



Evolutionary neuropathology & congenital mental retardation: Environmental cues predictive of maternal deprivation influence the fetus to minimize cerebral metabolism in order to express bioenergetic thrift

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Summary This article will propose that humans have an adaptive vulnerability to certain forms of mental retardation, specifically, neuropathological disorders that cause decreased energy expenditure in the hippocampus and the cerebral cortex. This hypothesis will be analyzed in terms of the thrifty phenotype paradigm according to which adverse prenatal events can cause differential gene expression resulting in a phenotype that is better suited, metabolically, for a deprived environment. For example, a malnourished mother has an increased propensity to give birth to offspring that feature a “thrifty phenotype” which permits highly efficient calorie utilization, increased fat deposition and a sedentary nature. This article interprets several prenatal occurrences, including maternal malnourishment, low birth weight, multiparity, short birth interval, advanced maternal age and maternal stress – which are currently identified by the epidemiological literature as risk factors for neuropathology – to be environmental cues that communicate to the fetus that, because it will be neglected of maternal investment, developing a metabolically conservative brain will be the most effective ecological strategy.

Success in hunting and foraging in mammals, primates and especially humans is known to be dependent on prolonged maternal investment. Low levels of maternal care are known to result in low survivorship of offspring, largely because the offspring are forced to subsist using simple, low-yield foraging strategies. A predictive, adaptive response, marked by cerebral hypometabolism, may produce a level of metabolic conservancy that mitigates the risks associated with low levels of maternal care. This article will suggest that certain, human neuropathological phenotypes would have been well suited for an ecological niche that closely resembled the less skill-intensive niche of our less encephalized, primate ancestors.

The forms of congenital neuropathology discussed in this article do not cause damage to vital homeostatic systems; most simply decrease the size and energy expenditure of the cerebral cortex and the hippocampus, the two structures known to show plasticity during changes in ecological rigor in vertebrates. Also, many disorders that present comorbidly with neuropathology, such as tendency toward obesity, decrement in anabolic hormones, hypotonic musculature, up-regulation of the hypothalamic–pituitary–adrenal axis, and decreased thyroid output are associated with energy conservancy and the thrifty phenotype, further implicating neuropathology in an ecological strategy.

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Determining the relative impact of evolutionary causation on neuropathological disease should prove informative for medical and gene therapeutic treatment modalities. Furthermore, use of the maternal deprivation paradigm presented here may help researchers more precisely identify the risk factors that determine cognitive trajectory.
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Introduction

The phenotypic characteristics of many organisms ranging from plants to insects to mammals are known to show plastic responses to environmental events, many of which are thought to represent adaptive, defensive responses or reproductive strategies [1]. This phenotypic plasticity through differential gene expression is often cued by maternal condition and is known to create profound alterations in the phenotypes of developing organisms [2]. The thrifty phenotype hypothesis [3,4] has been used widely to interpret studies showing that maternal malnutrition is a strong risk factor for the metabolic syndrome [5]. According to this hypothesis, phenotypes that are programmed by prenatal malnutrition to express low metabolic rates enjoy a survival advantage under deprived circumstances; however, if such a thrifty fetus is born into an environment marked by nutritional abundance it will face increased risk of negative health consequences [6]. Conversely, robust phenotypes that express larger size and rapid metabolism are thought to increase reproductive success when resources are more plentiful but are more susceptible to starvation if exposed to nutritional shortage. Specialists now believe that the association between maternal malnourishment and the offspring's proclivity for a low metabolism is adaptive specifically because the mother's deprived condition during pregnancy is often predictive of the environment into which the fetus will be born.

This article will focus on several risk factors for human neuropathology that are associated with maternal mortality, burden on maternal resources or fetal malnourishment. These environmental events include low birth weight, multiparity, short birth interval, advanced maternal age and maternal stress. Such risk factors may be associated with maternal deprivation: the impairment of a mother's ability to transfer both nourishment and important survival information (memes) to her offspring.

For example, we will analyze the relationship between advanced maternal age and cognitive deficits. Old age of the mother is one of the most powerful predictors of attention deficit hyperactivity disorder (ADHD) [7], Down syndrome [8], severe mental retardation excluding Down syndrome [9],

and mental retardation of unknown cause [10] in offspring. It is clear that an older mother is probabilistically more likely to die before she is able to provide the parental investment necessary to produce an ecologically self sufficient individual. Thus, the offspring of older mothers are at a disadvantage because they are less likely to receive adequate nourishment and memetic transference. It may be instructive to interpret the epidemiological data to be suggesting that older mothers engage in fetal programming – they switch on genes in the fetus that will elicit neuropathology – decreasing their child's reliance on them by lowering their caloric requirements and the inhibitory pressures on their instincts and natural reflexes.

Anthropologists contend that the human brain was able to evolve to such large proportions, despite the accompanying metabolic costs, because humans greatly benefited from the ability to store crucial lessons about food extraction and hunting [11–13]. The human ecological niche is well known to be cognitively rigorous and skill intensive [14,15]; consequently, large brains were valuable because they facilitated the acquisition, storage and implementation of these lessons [11]. Knowing this, it seems logical to assume that individuals that are deprived of maternal instruction, and thus deprived of many valuable lessons, might have had difficulty procuring food to meet their metabolic needs. Therefore, individuals exposed to prenatal risk factors for maternal deprivation should benefit from inhibiting the growth of metabolically excessive nerve tissue in order to assume a resting metabolic rate better suited for meme deprivation – the environment encountered after birth.

