Published in final edited form as:

Med Hypotheses. 2009 November ; 73(5): 682–686. doi:10.1016/j.mehy.2009.05.013.

Semantic Fluency: A Sensitive Marker for Cognitive Impairment in Children with Heavy Diarrhea Burdens?

Reinaldo B. Oriá, PhD^{1,3,*}, Carlos Maurício C. Costa, MD, PhD⁴, Aldo A. M. Lima, MD, PhD¹, Peter D. Patrick, PhD², and Richard L. Guerrant, MD¹

¹ Center for Global Health, Division of Infectious Diseases and International Health, School of Medicine, University of Virginia, Charlottesville, Virginia, USA

² Kluge Children's Rehabilitation Center, Division of Neuropsychology, Department of Pediatrics, University of Virginia, Charlottesville, Virginia, USA

³ Institute of Biomedicine of the Semiárid and Department of Morphology, Federal University of Ceará, Fortaleza, Ceará, Brazil

⁴ Institute of Biomedicine of the Semiárid and Department of Physiology and Pharmacology, Federal University of Ceará, Fortaleza, Ceará, Brazil

Abstract

One of the most affected cognitive impairments in children who experienced heavy burdens of diarrhea is semantic fluency, the same impairment that is most affected in Alzheimer's dementia. These findings are leading us into provocative genetic studies that may elucidate the evolution of such genetic polymorphisms as the APOE alleles. Alternatively, diarrhea could launch the cognitive deficits that might later progress in neurodegenerative diseases. In addition, they suggest that semantic fluency could provide a simple mean to assess cognitive impairment in impoverished settings so as to determine preventive measures.

Introduction

Verbal fluency (phonetic and semantic fluency) has been an important component of neuropsychological screenings for executive functioning and linguistic skills (1,2). Performance on either semantic (category fluency) or phonetic fluency (letter or word fluency) has been successfully used as an index of frontal lobe function (the brain region related with executive commitment), as confirmed by recent neuropsychological, neuroimaging, and cognitive studies worldwide (3–6). Historically, the role of frontal lobes on executive functioning was comprehensively reviewed by Royall and colleagues (7).

In the most widely used semantic testing, the experimenter simply asks the subject or child to say aloud as many names of items belonging to a certain category such as animals or fruits in a one minute trial. On the other hand, in phonetic fluency, the experimenter asks the subject or child to name as many words as possible starting with a specific letter in one minute trial. Thus, these fluency tests require an elaborate retrieval of words from conceptual (semantic)

*Corresponding author Reinado B. Oriá, PhD, Institute of Biomedicine of the Semiárid, Rua Cel. Nunes de Melo, 1315 – Rodolfo Teófilo, Fortaleza, Ceará, Brazil, 60430-270, Phone: +55 85 3366-8239 / Fax: +55 85 3366-8445, rbo5u@virginia.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

and lexical (phonetic) memory involving specific areas of the brain in a restricted timeframe. This word retrieval process requires the operation of organized neural networks and sensorial-motor circuitry connecting sub cortical and cortical areas of the brain, in order to access and decode long-term memory stores. The neural circuitry and stores are initially developed and then continuously molded and adjusted in a hierarchal process that requires both structural and functional plasticity (8).

Interestingly, the role of executive functioning increases with the degree of retrieval difficulty in the fluency tasks. That is, the ability to retrieve correctly (without breaking the rules) a limited set of words demands more planning, monitoring, judgment, and decision-making, in order to inhibit irrelevant information and select the correct responses (9). In order to promptly retrieve the target words from memory, more strategic planning is required, making the test more challenging, consequently, semantic fluency provides a more refined test for potential executive impairments and to magnifying different performances between study groups. Furthermore, within semantic or phonetic fluency, degrees of difficulty can help to assess retrieval function and distinguish it from memory deficits. For example, fruit names (category fluency) and words beginning with the letter A (word fluency) are considered more difficult to identify in the English vocabulary than animal names or words starting with the letter F, respectively for which searches are more limited because of reduced availability, thus demanding more attention and executive skills (10).

