# Journals in Science

## Biological Psychology

Volume 88, Number 1
September 2011

**Sexual Arousal Patterns of Bisexual Men Revisited**

*A. M. Rosenthal et al.*

Men who identify themselves as bisexual report feeling sexually aroused by both men and women. However, past research has not demonstrated that such men exhibit substantial genital arousal to both male and female erotic stimuli, suggesting that they identify as bisexual for reasons other than their genital arousal pattern. The purpose of the present study was to examine arousal patterns among bisexual men who were recruited using stringent criteria involving sexual and romantic experience with both men and women in order to increase the likelihood of finding a bisexual arousal pattern. Bisexual men in the present study demonstrated bisexual patterns of both subjective and genital arousal. It remains unclear which pattern is most typical of contemporary bisexual men: the present results supporting a bisexual arousal pattern, or previous results not finding one. In either case, understanding men with bisexual arousal patterns could help illuminate the etiology and development of male sexual orientation.

## Cell

Volume 146, Number 3
August 5, 2011

**Direct Conversion of Alzheimer's Disease Patient Skin Fibroblasts into Functional Neurons**

*L. Qiang et al.*

Directed conversion of mature human cells, as from fibroblasts to neurons, is of potential clinical utility for neurological disease modeling as well as cell therapeutics. Here, we describe the efficient generation of human-induced neuronal (hiN) cells from adult skin fibroblasts of unaffected individuals and Alzheimer's patients, using virally transduced transcription regulators and extrinsic support factors. hiN cells from unaffected individuals display morphological, electrophysiological, and gene expression profiles that typify glutamatergic forebrain neurons and are competent to integrate functionally into the rodent CNS. hiN cells from familial Alzheimer disease (FAD) patients with presenilin-1 or -2 mutations exhibit altered processing and localization of amyloid precursor protein (APP) and increased production of Aβ, relative to the source patient fibroblasts or hiN cells from unaffected individuals. Together, our findings demonstrate directed conversion of human fibroblasts to a neuronal phenotype and reveal cell type-selective pathology in hiN cells derived from FAD patients.

Volume 146, Number 4
August 19, 2011

**Reconstitution of the Mouse Germ Cell Specification Pathway in Culture by Pluripotent Stem Cells**

*K. Hayashi et al.*

The generation of properly functioning gametes in vitro requires reconstitution of the multistepped pathway of germ cell development. We demonstrate here the generation of primordial germ cell-like cells (PGCLCs) in mice with robust capacity for spermatogenesis. PGCLCs were gener-

ated from embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs) through epiblast-like cells (EpiLCs), a cellular state highly similar to pregastrulating epiblasts but distinct from epiblast stem cells (EpiSCs). Reflecting epiblast development, EpiLC induction from ESCs/iPSCs is a progressive process, and EpiLCs highly competent for the PGC fate are a transient entity. The global transcription profiles, epigenetic reprogramming, and cellular dynamics during PGCLC induction from EpiLCs meticulously capture those associated with PGC specification from the epiblasts. Furthermore, we identify Integrin-β3 and SSEA1 as markers that allow the isolation of PGCLCs with spermatogenic capacity from tumorigenic undifferentiated cells. Our findings provide a paradigm for the first step of in vitro gametogenesis.

## Cell Research

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### Defining the Nature of Human Pluripotent Stem Cell Progeny