Apes and monkeys provide far less parental investment than humans; they have far smaller brains and they inhabit a less mentally demanding place on the food chain. It is likely that the niche filled by maternally deprived, mentally retarded humans would have closely resembled the less cognitively rigorous niche of our smaller brained, primate cousins. We will also concentrate on other parallels between mentally retarded individuals and apes including cerebrocortical and hippocampal size, thyroid activity, and regulation of the HPA axis and we will conclude that these similarities imply that the two groups would have shared a similar foraging strategy in ancestral times.

Background

Mental retardation and evolutionary medicine

Today, the costs of mental retardation (MR) are well documented but the defensive manifestations may be hidden because of discrepancies between our modern and ancestral environments. Many traits that are known to have been defensive in the ancestral environment are now seen as maladaptive in the present (“environmental mismatch”) and the science of evolutionary medicine attempts to identify and characterize these traits. Williams and Nesse [16] suggest that in order to show that a trait may be a form of evolutionary medicine, it is important to provide evidence that the trait is relatively prevalent, that it is heritable and that susceptibility varies within populations. It is also necessary to show how the benefits associated with the trait may have outweighed the costs [16]. Researchers have identified many such “pathological” conditions such as anxiety, cystic fibrosis, diabetes mellitus, diarrhea, fever, inflammation, obesity, pain, sneezing, sickle cell anemia and vomiting and have helped to show that they actually represent evolved defenses [17–19].

Many articles in the last decade have analyzed various forms of psychopathology (anxiety, bipolar disorder, depression, obsessive compulsive disorder, etc.) in terms of evolutionary theory and evolutionary medicine [19,20], and this area of research is often referred to as “evolutionary psychopathology.” Mental retardation and the underlying neuropathology though, have not been analyzed in terms of evolutionary medicine and have not received a great deal of theoretical attention. Unlike the present article, evolutionary analyses of mental retardation are typically population-based and fail to offer an explanation for why the disease arises in affected individuals [21].

It can surely be argued that the rather diverse assortment of relatively prevalent forms of mental retardation are unrelated, purely pathological, and have no evolutionary significance. However, this article will explore the assertion that some forms are related and do represent a type of contingency based, ecological strategy. It is not expected that this paradigm will apply to every form of organic, congenital neuropathology but several diseases will be identified as candidates. It is hoped that this article influences researchers to use the present paradigm to identify other candidates. Through an analysis of epidemiological, etiological, neuroanatomical and physiological similarities between attention deficit

hyperactivity disorder, Down syndrome, microcephaly, schizophrenia, syndromic mental retardation and mental retardation of unknown cause, I hope to characterize their evolutionary significance.

The metabolic costs associated with brain cells

It is clear that there are grave costs associated with encephalization – the accumulation of neurons within the animal brain. One cost identified by researchers is the high energy demand of nervous tissue [22–24]. For instance, the mass specific metabolic rate of brain tissue is over 22 times the mass specific metabolic rate of skeletal muscle [23]. In fact, humans utilize 20–25% of their resting metabolic rate in their brains alone, whereas most primates utilize between 8% and 9% [25]. This is a very expensive organ considering that it accounts for only 2% of total human body weight [26]. Many studies have identified a mechanism, common in most animals, that acts to minimize unnecessary neural energy expenditure by reducing neuron number through cell death. One function of neuron death is to remove neurons that have not made correct or sufficiently numerous connections [27–31]. It is widely believed that this mechanism may be related to an ecological strategy where terminating extraneous neurons increases metabolic efficiency [32–35].

Research has shown that even within populations of a single species, a large degree of variation in absolute number of neurons exists between individuals. Intraspecific diversity in number of neurons has been found in every group that has been comprehensively analyzed [35]. Furthermore, researchers have argued that this diversity is crucial for evolutionary adaptability and the plasticity of the species [36,37]. Surely the large variation in human cognitive ability, in part, stems from the benefits of intraspecific diversity. However, this article will go further and explore the possibility that all humans have a variety of cognitive trajectories available to them before critical developmental stages are reached and the trajectories are canalized (determined) by environmental factors.

Hippocampal size varies with ecological rigor in birds and mammals

Neuron number has been known to fluctuate in individual animals and these fluctuations often seem to correlate with meaningful environmental cues. For instance, a pattern of loss and replacement of neurons in the hippocampus [38,39] and the hyperstriatal complex [40] (an area known to be involved

in the production and recognition of song) of adult canaries corresponds to seasonal variation, with increased number of individual neurons in the spring (the mating season) and less in the fall and winter. Ethological research has shown that food-hoarding bird species that must utilize spatial memory to relocate their food caches in the fall also have a seasonal pattern of loss and replacement of neurons in the hippocampus [41]. Furthermore, more subtle environmental effects, such as spatial tasks also increase hippocampal size in food caching birds [42].

