Multi-modal Neuroimaging Training Program (MNTP)
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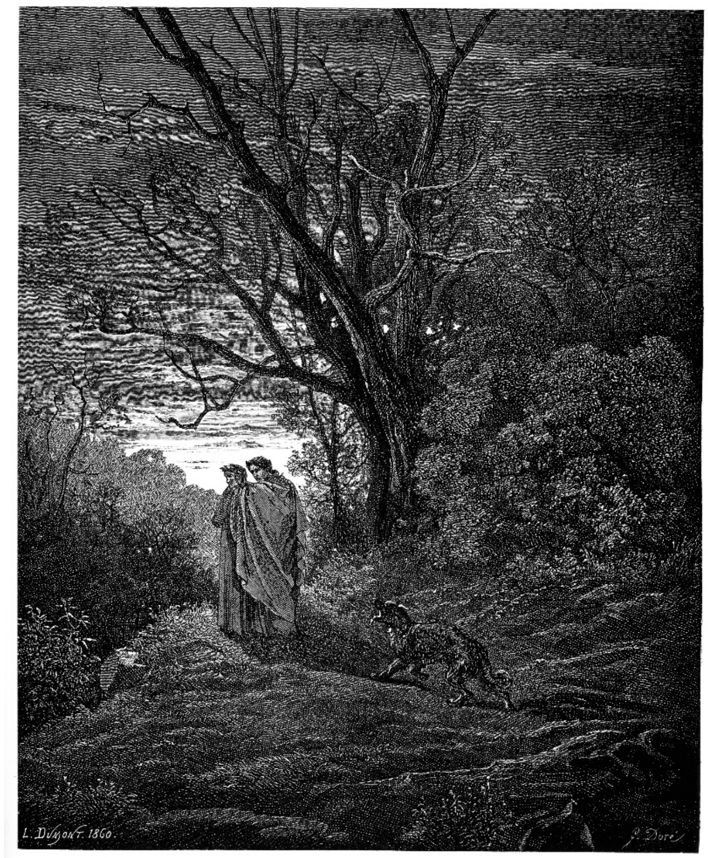
A Model of Human Design

How we work, what goes wrong, and some principles for healing



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Medicine lacks an overarching principle. We teach Bernoulli's principle for blood flow, Fick's law for gaseous diffusion, and the Michaelis-Menten equation for enzyme kinetics. Each equation governs some part of our mechanism, but none constrains our overall design. Here I suggest that the single deepest constraint on human design is the need for energy efficiency. Organisms struggle constantly to find their dinner and not *become* dinner. Therefore, they are constrained by natural selection to build and operate as economically as possible. Selection for energy efficiency in a complex environment drives specialization at all levels: molecules, cells, bodies, and brains. Ultimately humans specialize as individuals with particular skills and the capacity to cooperate to form efficient communities. Here I sketch some aspects of human design that emerge from the need for energy efficiency.

Energy efficiency from the bottom up

Proteins evolved to be just stable enough to resist buffeting by thermal noise (mean energy ~1k_BT). When a protein needs an energy boost, it should be just large enough to shift the conformation but not collapse it or waste fuel, roughly 25 k_BT. This is the boost provided by hydrolysis of one molecule of ATP. Adopting ATP as the universal energy donor, the cell's power plant (mitochondrion) burns glucose to spin nano-turbines that spit out ATP with 90% efficiency. Thus, single cells operate just above thermal noise, powered by energy packets of optimal size, synthesized with near optimal efficiency.

A cell signals with optimal efficiency. When a nutrient molecule binds to a receptor protein on the membrane, it triggers a conformational change that passes the message ('food') across the membrane to the cytoplasm. The receptor protein has thus transferred one bit of information at an energetic cost to reset the protein of ~25 k_BT. This is the cheapest signal that can reliably exceed thermal noise. This design for energetically optimal signaling evolved in single cells for exogenous molecules and was adapted by multicellular species for signaling with endogenous molecules such as hormones, neuromodulators, and neurotransmitters. Human signaling proteins were already expressed in the first organism with a bilaterally symmetrical body plan, a marine worm resembling *Platynereis*.

Platynereis placed its eyes and brain optimally -- in the head. This allowed him to know what was coming and where he was going. Moreover, *Platynereis'* brain could predict where else he might profitably go, delivering the conclusion to segmental motor circuits with minimum wire. The brain used clock neurons to predict when to forage and when to rest, prefiguring our suprachiasmatic nucleus. *Platynereis* also employed a dopamine circuit for reward prediction learning that, because it is optimal, Sapiens preserved.