*M. Patterson et al.*

While it is clear that human pluripotent stem cells (hPSCs) can differentiate to generate a panoply of various cell types, it is unknown how closely in vitro development mirrors that which occurs in vivo. To determine whether human embryonic stem cells (hESCs) and human-induced pluripotent stem cells (hiPSCs) make equivalent progeny, and whether either makes cells that are analogous to tissue-derived cells, we performed comprehensive transcriptome profiling of purified PSC derivatives and their tissue-derived counterparts. Expression profiling demonstrated that hESCs and hiPSCs make nearly identical progeny for the neural, hepatic, and mesenchymal lineages, and an absence of re-expression from exogenous reprogramming factors in hiPSC progeny. However, when compared to a tissue-derived counterpart, the progeny of both hESCs and hiPSCs maintained expression of a subset of genes normally associated with early mammalian development, regardless of the type of cell generated. While pluripotent genes (OCT4, SOX2, REX1, and NANOG) appeared to be silenced immediately upon differentiation from hPSCs, genes normally unique to early embryos (LIN28A, LIN28B, DPPA4, and others) were not fully silenced in hPSC derivatives. These data and evidence from expression patterns in early human fetal tissue (3-16 weeks of development) suggest that the differentiated progeny of hPSCs are reflective of very early human development (< 6 weeks). These findings provide support for the idea that hPSCs can serve as useful in vitro models of early human development, but also raise important issues for disease modeling and the clinical application of hPSC derivatives.

## Cell Stem Cell

Volume 9, Number 2
August 5, 2011

### Direct Reprogramming of Adult Human Fibroblasts to Functional Neurons under Defined Conditions

*R. Ambasudhan et al.*

Human induced pluripotent stem cells (hiPSCs) have been generated by reprogramming a number of different somatic cell types using a variety of approaches. In addition, direct reprogramming of mature cells from one lineage to another has emerged recently as an alternative strategy for generating cell types of interest. Here we show that a combination of a microRNA (miR-124) and two transcription factors (*MYT1L* and *BRN2*) is sufficient to directly reprogram postnatal and adult human primary dermal fibroblasts (mesoderm) to functional neurons (ectoderm) under precisely defined conditions. These human induced neurons (hiNs) exhibit typical neuronal morphology and marker gene expression, fire action potentials, and produce functional synapses between each other. Our findings have major implications for cell-replacement strategies in neurode-

generative diseases, disease modeling, and neural developmental studies.

Volume 9, Number 3
September 2, 2011

**Conversion of Mouse and Human Fibroblasts into Functional Spinal Motor Neurons**

*E. Y. Son et al.*

The mammalian nervous system comprises many distinct neuronal subtypes, each with its own phenotype and differential sensitivity to degenerative disease. Although specific neuronal types can be isolated from rodent embryos or engineered from stem cells for translational studies, transcription factor-mediated reprogramming might provide a more direct route to their generation. Here we report that the forced expression of select transcription factors is sufficient to convert mouse and human fibroblasts into induced motor neurons (iMNs). iMNs displayed a morphology, gene expression signature, electrophysiology, synaptic functionality, in vivo engraftment capacity, and sensitivity to degenerative stimuli similar to those of embryo-derived motor neurons. We show that the converting fibroblasts do not transit through a proliferative neural progenitor state, and thus form bona fide motor neurons via a route distinct from embryonic development. Our findings demonstrate that fibroblasts can be converted directly into a specific differentiated and functional neural subtype, the spinal motor neuron.

## Current Biology

Volume 21, Number 18
September 27, 2011

**A Shift in Sensory Processing that Enables the Developing Human Brain to Discriminate Touch from Pain**

*L. Fabrizi et al.*

When and how infants begin to discriminate noxious from innocuous stimuli is a fundamental question in neuroscience. However, little is known about the development of the necessary cortical somatosensory functional prerequisites in the intact human brain. Recent studies of developing brain networks have emphasized the importance of transient spontaneous and evoked neuronal bursting activity in the formation of functional circuits. These neuronal bursts are present during development and precede the onset of sensory functions. Their disappearance and the emergence of more adult-like activity are therefore thought to signal the maturation of functional brain circuitry. Here we show the changing patterns of neuronal activity that underlie the onset of nociception and touch discrimination in the preterm infant. We have conducted noninvasive electroencephalogram (EEG) recording of the brain neuronal activity in response to time-locked touches and clinically essential noxious lances of the heel in infants aged 28–45 weeks gestation. We show a transition in brain response following tactile and noxious stimulation from nonspecific, evenly dispersed neuronal bursts to modality-specific, localized, evoked potentials. The results suggest that specific neural circuits necessary for discrimination between touch and nociception emerge from 35–37 weeks gestation in the human brain.