Research has strongly suggested that a similar, functional relationship exists between behavioral activity and the regulation of neurogenesis in the mammalian hippocampus [43–45]. For instance, food caching rat species have larger relative hippocampal size than similar species that do not cache in scattered locations [46]. In fact, neurogenesis in the hippocampi of individual adult mammals is known to increase with environmental stimulation and enrichment [43,47–49] and decrease along with the diminishment of body size, metabolic rate and need to forage [50]. This relationship, between environmental demands and investment in hippocampal neurons is commonly interpreted to be an ecological strategy [45,51].

Individual humans that are destined to be deprived of maternal investment and meme transference would probably not pass through their developmental stages in an enriched environment. For this reason, these individuals would probably be forced to subsist using simple, low-yield foraging strategies. Therefore, the forms of neuropathology discussed in this article, all of which feature decreased hippocampal volume, may be analogous to the phenotypes of other enrichment deprived mammals that are forced to employ less complicated foraging strategies.

Neuropathology may allow humans to adopt a less cognitively rigorous niche

One of the most consistent and conspicuous findings in ADHD, idiopathic MR, the stress cascade effect and schizophrenia is disproportionately small size or hypometabolism of the hippocampus (see figure below). Furthermore, a comprehensive review reports that each of the four major identifiable prenatal causes of MR: Down syndrome, fragile X syndrome, Prader–Willi syndrome, and Angelman syndrome, each feature significant hippocampal neuroanatomical abnormalities [52]. The hippocampal diminishment in said neuropathologic groups may be analogous to the adaptive hippocampal plasticity in the aforementioned birds and mammals.

Disorder	Hippocampal diminishment and/or hypometabolism
ADHD	Yes [53]
Angelman syndrome	Yes [52]
Down syndrome	Yes [54,55]
Fragile X	Yes [56,52]
Idiopathic MR	Yes [52]
Prader–Willi syndrome	Yes [52]
Schizophrenia	Yes [57,58]
Stress cascade	Yes [59,60]

The cerebral cortex and hippocampus, are thought to be very important in sophisticated hunting and food extraction techniques. Clutton-Brock and Harvery [61] posited that animal species with widely dispersed food resources should be selected for increased memory and spatial capacities. Gibson [62] also pointed out that primate and especially human foraging strategies involve widely dispersed resources as well as complex extractive techniques. This observation caused him to posit the “food extraction hypothesis” which explains large cerebrocortical size in monkeys and humans in terms of the relative complexity of their foraging strategies. Researchers have made marked comments on the importance of the hippocampus [63,64] and the cerebral cortex in storing spatial information, creating mental maps and allowing sophisticated food procurement strategies [65–67]. In the study of behavioral ecology, natural selection is thought to favor adaptations that increase foraging efficiency and the evolution of these types of adaptations is the domain of optimal foraging theory (OFT) [26]. OFT is often used to explain subtle variations in metabolic processes and is applied to anthropological, primatological and zoological phenomena. It makes sense, in terms of OFT, that if the most prevalent forms of mental retardation were adaptive, they would not affect vital neurological systems (and most do not), yet would instead affect those metabolically expensive systems associated with the storage and utilization of ecologically relevant information, the cerebral cortex and the hippocampus.

Studies with female mammals have shown that brain areas responsible for learning and memory, especially the hippocampus, become hypermetabolic during pregnancy and early motherhood and this response is thought to be an ecological strategy that helps mothers become better at protecting, caring for, and providing for their young [68]. It is accepted that mothers up-regulate hippocampal and cerebrocortical activity to prepare for motherhood, and this article is attempting to show that fetuses

down-regulate the same activity when preparing for maternal deprivation.

Results/pertinent data

The epidemiological risk factors that link neuropathology to maternal deprivation

This section will identify specific epidemiological risk factors for neuropathology, which might be related to deficits in maternal investment.

As mentioned previously, advanced maternal age at birth is one of the most powerful predictors of ADHD [7], Down syndrome [8], severe mental retardation excluding Down syndrome [9], and mental retardation of unknown cause [10] in offspring. A human mother that is older is more likely to die before she is able to provide the nearly two decades of maternal investment and memetic transference that is required to enable her offspring to become self-sufficient within the notoriously skill-intensive human ecological niche. Furthermore, older mothers are much more likely to die during or after childbirth and during or after infection and thus are more likely than younger mothers to leave orphans behind. It should be instructive to identify the proximate factors that cause the brain of the human fetus to be vulnerable to physiological indicators of maternal age.

Short birth interval, a risk factor for Down syndrome [69], schizophrenia [70] and other neurodegenerative disorders [71], is also associated with increased burden on maternal resources. A mother who spaces her births close together will have increased difficulty partitioning nutrients and memes. If the second child has a proclivity for energy conservancy it is more likely that it will survive to reproductive age.

The same reasoning applies to multiple birth, which is also a significant risk factor for certain forms of human mental retardation including Down syndrome [72,73], general mental retardation [74], mental retardation of unknown cause [10] and schizophrenia [75]. It is important to point out that both closely spaced births and multiparity are characteristic of r-selected animals. Sociobiological literature predicts that r-selected animals are less intelligent than K-selected animals because they will receive less parental investment [76]. This reasoning further implicates neuropathology in an ecological strategy by associating it with the r-strategy. For this reason, it is also interesting to note that mental retardation is strongly associated with precocious puberty [77], another characteristic of the r-strategy.