Impairments in semantic fluency are either related to blunt executive functioning (lack of sustained retrieval management) or to a breakdown of semantic knowledge (associated with semantic/conceptual memory disruption or/and storage shrinkage). In phonetic tasks, words are retrieved without a complex track of meaning. In contrast, in semantic fluency, knowledge of meaning is critical for the test performance, because words are needed to fit into categories, by grouping targets, according to meaningful and conceptual features. It has been recognized that this structural semantic knowledge is mainly impaired in Alzheimer's patients (11–15).

The temporal neocortex, particularly its posterior aspects, has been indicated as the anatomical substrate of semantic storage, whereas frontal lobe functioning (especially the left frontal cortex) and frontal-subcortical neural pathways have been implicated in retrieval actions (16, 17). Semantic fluency appears to require a much more widely distributed neural system than phonetic fluency, since semantic cues are more jeopardized after diffuse axonal injury than letter retrieval (18).

In Alzheimer's dementia, there is a disproportional impairment in semantic (categorical) but not phonetic (letter) fluency, which means that the conceptual memory and its representation in cortical areas are critically affected (19,20). The retrieval process, which relies on the activation of frontal lobes, is not jeopardized to the same degree (21,22), explaining why phonetic fluency is not similarly compromised. On the other hand, in Huntington's and Parkinson's dementia (10), which are characterized by major sub cortical impairments, the retrieval process is most impaired, leading to equivalent declines in semantic and phonetic performance, because retrieving information is a mandatory pathway to reach efficiently stored pools of verbal memory (Figure 1).

Semantic Fluency and Early Childhood Diarrhea/Malnutrition

In our cohort studies in Brazilian shantytown children under active surveillance since birth, we have found that, in addition to physical growth and fitness, cognitive functioning on WISC Coding, TONI and total verbal fluency testing and schooling were proportionally disrupted at 6–12 years of age in significant linear relationships with diarrhea in their first 2 years of life (23–25). Furthermore, when we tested for higher executive functioning, it was semantic but not phonetic fluency that was most impaired in children (age: 6–12 years) with a history of

heavy diarrhea burdens in their first 2 years of life (26). In contrast, children with heavy or persistent diarrhea burdens in early life, performed at least as well on naming words (phonetic fluency) than children in the cohort who did not have heavy or persistent diarrhea. Moreover, semantic but not phonetic scores were directly correlated with diarrhea burdens in their most formative first 2 years of life. Although this correlation was significant, the r-square values revealed that this variable accounts for around 8% of the variance, suggesting that additional genetic or environmental factors might also be relevant for causality in this setting. The disproportional semantic but not phonetic fluency pattern seen in Brazilian shantytown children seen with a history of heavy diarrhea burdens is unlikely due to imbalances in vocabulary, since both groups had had similar educational backgrounds and because their mother's educational status (almost uniformly < 8th grade in this setting), was not correlated with total fluency scores.

Hypothesis

Our observed studies raised a hypothesis that the vicious cycle of early childhood diarrhea and malnutrition during the first most formative years (1–3 years old) may cause a cognitive Alzheimer-like deficit (over proportional effect on semantic rather than phonetic fluency), affecting brain regions where the semantic memory is stored. Additional studies are required to confirm the hypothesis of this disproportional effect, as the etiological factor of diarrhea (virus, bacteria, helminths) may have a role on the degree, extension and selectiveness of the brain injury observed in this previous study. Regardless of this effect, semantic fluency may be a surrogate marker for later cognitive deficits due to early childhood diarrhea. Changes upon time in verbal fluency scores during childhood can be compared with a study on Italian healthy children described by Riva and colleagues (3).

Interestingly, the semantic deficit in the children most afflicted with diarrhea correlated with *Giardia lamblia* infection, but not with other parasites, suggesting that giardiasis might specifically alter cognitive development or provide an additional indicator of environmental contamination that might affect cognitive function, as postulated by Berkman and colleagues (27).

Evaluation and Discussion of the Hypothesis

Evidence supporting the potential usefulness of category fluency in assessing poor nutrition came from Grantham-McGregor and Simeon (28,29), who studied the short-term impact of school feeding programs on cognitive outcomes in undernourished children. These authors noted a primary deficit in the motivational capacity of the undernourished child, since lassitude is linked to a lack energy not only for physical activity but also for mental and behavioral effort (30).

