REVIEW ARTICLE

Comparative Approaches in Evolutionary Psychology: Molecular Neuroscience Meets the Mind

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Abstract

Evolutionary psychologists often overlook a wealth of information existing between the proximate genotypic level and the ultimate phenotypic level. This commonly ignored level of biological organization is the ongoing activity of neurobiological systems. In this paper, we extend our previous arguments concerning strategic weaknesses of evolutionary psychology by advocating a foundational view that focuses on similarities in brain, behavior, and various basic psychological features across mammalian species. Such an approach offers the potential to link the emerging discipline of evolutionary psychology to its parent scientific disciplines such as biochemistry, physiology, molecular genetics, developmental biology and the neuroscientific analysis of animal behavior. We detail an example of this through our impending work using gene microarray technology to characterize gene expression patterns in rats during aggressive and playful social interactions. Through a focus on functional homologies and the experimental analysis of conserved, subcortical emotional and motivational brain systems, *neuroevolutionary psychobiology* can reveal ancient features of the human mind that are still shared with other animals. Claims regarding evolved, uniquely human, psychological constructs should be constrained by the rigorous evidentiary standards that are routine in other sciences.

Introduction

Evolutionary psychology seeks to explain the evolved, *functional* characteristics of the human mind and thus their past and/or present *adaptive* value. This objective has been typically examined through the lens of an explanatory framework where special-purpose brain 'modules' are postulated to have been critical for hominid survival and reproductive success (herein referred to as the EP approach).

One accomplishment of the EP approach is that it has energized a variety of social psychological experiments that have revealed consistent aspects of the human mind [reviewed in 1, 2, 3]. Moreover, a second success of the EP approach is that most scholars now concede the existence of a core human psyche that is largely a product of biological evolution (specifically a result of natural selection). Disagreement, however, centers on the degree to which these accomplishments are related. For instance, although the validity and testability of determining what aspects of the human mind were designed by natural selection have been entertained [4, 5], there has been little consensus on what criteria should constitute an adequate weight of evidence for identifying evolutionary adaptations.

Constructs such as adaptation, special design, and module figure prominently in these debates and continue to rival competing counterpart concepts such as exaptation, plasticity, and general learning mechanism. Understanding precisely how such evolutionary explanations fit into a comprehensive framework for studying the human brain and mind remains a major challenge for evolutionary psychology. Although some investigators have recently addressed the need to incorporate an understanding of organic systems into the EP approach [e.g., 2,6], rigorous neurobiological and genetic data are not typically included among the standard criteria for falsifying hypotheses in evolutionary psychology.

The proposition that the human brain is constituted of adaptive modules is reminiscent of past approaches to understand human behavior, such as phrenology. The existence of a variety of genetically inherited, adaptive sociobiological modules (unique to the hominid lineage and located in neocortex) is dubious at best when considered simultaneously with our current understanding of mammalian brain organization. For instance, pre-existing genetic constraints and epistatic interactions may impart substantial effects on the polygenic and pleiotropic phenotypic traits with which evolutionary psychologists are concerned. Moreover, the organization of neocortex, which is commonly assumed to be a prime anatomical substrate for unique cognitive modules in the human brain, exhibits no robust signs of localized anatomical specialization above and beyond specific sensory and motor connections, and their polymodal interactions.

Such considerations have previously led us to argue that the human brain can *acquire* a large variety of *epigenetically* derived functions via interactions of a limited number of evolutionarily conserved affective/motivational systems (situated largely in subcortical areas) with a set of plastic general-purpose learning mechanisms in neocortex [7,8]. We do not deny the existence of certain special-purpose learning systems in the brain, such as fear learning, which is shared with other animals. However, the human neocortex includes much more than a conglomeration of special-purpose learning mechanisms. It contains a neural architecture that can generate flexible features which may be best conceptualized as *rewriteable*. There has been little substantive research into how the de novo, evolved functions of the mind can be distinguished from the phenotypic consequences of individual, social, and cultural learning experiences. Until such issues are addressed by evolutionary psychology, a scientifically coherent framework for studying the evolution of human and animal minds will remain elusive.

In the first part of this paper, we will argue that much of human mental activity is driven by the ancient affective emotional and motivational brain systems that are shared with other animals. This is not to deny that propositional thoughts are uniquely efficacious in controlling human behavior, but to suggest that such cognitive activities are often driven by affective urges. Thus, it is suggested that most specialized learning functions are closely linked to, and perhaps critically dependent upon, such affect/motivation generating systems. The present arguments will be framed through a summary of our past concerns with the EP approach [7]. In the latter part of the paper, we will proceed to argue for the utility of examining the human mind with the concept of homology rather than those of analogy or reverse engineering – the perspectives commonly employed by investigators using the EP approach.

