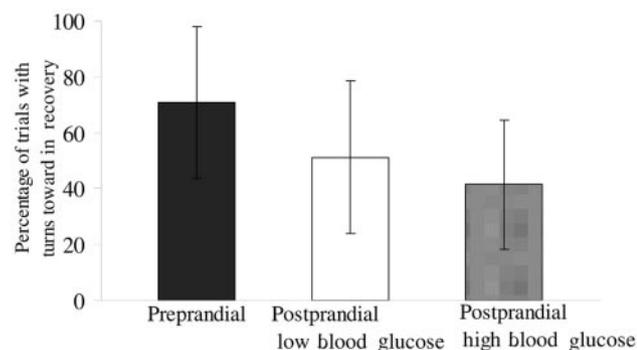
respectively. A 3 (group) × 3 (phase) repeated measures ANOVA on infant positive state revealed a significant main effect of phase, ($F_{2,114}$ = 3.8; P = .03; effect size = .06) but no group effect ($F_{2,114}$ = 0.5; P = .63; effect size = .03, posthoc power = .12), or group × phase interaction ($F_{4,114}$ = 0.2; P = .89; effect size = .02, posthoc power = .10). Tukey's posthoc analyses of the effect of phase revealed that relative to the familiarization phase, positive affect decreased during recovery (P = .04) and novelty phases (P = .04), during which times infant state remained unchanged (P = 1.00).

Although all groups were equally responsive across the 3 phases, head-turning occurred 78.9%, 78.9%, and 89.8% of the time in familiarization, recovery, and novelty phases, respectively. A 3 (group) × 3 (phase) repeated measures ANOVA on responsiveness revealed a significant main effect of phase ($F_{2,114}$ = 8.1; P < .001; effect size = .12) but no group effect ($F_{2,114}$ = 1.0; P = .37; effect size = .04, posthoc power = .22), or group × phase interaction ($F_{4,114}$ = 1.6; P = .20; effect size = .05, posthoc power = .43). Tukey's posthoc analyses of the effect of phase revealed that responsiveness increased slightly for all 3 groups during the novelty phase compared with both the familiarization (P < .001) and recovery (P = .01) phases, during which times infants were similarly responsive (P = 1.00). These data indicate that lower levels of turns toward the word that were observed in postprandial groups during the recovery phase were not attributable to a change in responsiveness: all infants were actively processing the word stimulus, either attending to it (turning toward) or avoiding it (turning away) during testing.

Association Between Blood Glucose and Memory

There was no significant correlation between glucose and our measure of memory (ie, percentage of turns toward the word during the recovery phase) for the preprandial (r = −0.11; P = .65), postprandial high-glucose (r = −0.31; P = .21), and postprandial low-glucose (r = −0.21; P = .35) groups, although there was a tendency toward significance for the postprandial combined (r = −0.30; P = .06) group.

DISCUSSION

The findings support the main hypothesis that healthy 2- to 3-day-old human newborns have better memory for spoken words after a typical feeding under naturalistic conditions than before a feeding. This is consistent with the idea that auditory memory in neonates is not constant but varies depending on the infant's acute nutritional intake. All infants oriented and habituated to the word at the same rate, indicating that attention to the word was similar across the groups and that all infants took similar amounts of time to learn it. Thus, the effect of feeding seems to have been specific to memory.

To date, only 1 other study has examined the effects

FIGURE 4
Measure of memory during the recovery phase.

of feeding on newborn memory processes. Visual recognition memory before and after a feeding (breast milk and formula) was examined in healthy infants (newborns, 1 and 4 months of age) using the familiarity-novelty paradigm with black and white visual patterns.[26] In this method, infants initially orient to (ie, look at) 2 identical visual stimuli. Immediately after familiarization, infants are presented with the familiar stimulus paired with a novel one, and duration of looking at the stimuli is recorded. Results showed that when tested after a feeding, newborns and 1-month-olds "prefer" the novel stimulus (ie, looking time is greater), indicating that they recognize the familiar stimulus. However, when tested before a feeding, they prefer the familiar stimulus, indicating that it is not recognized as familiar. Although the study used a cue-primed recognition paradigm and assessed immediate as opposed to delayed recognition memory, the findings suggest that there are effects of acute nutritional state on early memory. Moreover, the study generalizes the feeding enhancement of memory effect to a different modality and paradigm.