In Grantham-McGregor's studies relating cognitive performance of school children with heavy loads of *Trichuris trichura* infection, these authors found that semantic fluency was one of three neuropsychological tests that have shown to be consistently impaired as compared to uninfected children. The other two being visual search, and paired associated learning (French vocabulary test) (31). They also described improvements in semantic fluency in a subset of children treated with antihelminthic therapy (32), even though this finding was not replicable in another subset with moderate infection burdens (33). The variability of semantic performance because of interventions, in these early studies, might be due to differences of motivation, as speculated by these authors, leading to improved executive function.

The fluency test is triggered by an auditory request stimulus, but it involves a self-initiation and maintenance of a mental process in the absence of any ongoing external cues. The fluency task is therefore self-driven, requiring motivation and self-control, thus strengthening the idea

of its greater discriminative efficacy (over most other tasks) in detecting impaired executive function under the challenge of diarrhea, enteric infections or malnutrition.

The mechanisms involved in this semantic deficit seen in a subset of shantytown children challenged by a heavy load of diarrhea episodes early in life are unclear at present. Among these possibilities could be an early event perturbs the development of an anterior neural network related to speech, as recently postulated by Levin and colleagues (34). Children have a more widespread frontal activation than adults, especially before mid childhood (35,36), therefore relying on fine functional and structural changes over time, which, if disrupted, could predispose to impairments. However, our pilot findings that phonetic fluency is not much altered (like semantic fluency is) suggest that frontal-sub cortical networks are not primarily affected or that an etiological and a regional specific pathogen effect is seen.

Interestingly, hippocampal damage was considered a detrimental factor for right temporal lobe epileptic patients to perform semantic but not phonetic tasks, suggesting a critical role of the hippocampus in semantic fluency (37). Furthermore, new evidences have pointed out to the importance of the hippocampus function in establishing semantic associations (38). It is well-recognized that the hippocampus, a highly plastic structure during development, is strongly affected by early malnutrition (39–41). Recent studies have highlighted changes in cell proliferation and apoptosis (42) and behavioral deficits (43,44), because of the involvement of the hippocampus in the malnutrition challenge. In addition, hippocampus plasticity is considered particularly vulnerable to altered glucose metabolism and hypothermia induced by starvation (45,46) and selective nutrient deficiency that might predispose neurodegenerative diseases later in life (47). Furthermore, the same proteins that are related with Alzheimer's physiopathology, namely the amyloid precursor protein and presenilins may play a role during the construction of neuronal networks and synaptic plasticity in the immature hippocampus (48).

Although motivational issues are clearly important variables for semantic performance, the patterns of specific impairment seen in Brazilian shantytown children might be related with altered semantic memory. The latter is suggested by the lack of phonetic impairment in cohort children with heavy diarrhea burdens. If a representation of conceptual knowledge is compromised, this would represent a type of identifiable "brain injury" due to malnourishing diarrhea in the first years of life, a well-known sensitive period of rapid brain development in a period of high plasticity. In order to assess the degree of impairment in semantic storage, it is necessary to further examine the methodological approach for the testing. As indicated by Roher and colleagues (10), one way to address the role of semantic memory in fluency tasks is simply by timing the list of categorical words retrieved in one minute trial. When the semantic storage is limited (e.g.: cortical atrophy), subjects concentrate the semantic retrieval in the first quarters of the test, depleting the reduced storage of words in the memory, thus failing to retrieve words during the last quarters of the test. The same degree of response is seen in Alzheimer's type of dementia, but not in sub cortical type of dementia, where the retrieval (but not stored memory) is profoundly blocked, which allows a more even naming of words throughout the test timeframe, although with reduced numbers. That is sub cortically demented subjects retrieve fewer words but more evenly distributed throughout the 1 minute test period (Figure 2). If this same pattern is repeated in children with history of heavy diarrhea, it would strongly suggest an executive failure, but if the pattern is the same from Alzheimer's patients, it would point out for a primarily memory defect. Early linguistic deficits have been indicated as a strong predictor of later cognitive impairment (49).