Specifically, we will advocate a multidisciplinary approach that aims to 'triangulate' between:

(i) behavioral genetic studies that focus on heritability and individual gene contributions;
(ii) molecular biological studies that directly analyze differential gene expression within the brain in a variety of relevant behavioral contexts; and
(iii) traditional psychobiological and neuroethological studies that can characterize brain-behavior, structure-function relationships.

An example of this strategy will be detailed through a description of our upcoming work on messenger ribonucleic acid (mRNA) expression patterns in rats during social interactions. Examination of mRNA transcription patterns in specific brain areas can begin to provide insight into how individual patterns of gene expression during behavioral, motivational, and affective states relate to dynamic patterns of social organization. If, what might be aptly termed, homologous patterns of gene expression are identified in such experimental paradigms, then the existence of a unique, evolutionary origin for human behavior and underlying mental processes may require re-evaluation.

Similar principles have been guiding biomedical research for years and a parallel strategy can be developed for studying the human mind. Ultimately, the

importance of such gene expression patterns for evolutionary psychology can be evaluated, and we assume demonstrated, by the design of new pharmacological therapies in humans (see *From Brain Molecules to Mind Medicines* section). Molecular biological studies alone, however, will not suffice. Together with approaches such as comparative brain imaging and the phylogenetic analysis of psycho-behavioral traits [9, 10], an evolutionary psychology that incorporates homology and the experimental analysis of neural systems into its explanatory scheme should be scientifically more successful than approaches that are built purely from conceptual perspectives.

A Summary of the 'Seven Sins of Evolutionary Psychology'

Our previous critique of the EP approach [7] was motivated by the following convergent issues:

(i) the general failure of the EP approach to incorporate the many existing lines of behavioral brain research;
(ii) the tendency of the EP approach to generate adaptive scenarios regarding socio-emotional processes in humans without apparent concern for how such processes might be interfaced with brain structure and function; and
(iii) the concurrent claim that the EP approach now provides one of the most robust lines of inquiry for identifying the types of adaptations that actually exist in the human brain. We agreed with the EP approach insofar that it has been premised on the acceptance of evolutionary thought as one of the most important ways to determine the psychological 'natural kinds' that exist within the brains of humans as well as other animals.

We extended our critique by elaborating a general framework through which the origin of many (but certainly not all) aspects of the human mind can be conceptualized: The human brain contains various ancient subcortical systems that foster affective/motivational processes, which interact with neocortex, a tissue comprised of a relatively homogenous field of columnar units which support many of the seemingly unique higher functions of the human brain. We argued that much of the modern human mind arises as a consequence of those subcortical-neocortical interactions operating in various environmental contexts. Although the respective functions of subcortical and neocortical systems may be adaptive in their own right, the phenotypic expressions that resulted from interactions between these brain areas, especially with the massive expansion of neocortex in humans, led to a dramatic shift in the structure of the hominid mind. Importantly, *such changes were not necessarily due to genetic selection and may have emerged culturally and epigenetically because of the mushrooming of general-purpose neocortex* .

In other words, the progressive accumulation of interactions between environment (both physical and social), evolutionary conserved brain systems (e.g., the limbic system, which includes paleocortical zones such as cingulate, insular, orbitofrontal and periamygdaloid cortices), and a new standard for neural plasticity (i.e., via neocortical expansions) gave rise to a qualitatively different shade of mind – one that could communicate not merely with *signs*, but in *symbolic* terms. Our ideas were aimed at serving as a more neurobiologically oriented extension of previous formulations, such as Lumsden and Wilson's [11] gene-culture co-evolution and the role of exaptations in evolution [12]. The time is finally ripe to begin building an evolutionary viewpoint of the mind based on comparative concepts that incorporate the intrinsic systems found in all mammalian brains [10]. To underscore the major points that led to this assertion, we will now briefly summarize the specific 'sins' that were discussed in our previous articles [7, 8].

I. Are there Pleistocene sources of current human social adaptations?

Evolutionary psychologists have generally backed off from this assumption, as they have realized that neocortex was the main type of brain tissue that emerged two million years ago when hominid brains began to diverge from the chimp-sized brains of our ancestral stock. As we noted before, "let us recall that the 'chips' of the human cortex – the columnar structures containing approximately 3,000 neurons each – are very similar throughout the brain and also from one mammalian species to another. These features are suggestive of highly generalized (almost 'random access'), chip-based computational devices" (pp. 116) [7]. Thus, the critical question remains: Did modular, special purpose brain functions result largely from the process of genetically-based natural selection during the homonid cerebral expansion of the past few million years, or rather have most higher *hominid* brain functions become modularized epigenetically and emergently through learning and cultural experiences? The specializations in cortical areas that we share with other animals (i.e., limbic and sensory cortices), that are accepted by most neuroscientists, are not at issue here. In any event, the effects of natural selection must be distinguished from the consequences of epigenetic influences To our knowledge, evolutionary psychologists have yet to tackle such crucial problems.