Advanced paternal age is also a risk factor for schizophrenia and some neurodegenerative disorders [78,79] and it is logical to assume that the presence of a father could also be relevant to the transference of nourishment and survival memes.

There is a strong relationship between maternal stress during pregnancy and neurodevelopmental disorders in offspring [80–83]. A mother that has been exposed to a stressful environment will probably be less likely to provide adequate nourishment and memes to her offspring and therefore should program her child for bioenergetic thrift. In fact, many studies have shown that high levels of maternal stress in humans are associated with impoverished childcare [84–86].

Very low birth weight is a very strong perinatal predictor of several metabolic disorders including obesity, heart disease and diabetes each of which is characterized, in the thrifty phenotype literature, as a predictive adaptive response to malnutrition [6]. Low birth weight is also a very strong predictor of different forms of neuropathology including: ADHD [87,88], mental retardation of unknown cause [10], microcephaly [89] and schizophrenia [75,90]. These relationships must be explored in more detail, but this preliminary evidence supports the hypothesis that neuropathology may be a predictive, adaptive response to early environmental adversity and another nosological facet of the thrifty phenotype phenomenon.

Known risk factors	References
Advanced maternal age	
ADHD	[7]
Down syndrome	[8]
Mental retardation excluding Down syndrome	[9]
Mental retardation of unknown cause	[10]
Advanced paternal age	
Schizophrenia	[78,79]
Short birth interval	
Down syndrome	[69]
Other neurodegenerative disorders	[71]
Schizophrenia	[70]
Multiple births	
Down syndrome	[72,73]
Mental retardation	[74]
Mental retardation of unknown cause	[10]
Schizophrenia	[75]

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Known risk factors	References
Maternal stress	
ADHD	[83]
Schizophrenia	[80–82]
Very low birth weight	
ADHD	[87,88]
Mental retardation of unknown cause	[10]
Microcephaly	[89]
Schizophrenia	[75,90]

It is possible that the relationships identified here are not evidence of fetal programming or an adaptive link between maternal deprivation and neuropathology. For instance, the effects of maternal age might simply be due to increasing germ cell mutations, and the effects of stress and short birth intervals might simply be due to lowered maternal folate. However, the rate of germ cell mutations and the level of folate depletion may be the ultimate, epigenetic mechanisms by which phenotypic plasticity instates this adaptive phenotype. A review of the data suggests a larger, more meaningful relationship in which these forms of mental retardation would have significantly increased reproductive fitness for at-risk individuals in the human ancestral environment.

It is also important to note that the most common forms of mental retardation do not affect vital homeostatic systems. One might assume that the random, purely pathological consequences of germ cell mutations and vitamin deficiencies would create indiscriminate pathological symptoms, many of which would be severely debilitating. Yet most forms of mental retardation simply cause reductions in the overall energy output of the brain focusing their effect on specific, phylogenetically new, neuroanatomical structures such as the hippocampus and the cerebral cortex. For these reasons, the symptoms of many forms of neuropathology can be interpreted as adaptive and not purely arbitrary or pathological.

Analogous/homologous neuropathological responses to maternal deprivation in rats

It has been established that many other animals share similar plastic responses to environmental cues and this requires us to concede that our own tendency to react plastically may derive from phylogenetically earlier forms because of a shared evolutionary history [91]. Interestingly, the rodent

hippocampus and its inputs are known to be highly sensitive to a range of environmental insults. In fact, a well investigated mouse model for the association between maternal deprivation and hippocampal neuropathology [92,93] provides a wealth of relevant information. The offspring of mothers that show high levels of care in the form of pup licking, grooming and arched back nursing show multiple neurological signs of mental health, increased hippocampal innervation and enhanced spatial and learning memory [94]. This makes sense in terms of the present hypothesis because a rat that receives this physical attention will probably also receive nourishment and the relevant survival memes from its mother as well and thus should be able to afford the metabolically expensive organs necessary for acquiring and utilizing memes and for initiating high-yield foraging strategies.

Maternal deprivation, removing young rats from the nest or depriving them of pup licking and grooming, is predictive of impaired learning and memory [95] and also results in the disruption of attentional processes [96]. Maternal deprivation is known to decrease the expression of brain-derived neurotrophic factor (BDNF) in rat pups [97] and the expression of several growth factors (BDNF, bFGF and β -NGF) in pup hippocampal samples [98]. The maternal deprivation model has also been shown to be associated with overall decreased neuron survival in the hippocampus [99]. Furthermore, evidence suggests that the mechanism that up-regulates the neurotrophic factors responsible for increased spatial learning is not the physical presence or absence of a mother, but instead, the stimulation provided by a licking action as shown in experiments that feature artificial “licking-like” tactile stimulation [100]. If it were possible to show that pup licking is predictive of meme transference, it would seem that this “licking-like” stimulation might be the environmental cue that canalizes young rats’ cognitive-ecological strategy.