In addition, new multidimensional statistical approaches to verbal fluency tests are now available, which have been proved to further clarify other aspects of verbal cognitive domains,

by evaluating sequential structure and composition of individual responses and by building maps of semantic words according to different study groups (50).

Conclusions

Our group has found that early childhood diarrhea is associated with lasting growth shortfalls depicted by height-per-age z scores (HAZ) (24,51,52). In fact, the best surrogate to reflect diarrhea and to predict later fitness and cognitive impairment is the HAZ most affected by diarrhea, namely that at 2 years of age (HAZ-2) (26,53,54). Our preliminary studies in Brazilian shantytown children further suggest the sensitivity of simple semantic testing to reflect potentially important cognitive deficits in children with heavy diarrhea burdens or malnutrition.

An Alzheimer-like effect of a profound disruption of the semantic memory due to early childhood diarrhea requires further investigation. If this semantic memory reservoir is prematurely used by the malnutrition/diarrhea-driven brain injury early in life, these effects prompt us to a possible increased vulnerability later in life for neurodegenerative diseases. The consequences of a higher risk of Alzheimer's diseases later in life for this growing population raise important health public questions, especially in emerging countries like Brazil (55).

Furthermore, our genetic studies showing the benefit of the APOE4 allele (the same related with increased risk for acquiring late-onset Alzheimer's disease) in Brazilian shantytown children afflicted with heavy diarrhea burdens early in life support the hypothesis of an antagonism pleiotropy played by a set of genes associated with energy intake and usage (55, 56).

Semantic fluency testing would be a low-cost and simple means to evaluate cognitive development in children with diarrhea in the field, feasible in impoverished settings. Much like HAZ provides a marker for growth faltering, semantic fluency could provide a useful marker for cognitive decline related to enteric infections, offering a simple and feasible means to identify groups in need for early interventions.

References

1. Baldo JV, Shimamura AP. Letter and category fluency in patients with frontal lobe lesions. *Neuropsychology* 1998;12:259–67. [PubMed: 9556772]
2. Ruff RM, Light RH, Parker SB, Levin HS. The psychological construct of word fluency. *Brain Lang* 1997;57:394–405. [PubMed: 9126423]
3. Riva D, Nichelli F, Devoti M. Developmental aspects of verbal fluency and confrontation naming in children. *Brain Lang* 2000;71:267–84. [PubMed: 10716861]
4. Ricci PT, Zolkowicz BJ, Nebes RD, Meltzer CC, Mintun MA, Becker JT. Functional neuroanatomy of semantic memory: recognition of semantic associations. *Neuroimage* 1999;9:88–96. [PubMed: 9918730]
5. Thompson-Schill SL, Swick D, Farah MJ, D'Esposito M, Kan IP, Knight RT. Verb generation in patients with focal frontal lesions: a neuropsychological test of neuroimaging findings. *Proc Natl Acad Sci USA* 1998;95:15855–60. [PubMed: 9861060]
6. Jurado MA, Mataro M, Verger K, Bartumeus F, Junque C. Phonemic and semantic fluencies in traumatic brain injury patients with focal frontal lesions. *Brain Inj* 2000;14:789–95. [PubMed: 11030453]
7. Royall DR, Lauterbach EC, Cummings JL, et al. Executive control function: a review of its promise and challenges for clinical research. A report from the Committee on Research of the American Neuropsychiatric Association. *J Neuropsychiatry Clin Neurosci* 2002;14:377–405. [PubMed: 12426407]
8. Funahashi S. Neuronal mechanisms of executive control by the prefrontal cortex. *Neurosci Res* 2001;39:147–65. [PubMed: 11223461]