II. Why focus on one species?

Without a clear understanding of what humans share with other animals, it is difficult to specify the truly unique capacities of the human mind. Neuroanatomical and neurochemical homologies offer a productive way to specify the intrinsic, evolved faculties of the human brain and mind. Many of these homologies will be evident in instinctual behavior patterns which exhibit class-typical ethological resemblances across mammalian species. Likewise, as homologous overlap areas between human and animal brain functions are

characterized, the utilization of anthropomorphic reasoning can become a fertile source of testable hypotheses [13].

III. Which psychological adaptations have been specially designed?

Adaptive brain functions should always be discriminated from phenotypic effects that appear functional, but were actually derived from sources of evolutionary change other than natural selection, such as exaptations, spandrels, genetic drift, and especially the general ability to learn new skills and strategies. As already mentioned in the first item, delineating genetic and epigenetic influences on brain functions remains a major challenge that must be increasingly acknowledged and empirically confronted by evolutionary psychologists. Furthermore, the roles of developmental programs and the cultural transmission of learned traits must be examined through the lens of evolutionary psychology as well.

IV. Are there massive modules for mental traits?

The concept of 'brain centers' was discarded in functional neuroscience several decades ago. There are indeed various special-purpose circuits and systems in subcortical regions of the brain, but such systems are not encapsulated and appear to interact with each other extensively [10]. For instance, Mesulam [14] has described 'channel' and 'state' brain functions. State functions, or the widely ramifying background processes of the brain (e.g., attention, emotions, and motivations), are more likely to exhibit robust genetic controls than the channel functions of the brain which elaborate detailed aspects of information processing in the brain (e.g., specific perceptions, thoughts, or strategies). Moreover, the forces that drove the expansion of heteromodal neocortex during primate brain evolution may have been substantially different than those that shaped sensory and motor processing systems (i.e., internal vs. environmental selective pressures as described in [15]).

V. Why conflate emotions and cognitions?

There is considerable pressure currently to envision emotions largely as a subset of cognitive processes [16], as many scholars have generally failed to consider evolutionary evidence underscoring the traditionally understood distinction between reason and passion, or cognitions and emotions [17]. Clore & Ortony [18] suggested that emotions are best understood with regard to their propositional contents (i.e., what they refer to) rather then considering the possibility that affective states can exist both with and without cognitive contents (albeit they usually do have such contents). The existence of phenomena such as dreaming, psychomotor epilepsy (characterized by emotional auras), and brain stimulation induced emotional states suggests that primitive emotional and motivational systems can generate psychological urgencies (i.e., non-sensory states of consciousness) that exist independently of externally (e.g., perceptually) and internally (e.g., thought) driven cognitive contents. That emotions and cognitions function synergistically in the intact brain is not a compelling rationale to avoid scientific dissection of such interactive albeit evolutionarily distinguishable processes.

VI. Why ignore the brain?

This is a criticism of the general failure to constrain theories of mind with explicit neurobiological criteria. Modern neuroscience has provided a suitable foundation to begin thinking more clearly about the underlying organic basis of mental processes. Molecular biology is now providing equally fruitful approaches for uncovering the functional characteristics of biological systems that are inherited via genetic transmission. The social sciences must deal with such underlying levels of organization and some have started to do so, albeit at a markedly slow pace.

VII. Do anti-organic biases help create a computationalist/representationalist myth?

Evolutionary psychologists have suggested that the underlying operations of mind can be conceptualized adequately as computations carried out by the brain – or rather as functional sets of neural algorithms. An algorithm *is a formal procedure for any mathematical operatio*n. While specific neural algorithms may underpin certain aspects of sensory/perceptual and motor/action, channel functions [e.g., 19], the central neural substrates underlying psychobehavioral states are unlikely to be organized in a similar manner. Such functions are more fundamentally organic and analog, exerting global brain/mind influences. In other words, the brain can produce behavioral and mental phenotypes via neuronal mechanisms that are markedly different in their constitution when compared with mathematical computations, whether manifested at the level of anatomical reorganizations and/or dynamic changes in the elements of individual synapses.