## Frontiers in Human Neuroscience

Volume 5, Number 5
January 27, 2011

**Functional Imaging Reveals Movement Preparatory Activity in the Vegetative State**

*T. A. Bekinschtein et al.*

The vegetative state (VS) is characterized by the absence of awareness of self or the environment and preserved autonomic functions. The diagnosis relies critically on the lack of consistent signs of purposeful behavior in response to external stimulation. Yet, given that patients with disorders of consciousness often exhibit fragmented movement patterns, voluntary actions may go unnoticed. Here we designed a simple motor paradigm

that could potentially detect signs of purposeful behavior in VS patients with mild to severe brain damage by examining the neural correlates of motor preparation in response to verbal commands. Twenty-four patients who met the diagnostic criteria for VS were recruited for this study. Eleven of these patients showing preserved auditory evoked potentials underwent functional magnetic resonance imaging (fMRI) to test for basic speech processing. Five of these patients, who showed word related activity, were included in a second fMRI study aimed at detecting functional changes in premotor cortex elicited by specific verbal instructions to move either their left or their right hand. Despite the lack of overt muscle activity, two patients out of five activated the dorsal premotor cortex contralateral to the instructed hand, consistent with movement preparation. Our results may reflect residual voluntary processing in these two patients. We believe that the identification of positive results with fMRI using this simple task, may complement the clinical assessment by helping attain a more precise diagnosis in patients with disorders of consciousness.

## Nature

Volume 474, Number 7353
June 30, 2011

### *De novo* Cardiomyocytes from within the Activated Adult Heart after Injury

*N. Smart et al.*

A significant bottleneck in cardiovascular regenerative medicine is the identification of a viable source of stem/progenitor cells that could contribute new muscle after ischaemic heart disease and acute myocardial infarction. A therapeutic ideal—relative to cell transplantation—would be to stimulate a resident source, thus avoiding the caveats of limited graft survival, restricted homing to the site of injury and host immune rejection. Here we demonstrate in mice that the adult heart contains a resident stem or progenitor cell population, which has the potential to contribute bona fide terminally differentiated cardiomyocytes after myocardial infarction. We reveal a novel genetic label of the activated adult progenitors via re-expression of a key embryonic epicardial gene, Wilm's tumour 1 (*Wt1*), through priming by thymosin β4, a peptide previously shown to restore vascular potential to adult epicardium-derived progenitor cells with injury. Cumulative evidence indicates an epicardial origin of the progenitor population, and embryonic reprogramming results in the mobilization of this population and concomitant differentiation to give rise to *de novo* cardiomyocytes. Cell transplantation confirmed a progenitor source and chromosome painting of labelled donor cells revealed transdifferentiation to a myocyte fate in the absence of cell fusion. Derived cardiomyocytes are shown here to structurally and functionally integrate with resident muscle; as such, stimulation of this adult progenitor pool represents a significant step towards resident-cell-based therapy in human ischaemic heart disease.

Volume 476, Number 7358
August 4, 2011

### DMRT1 Prevents Female Reprogramming in the Postnatal Mammalian Testis

*C. K. Matson et al.*

Sex in mammals is determined in the fetal gonad by the presence or absence of the Y chromosome gene *Sry*, which controls whether bipotential precursor cells differentiate into testicular Sertoli cells or ovarian granulosa cells. This pivotal decision in a single gonadal cell type ultimately controls sexual differentiation throughout the body. Sex determination can be viewed as a battle for primacy in the fetal gonad between a male regulatory gene network in which *Sry* activates *Sox9* and a female network involving WNT/β-catenin signalling. In females the primary sex-determining decision is not final: loss of the FOXL2 transcription factor in adult granulosa cells can reprogram granulosa cells into Sertoli cells. Here we show