9. Ewing-Cobbs L, Brookshire B, Scott MA, Fletcher JM. Children's narratives following traumatic brain injury: linguistic structure, cohesion, and thematic recall. *Brain Lang* 1998;61:395–419. [PubMed: 9570871]
10. Rohrer D, Salmon DP, Wixted JT, Paulsen JS. The disparate effects of Alzheimer's disease and Huntington's disease on semantic memory. *Neuropsychology* 1999;13:381–8. [PubMed: 10447299]
11. Tierney MC, Black SE, Szalai JP, et al. Recognition memory and verbal fluency differentiate probable Alzheimer disease from subcortical ischemic vascular dementia. *Arch Neurol* 2001;58:1654–59. [PubMed: 11594925]
12. Chan AS, Butters N, Salmon DP. The deterioration of semantic networks in patients with Alzheimer's disease: a cross-sectional study. *Neuropsychologia* 1997;35:241–48. [PubMed: 9051673]
13. Fama R, Sullivan EV, Shear PK, et al. Structural brain correlates of verbal and nonverbal fluency measures in Alzheimer's disease. *Neuropsychology* 2000;14:29–40. [PubMed: 10674796]
14. Lafosse JM, Reed BR, Mungas D, Sterling SB, Wahbeh H, Jagust WJ. Fluency and memory differences between ischemic vascular dementia and Alzheimer's disease. *Neuropsychology* 1997;11:514–22. [PubMed: 9345695]
15. Laatu S, Revonsuo A, Jaykka H, Portin R, Rinne JO. Visual object recognition in early Alzheimer's disease: deficits in semantic processing. *Acta Neurol Scand* 2003;108:82–89. [PubMed: 12859283]
16. Barr A, Brandt J. Word-list generation deficits in dementia. *J Clin Exp Neuropsychol* 1996;18:810–22. [PubMed: 9157106]
17. Martin A, Wiggs CL, Lalonde F, Mack C. Word retrieval to letter and semantic cues: a double dissociation in normal subjects using interference tasks. *Neuropsychologia* 1994;32:1487–94. [PubMed: 7885578]
18. Wallesch CW, Curio N, Galazky I, Jost S, Synowitz H. The neuropsychology of blunt head injury in the early postacute stage: effects of focal lesions and diffuse axonal injury. *J Neurotrauma* 2001;18:11–20. [PubMed: 11200246]
19. Lambon Ralph MA, Powell J, Howard D, Whitworth AB, Garrard P, Hodges JR. Semantic memory is impaired in both dementia with Lewy bodies and dementia of Alzheimer's type: a comparative neuropsychological study and literature review. *J Neurol Neurosurg Psychiatry* 2001;70:149–56. [PubMed: 11160461]
20. Watson JM, Balota DA, Sergent-Marshall SD. Semantic, phonological, and hybrid veridical and false memories in healthy older adults and in individuals with dementia of the Alzheimer type. *Neuropsychology* 2001;15:254–267. [PubMed: 11324868]
21. Rohrer D, Wixted JT, Salmon DP, Butters N. Retrieval from semantic memory and its implications for Alzheimer's disease. *J Exp Psychol Learn Mem Cogn* 1995;21:1127–39. [PubMed: 8744958]
22. Duke LM, Kaszniak AW. Executive control functions in degenerative dementias: a comparative review. *Neuropsychol Rev* 2000;10:75–99. [PubMed: 10937917]
23. Guerrant DI, Moore SR, Lima AA, Patrick PD, Schorling JB, Guerrant RL. Association of early childhood diarrhea and cryptosporidiosis with impaired physical fitness and cognitive function four-seven years later in a poor urban community in northeast Brazil. *Am J Trop Med Hyg* 1999;61:707–13. [PubMed: 10586898]
24. Guerrant RL, Kosek M, Moore S, Lorntz B, Brantley R, Lima AA. Magnitude and impact of diarrheal diseases. *Arch Med Res* 2002;33:351–5. [PubMed: 12234524]
25. Niehaus MD, Moore SR, Patrick PD, et al. Early childhood diarrhea is associated with diminished cognitive function 4 to 7 years later in children in a northeast Brazilian shantytown. *Am J Trop Med Hyg* 2002;66:590–93. [PubMed: 12201596]
26. Patrick PD, Oriá RB, Madhavan V, Pinkerton RC, Lorntz B, Lima AA, Guerrant RL. Limitations in verbal fluency following heavy burdens of early childhood diarrhea in Brazilian shantytown children. *Child Neuropsychol* 2005;11:233–244. [PubMed: 16036449]
27. Berkman DS, Lescano AG, Gilman RH, Lopez SL, Black MM. Effects of stunting, diarrhoeal disease, and parasitic infection during infancy on cognition in late childhood: a follow-up study. *Lancet* 2002;359:564–71. [PubMed: 11867110]
28. Chandler AM, Walker SP, Connolly K, Grantham-McGregor SM. School breakfast improves verbal fluency in undernourished Jamaican children. *J Nutr* 1995;125:894–900. [PubMed: 7722692]