Prenatal maternal stress is strongly associated with forms of congenital neuropathology in rats [101], monkeys [102] and humans [103]. Prenatal stress in mother rats and monkeys is known to create learning deficits in the offspring that are associated with decreased neurogenesis in the hippocampus and cerebral cortex [102,104]. It is clear that this fetal response to stress in rats and monkeys is very similar to the neuropathological responses to stress that we just identified in humans. It seems logical that an environment that would cause great psychological stress in a pregnant mother would not be conducive to maternal investment and adequate meme transference.

Healthy, normal mice are known to respond plastically to starvation by decreasing hippocampal bio-electrical activity. This is achieved through an increase in the number of hyperphosphorylated tau proteins in their hippocampi [105,106]. Hyperphosphorylated tau is one of the primary pathohistological hallmarks of Alzheimer's disease and is also a histological component of Down syndrome. This reversible, phenotypic change in mice is analogous to the permanent hippocampal hypometabolism seen in forms of human congenital neuropathology because both may protect against starvation.

Ecologically significant traits that present comorbidly with neuropathology

Animals respond plastically to starvation in order to minimize energy expenditure

Many animals are well known to demonstrate consistent plastic responses to starvation that help to minimize energy expenditure. Starvation evokes several physiological changes, the most dramatic of which include suppression of metabolic rate, reduction of thyroid hormone levels and growth hormone levels, a reduction in fertility (through the suppression of gonadal function) and an increased activation of the hypothalamic–pituitary–adrenal axis [107,108]. Many forms of neuropathology feature these same physiological alterations and I will argue that this is because maternally deprived humans in the environment of evolutionary adaptedness (EEA) would have benefited from the same physiological alterations as starving animals.

Low resting metabolic rate and obesity in individuals with neuropathology

Individuals deprived of maternal investment would probably be forced to survive in a less cognitively demanding place on the food chain, for instance they might have to settle for less calorie rich foods and smaller meals. Correspondingly, many forms of mental retardation are associated with calorie hoarding, low metabolic rates, hypotonic musculature, and a sedentary lifestyle. A review of the literature identifies obesity as a prevalent problem in the retarded population, and points out that eating style does not seem to be the cause [109]. Obesity and musculo-skeletal impairment have been found to be significant health problems associated with both intellectual disability [110] and mental retardation [111]. Another analysis points out that the majority of studies that evaluated the cardiovascu-

lar fitness level of adults with mental retardation have reported levels representative of a highly sedentary population [112].

It is also important to note that many forms of syndromic mental retardation are characterized by obesity, and a sedentary lifestyle due to lowered overall metabolic rate and muscle hypotonicity [113]. These disorders include: Allan Herndon syndrome, Angelman syndrome, Bardet–Biedl syndrome, Borjeson–Forssman–Lehmann syndrome, Cohen syndrome, Cri du Chat, Down syndrome, Fragile X syndrome, Megalocornea syndrome, Mehmou syndrome and Prader Willi syndrome [113,114].

The genes that predispose mentally retarded individuals to obesity, probably only represent a liability in our modern environment. These genes were most probably an asset to survival in the Plio-Pleistocene because they would have caused the mentally retarded to conserve calories. The deprived conditions faced by the mentally retarded were probably analogous, in some ways, to those encountered by the ancestors of modern groups with high incidence of obesity such as the Pima Indians (who have been studied by Valencia et al. [115]). This propensity, seen in MR individuals, may also be analogous to the increased risk of obesity and the metabolic syndrome seen in low birth weight babies which is widely thought to be a predictive, adaptive response [116–118].

Many forms of mental retardation that feature low muscle tone and low metabolic rates also feature very low metabolic rates in infancy. This infantile hypotonia would have allowed these infants a low metabolism thereby ensuring that they necessitated less breast milk. A malnourished mother may not be able to provide sustenance to a baby with normal muscle tone, but may be able to produce sufficient milk for a hypotonic baby. Also, many infants with MR have smaller head circumferences that would have been easier for older or less robust women to give birth to. This reasoning frames infantile hypotonia and decreased head circumference as part of a quantitative reproductive strategy.

Diabetes and neuropathology

A currently popular theory, James Neel's thrifty gene hypothesis, contends that the genes for diabetes provide an adaptive advantage that makes their bearers less susceptible to starvation [119–122]. Low birth weight babies are at an increased risk of developing diabetes and this reaction to malnutrition is thought to be a predictive, adaptive response [116,117]. One should expect that individuals that were deprived of parental investment might be more susceptible to starvation and for

this reason, also expect to see evidence of deprived groups expressing the genes for diabetes in the epidemiologic record. It is recognized that several neurodegenerative disorders including Bardet–Biedl syndrome, Down syndrome, Prader–Willi syndrome, schizophrenia [123,124] and many others are strongly associated with increased incidence of diabetes mellitus [125]. It is important to mention though that diabetes mellitus often presents comorbidly with obesity, making it difficult to extricate the relative impact of diabetic propensity on the MR phenotype.

The risk for childhood [126,127] and gestational [128] diabetes increases rapidly with advanced age of the mother. This shared susceptibility to advanced maternal age creates a parallel between neuropathology and diabetes and further suggests that both neuropathology and advanced maternal age may be associated with the thrifty phenotype phenomenon.

Cardiovascular disease and neuropathology

Heart disease and cardiovascular disease have been associated with Down syndrome [129–131], schizophrenia [132,133] general mental retardation [134] and a wide variety of syndromic types of MR.