that sexual fate is also surprisingly labile in the testis: loss of the DMRT1 transcription factor in mouse Sertoli cells, even in adults, activates *Foxl2* and reprograms Sertoli cells into granulosa cells. In this environment, theca cells form, oestrogen is produced and germ cells appear feminized. Thus *Dmrt1* is essential to maintain mammalian testis determination, and competing regulatory networks maintain gonadal sex long after the fetal choice between male and female. *Dmrt1* and *Foxl2* are conserved throughout vertebrates and *Dmrt1*-related sexual regulators are conserved throughout metazoans. Antagonism between *Dmrt1* and *Foxl2* for control of gonadal sex may therefore extend beyond mammals. Reprogramming due to loss of *Dmrt1* also may help explain the aetiology of human syndromes linked to *DMRT1*, including disorders of sexual differentiation and testicular cancer.

Volume 476, Number 7359
August 11, 2011

**Direct Generation of Functional Dopaminergic Neurons from Mouse and Human Fibroblasts**

*M. Calazzo et al.*

Transplantation of dopaminergic neurons can potentially improve the clinical outcome of Parkinson's disease, a neurological disorder resulting from degeneration of mesencephalic dopaminergic neurons. In particular, transplantation of embryonic-stem-cell-derived dopaminergic neurons has been shown to be efficient in restoring motor symptoms in conditions of dopamine deficiency. However, the use of pluripotent-derived cells might lead to the development of tumours if not properly controlled. Here we identified a minimal set of three transcription factors—*Mash1* (also known as *Ascl1*), *Nurr1* (also known as *Nr4a2*) and *Lmx1a*—that are able to generate directly functional dopaminergic neurons from mouse and human fibroblasts without reverting to a progenitor cell stage. Induced dopaminergic (iDA) cells release dopamine and show spontaneous electrical activity organized in regular spikes consistent with the pacemaker activity featured by brain dopaminergic neurons. The three factors were able to elicit dopaminergic neuronal conversion in prenatal and adult fibroblasts from healthy donors and Parkinson's disease patients. Direct generation of iDA cells from somatic cells might have significant implications for understanding critical processes for neuronal development, in vitro disease modelling and cell replacement therapies.

**Induction of Human Neuronal Cells by Defined Transcription Factors**

*Z. P. Pang et al.*

Somatic cell nuclear transfer, cell fusion, or expression of lineage-specific factors have been shown to induce cell-fate changes in diverse somatic cell types. We recently observed that forced expression of a combination of three transcription factors, *Brn2* (also known as *Pou3f2*), *Ascl1* and *Myt1l*, can efficiently convert mouse fibroblasts into functional induced neuronal (iN) cells. Here we show that the same three factors can generate functional neurons from human pluripotent stem cells as early as 6 days after transgene activation. When combined with the basic helix-loop-helix transcription factor *NeuroD1*, these factors could also convert fetal and postnatal human fibroblasts into iN cells showing typical neuronal morphologies and expressing multiple neuronal markers, even after downregulation of the exogenous transcription factors. Importantly, the vast majority of human iN cells were able to generate action potentials and many matured to receive synaptic contacts when co-cultured with primary mouse cortical neurons. Our data demonstrate that non-neural human somatic cells, as well as pluripotent stem cells, can be converted directly into neurons by lineage-determining transcription factors. These methods may facilitate robust generation of patient-specific human neurons for in vitro disease modelling or future applications in regenerative medicine.