29. Simeon DT. School feeding in Jamaica: a review of its evaluation. *Am J Clin Nutr* 1998;67:790S–4S. [PubMed: 9537630]
30. Kvalsvig JD, Cooppan RM, Connolly KJ. The effects of parasite infections on cognitive processes in children. *Ann Trop Med Parasitol* 1991;85:551–68. [PubMed: 1809249]
31. Gardner JM, Grantham-McGregor S, Baddeley A. *Trichuris trichiura* infection and cognitive function in Jamaican school children. *Ann Trop Med Parasitol* 1996;90:55–63. [PubMed: 8729628]
32. Nokes C, Grantham-McGregor SM, Sawyer AW, Cooper ES, Robinson BA, Bundy DA. Moderate to heavy infections of *Trichuris trichiura* affect cognitive function in Jamaican school children. *Parasitology* 1992;104(Pt 3):539–47. [PubMed: 1641252]
33. Simeon DT, Grantham-McGregor SM, Wong MS. *Trichuris trichiura* infection and cognition in children: results of a randomized clinical trial. *Parasitology* 1995;110(Pt 4):457–64. [PubMed: 7753585]
34. Levin HS, Song J, Ewing-Cobbs L, Chapman SB, Mendelsohn D. Word fluency in relation to severity of closed head injury, associated frontal brain lesions, and age at injury in children. *Neuropsychologia* 2001;39:122–31. [PubMed: 11163370]
35. Tamm L, Menon V, Reiss AL. Maturation of brain function associated with response inhibition. *J Am Acad Child Adolesc Psychiatry* 2002;41:1231–8. [PubMed: 12364845]
36. Booth JR, Burman DD, Meyer JR, et al. Neural development of selective attention and response inhibition. *Neuroimage* 2003;20:737–51. [PubMed: 14568448]
37. Gleissner U, Elger CE. The hippocampal contribution to verbal fluency in patients with temporal lobe epilepsy. *Cortex* 2001;37:55–63. [PubMed: 11292161]
38. Henke K, Weber B, Kneifel S, Wieser HG, Buck A. Human hippocampus associates information in memory. *Proc Natl Acad Sci USA* 1999;96:5884–9. [PubMed: 10318979]
39. Bronzino JD, Austin-LaFrance RJ, Mokler D, Morgane PJ. Effects of prenatal protein malnutrition on hippocampal long-term potentiation in freely moving rats. *Exp Neurol* 1997;148:317–23. [PubMed: 9398474]
40. Levitsky DA, Strupp BJ. Malnutrition and the brain: changing concepts, changing concerns. *J Nutr* 1995;125:2212S–20S. [PubMed: 7542703]
41. Ciaroni S, Cecchini T, Ferri P, et al. Neural precursor proliferation and newborn cell survival in the adult rat dentate gyrus are affected by vitamin E deficiency. *Neurosci Res* 2002;44:369–77. [PubMed: 12445625]
42. Kim MJ, Kim Y, Kim SA, et al. Increases in cell proliferation and apoptosis in dentate gyrus of anorexia (anx/anx) mice. *Neurosci Lett* 2001;302:109–12. [PubMed: 11290399]
43. Lukoyanov NV, Andrade JP. Behavioral effects of protein deprivation and rehabilitation in adult rats: relevance to morphological alterations in the hippocampal formation. *Behav Brain Res* 2000;112:85–97. [PubMed: 10862939]
44. Fukuda MT, Francolin-Silva AL, Almeida SS. Early postnatal protein malnutrition affects learning and memory in the distal but not in the proximal cue version of the Morris water maze. *Behav Brain Res* 2002;133:271–7. [PubMed: 12110460]
45. Yanagisawa M, Planel E, Ishiguro K, Fujita SC. Starvation induces tau hyperphosphorylation in mouse brain: implications for Alzheimer's disease. *FEBS Lett* 1999;461:329–33. [PubMed: 10567721]
46. Planel E, Miyasaka T, Launey T, et al. Alterations in glucose metabolism induce hypothermia leading to tau hyperphosphorylation through differential inhibition of kinase and phosphatase activities: implications for Alzheimer's disease. *J Neurosci* 2004;24:2401–11. [PubMed: 15014115]
47. Kruman II, Kumaravel TS, Lohani A, et al. Folic acid deficiency and homocysteine impair DNA repair in hippocampal neurons and sensitize them to amyloid toxicity in experimental models of Alzheimer's disease. *J Neurosci* 2002;22:1752–62. [PubMed: 11880504]
48. Ribaut-Barassin C, Dupont JL, Haeberle AM, et al. Alzheimer's disease proteins in cerebellar and hippocampal synapses during postnatal development and aging of the rat. *Neuroscience* 2003;120:405–23. [PubMed: 12890511]
49. Snowdon DA, Kemper SJ, Mortimer JA, Greiner LH, Wekstein DR, Markesbery WR. Linguistic ability in early life and cognitive function and Alzheimer's disease in late life. Findings from the Nun Study. *JAMA* 1996;275:528–32. [PubMed: 8606473]