Heart disease due to a weaker, and less energy expensive heart is seen in humans with low body weight at birth and researchers have previously ascribed the thrifty phenotype hypothesis to this relationship [116,117,135,136]. This popular literature suggests that the high propensity for low birth weight babies to have heart disease is a predictive adaptive response to the maternal condition that allows the offspring to minimize energy expenditure in the heart in order to mitigate the risk of starvation.

In modern times people that express this adaptive response no longer enjoy the benefits because the excess of fatty foods consumed by these individuals puts a serious strain on their “thrifty” heart and makes them susceptible to heart disease [137]. For these reasons the heart disease that is characteristic of the Down syndrome, schizophrenic, and other MR phenotypes may represent yet another method of energy conservancy.

Hypothyroidism and neuropathology

One of the first major endocrinological differences found between humans and apes is a marked increase in thyroid output in humans [138,139]. Not just apes, but almost all other mammals have a larger adrenal glands to thyroid gland ratio whereas humans have the reverse ratio, featuring an enlarged thyroid [139]. A recent publication by Fred

Previc [139] favors Crile’s [140] interpretation of the adaptive value of a large thyroid to humans:

“Crile interpreted this difference (in thyroid output) as reflecting the need for more sustained exertion in humans as opposed to more transient activation in nonhumans, which is consistent with theories that early humans may have engaged in extended locomotion and sustained exertion during such activities as scavenging and chase hunting.”

In other words, a proportionately large thyroid allowed humans the constant energy supply that their hunting niche demanded. I argue that the MR niche would have closely resembled the less strenuous foraging niche seen in apes and monkeys and so it makes sense that an MR phenotype should feature a diminished thyroid gland. It is interesting to note that hypothyroidism is associated with ADHD [141] schizophrenia [142], Down syndrome [143] and congenital hypothyroidism (a form of MR). This association further paints these diseases as atavistic, energy saving, ecological strategies. A quote from Flier et al. [108] highlights the ecological importance of thyroid plasticity:

“In the well-studied rodent model, starvation rapidly suppresses T4 and T3 (thyroid) levels. The benefit of this suppression is clear: Starvation represents a severe threat to survival, and, in rodents, the capacity to survive without nutrition is measured in days. Because thyroid hormones set the basal metabolic rate, a drop in thyroid hormone levels should reduce the obligatory use of energy stores.”

Not only is starvation known to suppress thyroid levels [144] but hypothyroidism is also well known to cause degeneration of the hippocampus in rats [145] implicating it further in a cross-taxa ecological strategy.

Stress and neuropathology

A largely disproportionate number of people with mental retardation have an up-regulation of the hypothalamic–pituitary–adrenal axis and they are particularly susceptible to stress and stress diseases [146]. They react to only mildly threatening stimuli with an exaggerated adrenal/stress response. Maternally deprived rats, with poorly developed hippocampi, show the same exaggerated adrenal/stress response [93]. Zhang et al., emphasize that this fundamental reliance on stress is part of an ecological strategy that allows deprived rats rapid access to energy stores in order to react to potential threats.

Adrenaline secreted by the adrenal glands during a stress response is known to increase energy catabolism allowing an animal to react to environmental threats with force and speed. Modern theorists believe that unlike humans, most animals have larger adrenal glands than thyroid because it is more metabolically efficient to mobilize energy stores only in response to severe threat than to continually mobilize energy stores as thyroid hormones are well known to do [139]. It is possible that individuals with neuropathology and hypothyroidism, like their animal analogues, would have benefited from the ability to conserve energy that would have been exhausted had they had a proportionately larger thyroid. Like many other nonhuman mammals their disproportionately large adrenal glands and their "exaggerated stress response" should allow them to use energy stores more efficiently, and only when necessary.

Individuals deprived of parental guidance probably had much more difficulty in assessing dangerous situations and properly employing the fight or flight response. It would be better for such an individual to overreact to inconsequential stimuli than to under react in response to a potentially lethal threat. Similar adaptive benefits have been proposed to explain the link between maternal deprivation and the fetal programming of the stress response strategy in rats [93].

Associated "Thrifty" disorders	References
Cardiovascular disease	
Down syndrome	[129–131]
Mental retardation	[134]
Schizophrenia	[132,133]
Diabetes	
Down syndrome	[147]
Other neurodegenerative disorders	[125]
Schizophrenia	[123,124]
Hypothyroidism	
ADHD	[141]
Down syndrome	[143]
Schizophrenia	[142]
Obesity	
Down syndrome	[148,149]
Other neurodegenerative disorders	[114]
Other forms of syndromic MR	[113]
Schizophrenia	[150–152]

Associated "Thrifty" disorders	References
Exaggerated stress response	
Mental retardation	[146]
Fragile X	[153,154]
Profound mental retardation	[155]
Schizophrenia	[156,157]

The candidates for adaptive neuropathology that I list here may not be adaptive in the most stringent form of the word. In other words, the ecological causation that I suggest in this article may simply explain how MR individuals were subjected to less stringent selective pressures and thus why they are as prevalent as they are in modern times.