Features Sapiens inherited from the first bilaterian worm are often termed 'primitive', as though they were somehow inferior or shameful. To the contrary, while shedding features that were useless to our progress beyond the tidal shore, we retained features that serve efficiency such as brain layout, brain clock, predictive neural and endocrine regulation (allostasis), circuit for reward learning, and a nearly complete 'parts catalogue'. Thus 'primitive' should signify "fundamental" and "brilliant". What did Sapiens make of this rich endowment?

Sapiens specialized some more, complexifying organs, systems, and brain. Specialization expands efficiency because of the engineering principle that two specialized parts function more efficiently than one part doing two jobs. Thus, our cerebral cortex evolved nearly 200 distinct areas, and these further specialized between hemispheres. Finally, each *individual* receives a specialized bundle of innate abilities and deficits. The innate gifts are shaped by the dopamine system -- which drives us to practice what is most rewarding and thus to improve upon the gifts. This venerable learning mechanism produces a community with diverse skills that outcompetes a community where everyone has the same abilities.

On the other hand, a community where individuals differ in skills, temperament, intelligence, empathy, and so on, harbors innumerable possibilities for suspicion, tension, anxiety, anger, jealousy, and so forth. So, efficient communities evolved mechanisms to manage and discharge intra-psychic and inter-personal tensions. These included diverse sacred ceremonies concerning food, sex, birth and death -- expressed in dance, music, art, and monumental constructions. These practices accompanied the emergence of our species. Therefore, a comprehensive model of human design, building on molecular physiology, must also embrace the myriad ways that physiology responds to the demands of our extreme sociality. The model must help explain why the human life cycle is navigated with such difficulty, and how it is eased by various sacred practices.

What has gone wrong?

Sapiens now suffers an epidemic of obesity plus its accompaniments, diabetes and hypertension, plus their myriad associated pathologies. As nations 'develop' economically, they suffer epidemics of drug addiction and alcoholism, plus various 'behavioral' addictions such as gambling and pornography. Sapiens' suffers a profound addiction to fossil fuel, and it is heating up the Earth. These problems share a common cause: our profound dis-satisfaction that drives a restless search for relief. What worked efficiently for *Platynereis* and propelled Sapiens to world dominance, now threatens planetary catastrophe.

The biological root of the problem is the reward circuit. The brain predicts every need, and when one is fulfilled, the reward circuit delivers a pulse of dopamine that we experience as a pulse of satisfaction. Because all needs depend on this single source of reward, the pulse must necessarily be brief. Moreover, the pulse requires a behavior to deliver something better than predicted. The same food, same drink, same sex, and so on, release progressively less dopamine. By design this circuit rewards diverse, small surprises.

When Sapiens lived by foraging, as we during the first 90,000 years of our existence, every day was full of small surprises – a root, a berry, a fish, a mammoth; a dry cave, a warm fire. But once Watt's steam engine coupled the burning of carbon to a device for mechanical work, the opportunities for small surprises shrank rapidly. Now, just 250 years later, we are 'protected' from all discomfort, all need for strenuous effort, and all exposure to the vagaries of nature. Each new 'protection' further reduces the diversity of our small satisfactions.

This is a problem for the dopamine system. As diversity of satisfactions shrinks, the few remaining become less surprising and thus less satisfying. Never really hungry, we eat richer foods, and as those become predictable, we are driven to eat more. Ditto for drugs that directly increase dopamine. Thus, shrinking reward diversity drives the system into positive feedback, producing unbounded consumption that can never satisfy.

Sapiens' profound specialization creates another problem. Each individual harbors a unique bundle of gifts that serves community efficiency, plus a unique bundle of deficits that serves community efficiency better than if everyone's deficits were the same. The differences establish an unbridgeable strangeness between individuals. Couple that with Sapiens' extreme sociality -- two irreconcilable aspects of our nature – and we experience a 'double bind', an inescapable source of tension. This double bind, born of the constraint for energy efficiency, should figure prominently in a model of human design.

What to do?

In addressing the modern scourge of unbounded consumption, neuroscience research focuses on lower level mechanisms, such as hypothalamic circuits that regulate feeding, metabolism, and blood pressure; striatal circuits that drive learning, choice, and so on. Studies look for new drugs to target these circuits so as to ameliorate obesity and various addictions. Yet these circuits are not broken. Rather, our problems arise from trying to live contrary to our fundamental design. Since our core scourge is unrelieved dis-satisfaction, an integrated model of human design must attend to our species' need for diverse surprises and to our deep need for connection despite our intrinsic mutual strangeness.