50. Schwartz S, Baldo J, Graves RE, Brugger P. Pervasive influence of semantics in letter and category fluency: a multidimensional approach. *Brain Lang* 2003;87:400–11. [PubMed: 14642542]
51. Moore SR, Lima AA, Conaway MR, Schorling JB, Soares AM, Guerrant RL. Early childhood diarrhoea and helminthiasis associate with long-term linear growth faltering. *Int J Epidemiol* 2001;30:1457–64. [PubMed: 11821364]
52. Lima AA, Moore SR, Barboza MS Jr, et al. Persistent diarrhea signals a critical period of increased diarrhea burdens and nutritional shortfalls: a prospective cohort study among children in northeastern Brazil. *J Infect Dis* 2000;181:1643–51. [PubMed: 10823764]
53. Dillingham R, Guerrant RL. Childhood stunting: measuring and stemming the staggering costs of inadequate water and sanitation. *Lancet* 2004;363:94–95. [PubMed: 14726158]
54. Abbott RD, White LR, Ross GW, et al. Height as a marker of childhood development and late-life cognitive function: the Honolulu-Asia Aging Study. *Pediatrics* 1998;102:602–9. [PubMed: 9738183]
55. Oriá RB, Patrick PD, Blackman JA, Lima AA, Guerrant RL. Role of apolipoprotein E4 in protecting children against early childhood diarrhea outcomes and implications for later development. *Med Hypotheses* 2007;68:1099–1107. [PubMed: 17098371]
56. Oriá RB, Patrick PD, Zhang H, Lortz B, Castro Costa CM, Brito GA, Barrett LJ, Lima AA, Guerrant RL. APOE4 Protects the Cognitive Development in Children with Heavy Diarrhea Burdens in Northeast Brazil. *Pediatr Res* 2005;57:310–316. [PubMed: 15611352]

Function	Coordinated Retrieval ("Executive Function" and "Motivation")	Conceptual Memory (Long-term semantic category storage)
Site	Frontal Cortex Sub cortical Neural Networks	Temporal Cortex with Median Hippocampus
Main Dis- eases	Huntington's/Parkinson's diseases Frontal lobe or sub cortical lesions	Alzheimer's disease Temporal lobe lesions <i>Early Childhood Diarrhea?</i>
Test(s)	Phonemic and semantic performance	Only semantic performance

Figure 1.

Neuroanatomical areas involved in storage and retrieval of semantic memory required during semantic fluency assessments and proposed model for early childhood diarrhea/malnutrition effects.

Figure 2.

Idealized latency responses given in a single trial of semantic fluency for an Alzheimer's (AD) patients, Huntington's patients and their age-matched controls. The dementia responses are depicted by black circles; white circles are used for their respective controls. Horizontal lines indicate values of mean response latency and arrows show the difference between means (adapted with permission from Roher, Salmon, Wixted, and Paulsen, 1999).