Fitting this theory into an anthropological context: neuropathology obviates hunting

It is thought that highly productive yet very-hard-to-learn foraging skills differentiate humans from other primates [26]. The "difficult-to-acquire-food hypothesis" promulgated by Kaplan [11] contends that the human EEA selected individuals most actively on the basis of their ability to acquire food to feed their metabolically expensive bodies and brains. To quote the researchers:

"Thus, we propose that the long human life span co-evolved with lengthening of the juvenile period, increased brain capacities for information processing and storage and intergenerational resource flows, all as a result of an important dietary shift. Humans are specialists in that they consume only the highest-quality plant and animal resources in their local ecology and rely on creative, skill-intensive techniques to exploit them."

Difficult-to-acquire, extracted foods, including relatively large amounts of meat [158–160] made up a large part of the hunter/gatherer diet in the EEA. Such foods provide many more total calories and macronutrients than more easily acquired foods [161]. The physical anthropological literature suggests that brain expansion enabled early hominids to extract more difficult-to-acquire foods that, not incidentally, were more nutritious and thus could sustain the larger brains [11].

Human foraging is very cognitively demanding and it absolutely requires parental and social guidance [11]. In foraging groups babies that were deprived of maternal interaction and investment

were at an extreme disadvantage because they would probably not properly learn the language, would probably not learn to hunt or gather effectively, and would therefore be more susceptible to starvation. Much research has shown that it takes human hunter-gatherers many years of learning to become proficient [162] and that strategies associated with human hunting and gathering are extremely sophisticated [12,163]. In fact, chimpanzees are known to become fully capable foragers within their first decade [11] whereas most human hunter-gatherers are not at their peak rate of productivity until mid adulthood [163]. These points considered, it would seem that an individual that was deprived of parental investment would not be able to successfully develop the skills to warrant a metabolically expensive cerebral cortex or hippocampus. For this reason, the selective pressure to link maternal deprivation to neuropathology through phenotypic plasticity must have been strong in the EEA.

A hominid, or early human, that was mentally retarded would probably not be well adapted to the rigorous environmental niche of its peers. It would probably not have been able to catch large or mid-sized game, and might have had trouble extracting roots, tubers and other difficult-to-acquire, high calorie foodstuffs. The ancestral MR diet would have likely consisted of small game, easily accessible vegetation, insects and other invertebrates, dried fruit, and other relatively low quality foods that are easy to extract. The MR propensity for a lower metabolism would have allowed such a moderate diet to sustain their simple foraging activities. It is conceivable that the MR diet could have been supplemented by the efforts of close kin and community members; however, it is likely that it would have closely resembled that of monkeys and apes.

It is a common observation that carnivores, unlike herbivores, raised in captivity do not thrive when released into the wild [11]. To be successful in their specialized niche carnivores must receive early training, and must have dedicated, protective and didactic mothers. Herbivores on the other hand can often be deprived of maternal investment and yet can still subsist later in the wild using simple foraging strategies. Therefore, the life history of the ancestral MR individual may be analogous to the herbivore's because both enjoy relative independence of parental investment.

The fossil record shows that, for an extended period of time, many human-like hominids had very small brains. The huge variability in brain size in hominids found in the fossil record is proof that the near 1400cc brain possessed by modern humans is by no means a requirement for food procurement

in a bipedal ape. This forces us to recognize that the neurological "deficiencies" seen in MR individuals may have analogues in extinct hominids.

The psychological benefits neuropathology may confer on deprived individuals

Cognitive noise

I contend that r-selected animals (which have large numbers of offspring and offer little parental care) rarely have high encephalization quotients because intelligence is ineffective without parental guidance. Furthermore, I believe that the ultimate factor responsible for the absence of both large brains and advanced intelligence in r-selected animals is intimately related to a concept that I will term "cognitive noise." Cognitive noise consists of any thoughts, conceptualizations or cognitions that will direct, motivate or in any way effect the future behavior of an animal without producing a survival advantage for it. I suggest that if it were possible to increase the intelligence of an r-selected animal, without changing its ecological setting or increasing the amount of parental instruction it receives, that the animal's fitness would only be hindered, due to an increased proclivity for making irrelevant or fallacious conceptualizations.

It seems clear that an animal that is thoroughly instructed by its parents, and thereby well informed of the motivations and concerns of a successful hunter or forager, will be less likely to produce fitness-compromising levels of cognitive noise. But if a highly encephalized, highly intelligent animal is deprived of its parents and of parental instruction, it will improperly employ its ability for mental analysis and create conceptualizations and mental systematizations that do not facilitate threat avoidance, feeding or reproduction. Such an animal may also frequently engage in extraneous thinking, which could interfere with its ability to remain vigilant. I argue that the metabolically expensive, neurological organ that allows complex analysis in K-selected animals (the brain) is not equipped to produce adaptive behavior on its own, without memes. If it did, we might expect to see large brains in animal species that do not transfer memes, and yet we do not see this.