All of the flaws mentioned above ultimately relate to the failure of evolutionary psychology to assume a deeply organic perspective. Historically, the explanatory validity of most biological disciplines has depended on how successfully they were linked to fundamental lower (e.g., molecular) levels of organization. This will be true for evolutionary psychology as well. If such a linkage is not achieved with regard to the study of the human mind, a major negative consequence may be a massively inappropriate conflation of evolved, adaptive specificity with emergent, epigenetic processes. For instance, consider a concrete example: Rats will avoid foods that make them sick. Although they are likely to have evolved mechanisms for generating feelings of sickness and mechanisms to associate such feelings with recently consumed foods – especially novel foods – they probably do not possess adaptations that allow them to instinctually avoid palatable poisons. Such a specific behavioral phenotype may only be achieved thorough a general-purpose, food selection learning mechanism. Due to the power of long-interval associa-

tive learning, animals learn to avoid salient substances that *may* have made them sick. Thus, one might find many genes that affect learning in general, or the pleasures and displeasures of tastes and feelings of well-being and sickness, but not brain mechanisms that generate avoidance of specific foodstuffs.

Considering the large number of specific behavioral tendencies that can arise from a comparatively modest number of interacting adaptations, evolutionary psychology will benefit immensely from a rigorous analysis of the biological underpinnings of psychological traits. For example, Badcock's [2] confrontation with key biological issues addresses how aspects of culture may be related to genetic mechanisms, such as genomic imprinting. The provocative findings of Keverne *et al*. [20], indicating that development of neocortex is disproportionately influenced by maternally imprinted genes while the development of key emotional areas, such as the hypothalamus, are governed by paternally imprinted genes, may have profound implications for understanding sexual selection in evolutionary psychology.

A New Strategy for Evolutionary Psychology

We have thus far argued that comparative analyses of brain and behavior can offer new vistas for understanding the evolution of the mammalian mind, and thereby the mental functions that result exclusively from human brain activity. Identifying homologous brain functions will aid in defining the appropriate null hypotheses for human studies; namely, mental differences between species must be associated with differences in brain structure, connectivity, neurochemistry, and/or patterns of activation. For evolutionary psychologists, this type of approach may initially seem counterintuitive, as the EP approach has been typically concerned with *similarities* in organization of the human mind across individuals. However, unique species-specific traits can be confirmed only through an exclusion of the possibility that a respective trait is shared between phylogenetically related species.

Towards this goal, neurophysiological studies can help elucidate the details of single unit activity and synaptic interactions, but such levels of organization are difficult to translate to human research. It would be better to carry out concurrent investigations of global neurochemical systems (for which there exists much comparative data) and deeper genetic levels (e.g., analysis of DNA polymorphisms or RNA expression patterns). Such a paradigm can be established by employing two general strategies:

(i) investing in carefully selected animal models of basic behavior patterns that can be studied with regard to human psychological constructs and
(ii) taking the previous phase of investigation into the realm of modern neurochemistry and molecular biology.

The major advantage of this particular approach is that it can potentially extend the scope of evolutionary psychology to include levels of organization essential for understanding the evolution of complex organic systems. For instance, *neuroevolutionary psychobiology* has already revealed how separation distress systems and their relevant neurochemical controls (e.g., endogenous opioids) may have emerged from pre-existing pain systems of the brain [10]. One can easily envision how such evolutionary sculpting of new brain functions may have emerged while retaining ancestral neurochemical characteristics. Modern molecular biological analyses should be able to directly evaluate the relatedness of genetic controls in such systems across species.

Although no single approach can validate hypotheses regarding the evolution of the human mind and its relations to ancient brain functions, molecular biological studies can aid in providing a basis for the explanatory constraints that should be utilized by evolutionary psychologists. The remaining aim of this paper is to exemplify how molecular biological tools can be employed in evolutionary psychology. First, we will briefly summarize the overall utility of such technologies.

Gene Expression Arrays

A powerful, recent development in molecular biology has been the emergence of rapid throughput technologies that allow the concurrent evaluation of differential expression of many genes in virtually any tissue of interest. For example, a recent paper highlighted the overlapping and non-overlapping microbial gene expression patterns evoked by three pathogens [21]. Another study identified several new genes related to hemodynamic stress that may arise from hypertension [22]. The potential value of broad genome scans in the study of psychiatric disorders has been well described [23, 24, 25], but the main factor preventing their widespread use are the methodological complexities and comparatively high costs of such technologies.