**MicroRNA-Mediated Conversion of Human Fibroblasts to Neurons**

*A. S. Yoo et al.*

Neurogenic transcription factors and evolutionarily conserved signalling pathways have been found to be instrumental in the formation of neurons. However, the instructive role of microRNAs (miRNAs) in neurogenesis remains unexplored. We recently discovered that miR-9* and miR-124 instruct compositional changes of SWI/SNF-like BAF chromatin-remodelling complexes, a process important for neuronal differentiation and function. Nearing mitotic exit of neural progenitors, miR-9* and miR-124 repress the BAF53a subunit of the neural-progenitor (np)BAF chromatin-remodelling complex. After mitotic exit, BAF53a is replaced by BAF53b, and BAF45a by BAF45b and BAF45c, which are then incorporated into neuron-specific (n)BAF complexes essential for post-mitotic functions. Because miR-9/9* and miR-124 also control multiple genes regulating neuronal differentiation and function. We proposed that these miRNAs might contribute to neuronal fates. Here we show that expression of miR-9/9* and miR-124 (miR-9/9*-124) in human fibroblasts induces their conversion into neurons, a process facilitated by *NEUROD2*. Further addition of neurogenic transcription factors *ASCL1* and *MYT1L* enhances the rate of conversion and the maturation of the converted neurons, whereas expression of these transcription factors alone without miR-9/9*-124 was ineffective. These studies indicate that the genetic circuitry involving miR-9/9*-124 can have an instructive role in neural fate determination.

## Nature Communications

Volume 2, Number 417
August 9, 2011

**Rhythmic Actomyosin-Driven Contractions Induced by Sperm Entry Predict Mammalian Embryo Viability**

*A. Ajduk et al.*

Fertilization-induced cytoplasmic flows are a conserved feature of eggs in many species. However, until now the importance of cytoplasmic flows for the development of mammalian embryos has been unknown. Here, by combining a rapid imaging of the freshly fertilized mouse egg with advanced image analysis based on particle image velocimetry, we show that fertilization induces rhythmical cytoplasmic movements that coincide with pulsations of the protrusion forming above the sperm head. We find that these movements are caused by contractions of the actomyosin cytoskeleton triggered by Ca (2+) oscillations induced by fertilization. Most importantly, the relationship between the movements and the events of egg activation makes it possible to use the movements alone to predict developmental potential of the zygote. In conclusion, this method offers, thus far, the earliest and fastest, non-invasive way to predict the viability of eggs fertilized in vitro and therefore can potentially improve greatly the prospects for IVF treatment.

## Nature Methods

Volume 8, Number 10
October 2011

**Proteomic and Phosphoproteomic Comparison of Human ES and iPS Cells**

*D. H. Phanstiel et al.*

Combining high-mass-accuracy mass spectrometry, isobaric tagging and software for multiplexed, large-scale protein quantifica-

tion, we report deep proteomic coverage of four human embryonic stem cell and four induced pluripotent stem cell lines in biological triplicate. This 24-sample comparison resulted in a very large set of identified proteins and phosphorylation sites in pluripotent cells. The statistical analysis afforded by our approach revealed subtle but reproducible differences in protein expression and protein phosphorylation between embryonic stem cells and induced pluripotent cells. Merging these results with RNA-seq analysis data, we found functionally related differences across each tier of regulation. We also introduce the Stem Cell–Omics Repository (SCOR), a resource to collate and display quantitative information across multiple planes of measurement, including mRNA, protein and post-translational modifications.