"Unless you keep them (people) busy with some definite subject that will bridle and control them, they throw themselves in disorder hither and yon in the vague field of imagination." -Montaigne

This phenomenon must be due, in part, to the inhibitory nature of cognition. Encephalized animals have disproportionately large numbers of inhibitory interneurons in their brains. These interneurons allow complex thought but would be debilitating to animals (fish, insects...) that depend on instinct and quick reflexive reaction. Encephalization most probably inhibits an animal's propensity to use innate and instinctive behaviors to respond to environmental stimuli. Maternally deprived animals should thus benefit from an ability to dis-inhibit their instinctive drives because instincts guide animals in the absence of mothers. Because the brain of a maternally deprived animal will naturally expend more energy than it allows the animal to seek out and obtain, the best strategy to dis-inhibit instinct is the one characterized by "neuropathology." Thus, neuropathology in effect, minimizes the organism's reliance on nurture (memes) and maximizes their reliance on nature (genetic instincts).

- (1) Cognitive noise is directly proportional to encephalization.
- (2) Cognitive noise is inversely proportional to parental investment.
- (3) Cognitive noise, by definition, is inversely proportional to reproductive success.

Examples of the cognitive-ecological continuum in the animal kingdom

Sea squirts in Japanese seas metabolize their own brains once they have permanently attached themselves to a rock [164]. This is evidence of adaptive "neuropathology" at work in the animal world. The squirt needs its central and peripheral nervous systems to locate and attain food and subsequently find a rock to attach to. After it adheres to the rock, it can then sacrifice its own cognitive capabilities in order to decrease unnecessary energy expenditure. In other words, a change in its ecological niche obviates the need for encephalization and elicits "neuropathological" alteration.

Female praying mantises occasionally bite off the head of their partner during sex. According to Richard Dawkins' [165] interpretation of this act, the female bites off his head (and the males allows this) to ensure copulatory efficiency. Dawkins (possibly informed by the research of Ken Roeder) explains that by removing the male's head the female insures that the male's body will continue mating, and will not be impeded by any inhibitory associations within the head that might slow or stop the copulation. A male mantis that stops mating before it releases its germ cells is at a definite selective disadvantage. This is an example that

shows how maladaptive encephalization is if it inhibits the ability of the organism to reproduce. This suggests that, not only are large brains metabolically expensive, but they can also inhibit adaptive, instinctual behavior. I attribute the intact male mantis' reluctance to follow instinct to "cognitive noise." Mantises are in fact relatively encephalized insect predators, the intelligence necessary for their hunting niche may be the factor that predisposes them to cognitive noise.

Discussion and the introduction of an important concept: Meme utility

I offer the concept of "meme utility" to generalize some of the claims made in this paper. I define meme utility as the measure of the survival advantage that the utilization of memes provides for an individual animal – where memes are units of behavioral information that can be transferred from one animal to another [165]. It is clear that memes are necessary for reproductive success in many intelligent animals such as altricial (helpless when born), K strategists but are less important for precocial, r strategists that are less encephalized and have little need for parental guidance or social learning. For example, meme utility would be lower for r-selected animals like mollusks and fish compared to K-selected animals like monkeys and humans. I am advocating that maternal deprivation predicts a decrement in meme utility and thus the potential applicability of a "decephalization" strategy. Observations like these suggest that clinical neuroscientific phenomena may be explicable in terms of ethology, bioanthropology, bioenergetics and memetics.

A similar relationship may be applied to explain the stress cascade phenomenon. When meme utilization is effective a mature animal will often experience neuroendocrinological reward which helps to reinforce behaviors and consolidate memories. However, if meme utilization is ineffective an animal will often experience stress which has been shown to produce a marked deficit in hippocampal metabolic function, a "pathophysiological" phenomenon known as the stress cascade response [59,60]. The stress cascade may represent an ecological strategy to minimize reliance on ineffective memes, and reemphasize instinct, by decreasing hippocampal energy expenditure.

The concept of meme utility can also be applied to Alzheimer's and senile dementia. Natural aging and senescence are known to hinder human physical capabilities and it is physical health and strength that are necessary to utilize the memes previously

stored for human hunting and foraging. Therefore, it would make sense that someone who was no longer physically able to utilize the information, should experience low meme utility and should thus benefit from metabolizing less energy in the areas responsible for storing the information. This cognitive impairment is seen in the early and middle stages of Alzheimer's disease and, just like the other disorders, the metabolic deficit is most readily apparent in the hippocampus [166,167].

"It is not the strongest of the species that survives, nor the most intelligent, but the one most responsive to change."-Charles Darwin

Conclusion

It seems that maternal deprivation may be a powerful and informative indicator of environmental quality that has profound predictive affects on the developing fetus. This hypothesis cannot be fully substantiated; however, because of the scarcity of related research. It is evident that much more work is needed to define the parameters of the influence of maternal deprivation on congenital neuropathology.

Unfortunately, most forms of mental retardation cannot yet be effectively treated and providing care for the large number of retarded individuals puts a large strain on present day economies. However, providing a comprehensive, evolutionary explanation for susceptibility to retardation may explain the large prevalence in human populations and may also help to inform psycho-social, bio-medical and gene therapeutic treatment strategies.

I hope that this discussion will encourage researchers to use the maternal deprivation paradigm to more precisely identify the risk factors and environmental cues that determine cognitive trajectory. If science can clearly define each risk factor, then parents can be instructed how best to minimize inadvertent exposure of the fetus, and child, to neuropathology inducing environmental cues.

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