Our findings did not support the secondary hypothesis that better memory after a feeding would occur only in infants with higher blood glucose levels. However, this conclusion is limited by the relatively small sample size. The trend for significance for a glucose memory association in the larger postprandial combined group raises the possibility of a weak association between high blood glucose related to better memory. The lack of association or weak association could be attributable to a number of factors. First, blood glucose that is measured after the memory test may not reflect blood glucose concentrations at the time of testing. Second, whereby glucose can act directly in the brain,[27] levels of circulating glucose may not reflect brain glucose concentration. Third, insulin is thought to mediate part of the glucose effect on memory by crossing the brain-blood barrier and acting directly on insulin receptors in the brain.[28] In patients with mild Alzheimer's disease, studies using artificial insulin/glucose infusion clamps that set and maintain the concentration of circulating glucose and/or insulin at different levels have shown that hyperinsulinemia at constant blood glucose and hyperglycemia with insulin kept at free-floating levels enhance paragraph recall, with a greater facilitation during hyperinsulinemia. However, if insulin release is suppressed by somatostatin during hyperglycemia, then memory does not improve.[29,30] Thus, although glucose stimulates memory, the memory enhancement is not necessarily related directly to blood glucose concentrations. Last, although glucose has been reported to enhance memory, other mechanisms that enhance memory but do not involve glucose are also likely to operate after feeding. Meals of carbohydrate, protein, and fat all improved verbal declarative memory in healthy elderly individuals, although only carbohydrate raised blood glucose.[31] The

effects of protein and fat may be mediated by the release of gastrointestinal peptides such as cholecystokinin octapeptide, gastrin-releasing peptide, pancreastatin, and amylin, all of which enhance memory in rodents,[32] possibly by acting on the vagus nerve and its afferent fibers. Vagotomy blocks the memory-enhancing effects of cholecystokinin octapeptide and gastrin-releasing peptide in rodents,[33,34] whereas electrical stimulation of the vagus nerve enhances memory storage in rodents[33,34] and memory for a list of words in humans.[35] Presumably, in the present study, the enhanced memory after a feeding was mediated by several mechanisms, including the direct effect of glucose, enhanced release of insulin, and the release of various peripheral hormones that act on the vagus nerve. However, the ontogeny of glucoregulatory or other memory-modulating systems is complicated, and mechanisms that are operative with mature animals may or may not be operative in newborns.

Limitations of the Study

One limitation of the study, as with most studies of information processing in young infants, was the high attrition rate. Participant loss resulting from noncompletion of task, usually upward of 50% in most infant experiments, may not be random but rather may be related to individual characteristics of the infant.[36,37] In a recent study, infants who failed to complete a habituation task on one occasion not only tended to fail to complete the task 1 week later but also were less likely to complete a problem-solving task at 13 months.[38] Thus, the results of this study cannot necessarily be generalized to all infants. Nonetheless, our study does suggest that the enhancement of memory after feeding occurs in a significant proportion of neonates.

Another limitation is that the test is necessarily indirect and memory is inferred through a behavior, in this case head turning, yet a large body of data collected over the past 2 decades are consistent with the idea that the head-turning response after the delay is appropriate for examining the infant's capacity to retain previously familiar auditory information over short- and long-term durations, because the length of the delay during which the habituated response is retained provides a marker of the duration of memory.[23,39] Moreover, numerous studies using orientation-habituation-recovery–related paradigms with various modality-specific or multimodal stimuli have repeatedly demonstrated information-processing ability in young infants,[40,41] supporting the view that infants can create mental representations for events, retain a memory trace, and actively compare new information with mental representation.[42,43]

In the present study, the conclusion that recognition memory is better after a meal is consistent with many studies in rats and in human adults and children, suggesting that nutrients can enhance memory. Thus, the most plausible explanation for the lower level of head-

turning after a feeding is that memory is better after a feeding in neonates.

Implications

In this study, neonates demonstrated better memory for a spoken word after a pause of 100 seconds rather than before a feeding. Although this time interval is short, neonates have demonstrated memory traces for spoken words over a 24-hour period.[44] If the effects of food ingestion on memory last for at least the length of the interfeeding interval, this effect could have implications for development. Feeding occurs >2500 times in the first year of life, so the iterative effect might be significant over the early weeks and months. The more frequent feeding associated with a shorter interfeeding interval might be associated with more frequent enhancement of memory. Moreover, given that brief interactions can permit significant learning to occur with infants, post-feeding interactions may be both efficient and optimally beneficial. However, although our data show that memory is enhanced after a feeding, speculation about possible clinical benefits must await clinical trials. In sum, our results suggest that feeding effects in neonates are implicated in early cognitive as well as nutritional and emotional domains.

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A. Grace Valiante, Ronald G. Barr, Philip R. Zelazo, Apostolos N. Papageorgiou and Simon N. Young

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