## Neurobiology of Learning and Memory

Volume 96, Number 2
September 2011

### Hormonal Contraception Usage is Associated with Altered Memory for an Emotional Story

*S.E. Nielsen et al.*

Substantial evidence now documents sex-related influences on the neurobiology of emotional memory. Robust sex influences exist, for example, on the amygdala's role in emotional memory formation, as well as on retention of central information (gist) and detail for an emotional event. Evidence also suggests that the well-documented effects of stress hormones on memory depend upon sex hormone levels. Since hormonal contraception alters sex hormone levels, and must by extension alter sex/stress hormone interactions in memory, we examined whether the use of hormonal contraception also alters memory for an emotional story. Two groups of healthy female subjects—one naturally cycling, one using hormonal contraception—viewed either a brief, emotionally arousing story, or a closely matched, but more emotionally neutral story. Each subject's eye movements and pupil dilation changes were recorded as they viewed the story. Additionally, saliva samples were taken throughout the experimental session to examine salivary alpha-amylase, a biomarker for norepinephrine. A surprise free recall test one week later measured story memory in all subjects. Naturally cycling women exhibited enhanced memory of story details, but not of central information (gist), in the emotional compared with neutral story conditions. In contrast, women using hormonal contraception exhibited enhanced memory of gist, but not story details, in the emotional compared with neutral story conditions. Analysis of eye movements made while watching the stories indicated that the differences in memory could not be attributed either to a differential attention focus or to the degree of arousal induced by the stories in the two groups. These findings suggest that the use of hormonal contraception alters memory for an emotional event, perhaps by altering sex/stress hormone interactions in memory formation. They also suggest that further investigation of the mnemonic effects of these very widely used treatments is warranted.

## PLoS One

Volume 6, Number 8
September 2011

### Do Facial Expressions Develop before Birth?

*N. Reissland et al.*

*Background*: Fetal facial development is essential not only for postnatal bonding between parents and child, but also theoretically for the study of the origins of affect. However, how such movements become coordinated is poorly understood. 4-D ultrasound visualisation allows an objective coding of fetal facial movements. *Methodology/Findings*: Based on research using facial muscle movements to code recognisable facial expressions in adults and adapted for infants, we defined two distinct fetal facial movements, namely "cry-face-gestalt" and "laughter-gestalt," both made up of up to 7

distinct facial movements. In this conceptual study, two healthy fetuses were then scanned at different gestational ages in the second and third trimester. We observed that the number and complexity of simultaneous movements increased with gestational age. Thus, between 24 and 35 weeks the mean number of co-occurrences of 3 or more facial movements increased from 7% to 69%. Recognisable facial expressions were also observed to develop. Between 24 and 35 weeks the number of co-occurrences of 3 or more movements making up a "cry-face gestalt" facial movement increased from 0% to 42%. Similarly the number of co-occurrences of 3 or more facial movements combining to a "laughter-face gestalt" increased from 0% to 35%. These changes over age were all highly significant. *Significance*: This research provides the first evidence of developmental progression from individual unrelated facial movements toward fetal facial gestalts. We propose that there is considerable potential of this method for assessing fetal development: Subsequent discrimination of normal and abnormal fetal facial development might identify health problems in utero.

## Prenatal Diagnosis

Volume 31, Number 6
June 2011

### Distortions of Sex Ratios at Birth in the United States: Evidence for Prenatal Gender Selection

*J. F. Egan et al.*

*Objective*: The normal male to female live birth sex ratio ranges from 1.03 to 1.07. Higher ratios in China, India and Korea reflect prenatal sex selection. We reviewed sex ratios for US births to investigate potential prenatal sex selection. *Methods*: We reviewed all US live births from 1975 to 2002 using National Center for Health Statistics birth certificates in 4-year intervals. We compared the sex ratios of Blacks, Chinese, Filipinos, Asian Indians and Koreans relative to Whites. We also compared the sex ratios by birth order for first, second and third and more births (third+) from 1991 to 2002. *Results*: The male to female sex ratio from 1975 to 2002 was 1.053 for Whites, 1.030 ($p < 0.01$) for Blacks, 1.074 ($p < 0.01$) for Chinese and 1.073 ($p < 0.01$) for Filipinos. From 1991 to 2002, the sex ratio increased from 1.071 to 1.086 for Chinese, 1.060 to 1.074 for Filipinos, 1.043 to 1.087 for Asian Indians and 1.069 to 1.088 for Koreans. The highest sex ratios were seen for third+ births to Asian Indians (1.126), Chinese (1.111) and Koreans (1.109). *Conclusion*: The male to female live birth sex ratio in the United States exceeded expected biological variation for third+ births to Chinese, Asian Indians and Koreans strongly suggesting prenatal sex selection.