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Lisa Feldman Barrett, PhD
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Emotion inside out: From cartoon neuroscience to the predictive brain

This talk will outline a computational architecture for the brain's use of prediction and prediction error signals to construct experiences and perceptions of emotion. Theory and research will be organized around two themes: (1) the shift from taxonomic thinking (the belief that an emotion has a particular facial expression and autonomic fingerprint) to population thinking (evidence that emotion categories consist of unique instances that are tailored to the specifics of the immediate situation); (2) the shift from essentialism (the belief that all instances of an emotion category share an underlying neural circuit) to degeneracy (evidence that instances of an emotion category are constructed as different configurations within the brain's functional architecture of interacting core networks). Furthermore, allostasis and interoception are shown to be a key function of these core networks, revealing that whatever else a brain is doing (thinking, feeling, seeing), it is also predictively regulating the internal milieu of the body. These themes represent a shift in the scientific paradigm for measuring and understanding the nature of emotion and represents a transformative framework for a unified science of the mind and brain.

Moriah Thomason, PhD
Merrill Palmer Skillman Institute for Child and Family Development and Pediatrics
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Prenatal adversity and the developing fetal brain

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Abnormal neural connections seen in developmental disorders likely originate *in utero*, but it is difficult to determine what happens in the brain during the prenatal period. The primary objective of our research is to characterize the origins of human brain functional circuitry to provide a basis for comparisons between health and disease. We have confirmed the presence of bilateral functional connections in the fetal brain, as well as regional connections within each hemisphere. We have also shown that connection strength increases with fetal gestational age. I will share new data showing that neural development of fetuses that will be born preterm differs from those born at term. I will also present the very first evidence that fetal programming of maternal prenatal stress exerts influence on development of connections in the fetal brain. Using recent developments in fetal resting-state fMRI we examined neural functional connectivity in 47 human fetuses scanned between the 30-37th week of gestation. We discovered that neural efficiency, a measure reflecting how economically neural functional systems are organized, was reduced in fetuses of mothers reporting high prenatal stress. This effect was pronounced in areas of the cerebellum, postcentral gyrus, temporal lobes, and cingulate. It appears that reduced integration of neural systems across gestation may be a consequence of stress programming during pregnancy. This discovery confirms what has long been speculated, that the stress of a mother during her pregnancy has an impact on the brain of her unborn child.

Luke Chang, PhD

Department of Psychological and Brain Sciences
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Towards a computational social and affective neuroscience

This talk will explore a variety of approaches I've taken to better understand how emotions and social inferences are processed in the brain. Emotions can help us achieve our goals by providing motivational signals that impact how we value different decision outcomes. Model-based fMRI can be a useful tool to understand how different motivational signals influence our decisions in social contexts. In addition, I will also present evidence on how we can incorporate concepts from psychometrics to develop sensitive and specific predictive models of affective states that generalize to new participants, scanners, and tasks. Models that incorporate multiple systems can explain almost an order of magnitude more variance in emotion ratings then a single region of interest. Finally, I will present evidence that affective experiences emerge from an interaction between individual preferences and contextual information. This work has prompted the development of a new analytic paradigm that leverages endogenous variation in responses across participants to model affective experiences in response to naturalistic stimuli.

Thalia Wheatley, PhD

Psychological and Brain Sciences Department
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Towards a science of connection

The human brain evolved to be massively interactive with its social environment. A deep understanding of human thought and behavior will therefore require research that incorporates the social context. In this talk I will present research from my lab that investigates physiological signals that dynamically index social connection. I will argue that a rich understanding of the human mind will require a shift from traditional scientific practices (static stimuli, treating people as isolated units) to methods that better simulate the interactive, dynamic world that the brain evolved to solve.

Mauricio Delgado, PhD

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Positive memories, reward, and adapting to stress

The ability to generate positive emotions serves the adaptive function of enhancing psychological resources necessary for coping with stressors in daily life. One way to elicit positive emotions is to reminisce about past positive life events. Autobiographical memories are vivid representations of the past that trigger the re-experience of emotions tied to the original event, eliciting positive feelings and enhancing an individual's well-being. In this talk, I will present behavioral and neuroimaging data suggesting that the recall of positive memories is intrinsically valuable to an individual. Specifically, recalling the positive past can recruit neural circuits involved in reward processing, and can influence emotion and decision making. Further, I will discuss a) the restorative and protective function of self-generated positive emotions in coping with acute stress and b) the role of social context in bolstering this effect. Taken together, the findings highlight how reminiscing about the positive past serves an important function in the maintenance of positive emotion and the promotion of successful adaptation to stress.