## PNAS: Proceedings of the National Academy of Sciences USA

Volume 108, Number 34
August 23, 2011

### Efficient Generation of Transgene-Free Human Induced Pluripotent Stem Cells (iPSCs) by Temperature-Sensitive Sendai Virus Vectors

*H. Ban et al.*

After the first report of induced pluripotent stem cells (iPSCs), considerable efforts have been made to develop more efficient methods for generating iPSCs without foreign gene insertions. Here we show that Sendai virus vector, an RNA virus vector that carries no risk of integrating into the host genome, is a practical solution for the efficient generation of safer iPSCs. We improved the Sendai virus vectors by introducing temperature-sensitive mutations so that the vectors could be easily removed at nonpermissive temperatures. Using these vectors enabled the efficient production of viral/factor-free iPSCs from both human fibroblasts and CD34 ($^+$) cord blood cells. Temperature-shift treatment

was more effective in eliminating remaining viral vector-related genes. The resulting iPSCs expressed human embryonic stem cell markers and exhibited pluripotency. We suggest that generation of transgene-free iPSCs from cord blood cells should be an important step in providing allogeneic iPSC-derived therapy in the future.

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**Longitudinal Evidence that Fatherhood Decreases Testosterone in Human Males**

*L. T. Gettler et al.*

In species in which males care for young, testosterone (T) is often high during mating periods but then declines to allow for caregiving of resulting offspring. This model may apply to human males, but past human studies of T and fatherhood have been cross-sectional, making it unclear whether fatherhood suppresses T or if men with lower T are more likely to become fathers. Here, we use a large representative study in the Philippines ($n = 624$) to show that among single nonfathers at baseline (2005) (21.5 ± 0.3 y), men with high waking T were more likely to become partnered fathers by the time of follow-up 4.5 y later ($P < 0.05$). Men who became partnered fathers then experienced large declines in waking (median: −26%) and evening (median: −34%) T, which were significantly greater than declines in single nonfathers ($P < 0.001$). Consistent with the hypothesis that child interaction suppresses T, fathers reporting 3 h or more of daily childcare had lower T at follow-up compared with fathers not involved in care ($P < 0.05$). Using longitudinal data, these findings show that T and reproductive strategy have bidirectional relationships in human males, with high T predicting subsequent mating success but then declining rapidly after men become fathers. Our findings suggest that T mediates tradeoffs between mating and parenting in humans, as seen in other species in which fathers care for young. They also highlight one likely explanation for previously observed health disparities between partnered fathers and single men.

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September 13, 2011

**Placental Protection of the Fetal Brain during Short-Term Food Deprivation**

*K. D. Broad and E. B. Keverne*

The fetal genome regulates maternal physiology and behavior via its placenta, which produces hormones that act on the maternal hypothalamus. At the same time, the fetus itself develops a hypothalamus. In this study we show that many of the genes that regulate placental development also regulate the developing hypothalamus, and in mouse the coexpression of these genes is particularly high on embryonic days 12 and 13 (days E12–13). Such synchronized expression is regulated, in part, by the maternally imprinted gene, paternally expressed gene 3 (*Peg3*), which also is developmentally coexpressed in the hypothalamus and placenta at days E12–13. We further show that challenging this genomic linkage of hypothalamus and placenta with 24-h food deprivation results in disruption to coexpressed genes, primarily by affecting placental gene expression. Food deprivation also produces a significant decrease in *Peg3* gene expression in the placenta, with consequences similar to many of the placental gene changes induced by *Peg3* mutation. Such genomic dysregulation does not occur in the hypothalamus, where *Peg3* expression increases with food deprivation. Thus, changes in gene expression brought about by food deprivation are consistent with the fetal genome's maintaining hypothalamic development at a cost to its placenta. This biased change to gene dysregulation in the placenta is linked to autophagy and ribosomal turnover, which sustain, in the short term, nutrient supply for the developing hypothalamus. Thus, the fetus controls its own destiny in times of acute starvation by short-term sacrifice of the placenta to preserve brain development.