However, relevant studies are beginning to appear. For instance, Tononi & Cirelli [26] have shared provocative findings that indicate waking-specific and sleep-specific profiles of gene expression. Preliminary results have also emerged for complex brain disorders such as schizophrenia [27]. To our knowledge, this technology has not yet been applied systematically to a behavioral model that would be of direct relevance to evolutionary psychology.

We have recently begun to apply gene expression microarray technology to the study of behavior in rats and for the remainder of this paper we will outline our initial experimental strategies. Such experiments should be of broad interest in fields ranging from neuroethology to biological psychiatry and ultimately, we hope, evolutionary psychology. Considering that molecular screening techniques remain in their infancy, and methodological and conceptual concerns accompany their utilization as well [29], it may be initially as wise to employ a targeted (i.e., selected gene) as more

comprehensive approaches. Indeed, due to incomplete genomic information, a full scan is not yet possible in laboratory rats.

The Neurobiological Sources of Separation Distress

A consistently demonstrated finding regarding subcortical brain systems is that affective responses can be evoked by localized electrical stimulation [10]. A compelling question thus is whether differential, artificial activation of distinct emotional systems (e.g., electrical activation of SEEKING, RAGE, FEAR or PANIC circuits) can generate distinct gene expression profiles at various points in time following activation. If there are indeed selective patterns of gene expression under such conditions, and furthermore if some of the respective gene products (e.g., neuropeptides) can arouse predicted affective responses (monitored by place preference measures), there then emerges an opportunity to evaluate the role of the associated neurobiological substrates in human emotional experiences. In such human studies, there would be an additional interesting opportunity to explore whether certain patterns of cognitive activity accompany distinct states of emotional arousal. Namely, would individuals exhibit characteristic patterns of thought during or following pharmacologically induced shifts in emotional states?

However, since many distinct emotional circuits overlap extensively in the diencephalon and midbrain, electrical brain stimulation studies may not be an optimal initial strategy. Rather, it seems that a study of natural, easily generated instinctual-emotional behaviors (fear, anger, seeking, sex, maternal behavior, separation distress and rough-and-tumble play) might serve as better starting points. Behavioral and neurochemical alterations resulting from such affective states have been studied in animal behavior models, and may be foundational processes for many human mental tendencies and psychiatric disorders [10]. In particular, the psychological stress and depression that results from social subordination and loss in rats is well documented, and thereby serves as one provocative starting point for studies of gene expression changes that result from social-environmental challenges.

Following the seminal work of John Bowlby [30], it was gradually recognized that behaviors related to separation distress were extant throughout most mammalian taxa. Subsequent investigations were targeted at characterizing the anatomical and neurochemical organization of neural circuits related to separation distress [20, 31, 38]. Studies evaluating the effects of electrical brain stimulation on evoked separation calls identified the associated anatomical trajectories in midline diencephalic structures, while the cardinal neurochemistries that inhibited separation distress vocalizations were endogenous opioid, oxytocin, and prolactin systems. These findings have been corroborated by many investigators [reviewed in 10] and they have set the stage for understanding many of the basic socio-emotional processes carried out by the mammalian brain, like those that mediate social attachments [33]. Furthermore, such work has also led to new animal models of depressive disorders [e.g., 34] and has helped stimulate research programs that focus on understanding related behavioral phenomena, such as gregariousness and social bonding [reviewed in 35].

Findings from other research areas complement the initial work on mammalian separation distress circuits. For example, studies examining the neural consequences of social isolation revealed several major neurochemical changes; among the most prominent brain alterations were a reduction in serotonin turnover and increased dopamine receptor sensitivity, both of which can promote elevated aggressive tendencies during social encounters [34]. Moreover, the psychiatric community has increasingly recognized that, in addition to the classical concept of stress [37], there are particularly devastating effects of social loss and chronic social isolation on mental health – especially as an etiological factor in depression. A variety of retrospective studies have documented an increased tendency for depressive disorders to arise following the loss of a loved one [38,39]. However, our understanding of the neurobiological changes associated with the formation and maintenance of social bonds remains in its infancy [40]. A wide ranging screen of gene expression patterns related to social behavioral processes is essential for characterizing the effects of social loss on psychobiological processes, and ultimately may help elucidate the evolutionary derived features of the mammalian brain and mind.

An Ethological Model for Simulating the Depressive Cascade: Social Competition

Animal models have had clear implications for the biomedical sciences and can provide a comparable understanding for evolutionary psychology. For instance, here we suggest that the use of two well-established experimental paradigms for analyzing social dominance in rodents may serve as potential models for the cascade of brain changes that result from depressive disorders, as well as a consequence of adaptive social behaviors. Contemporary psychiatry currently recognizes that the absence of social support and persistent losses in social encounters can serve as major vectors that lead to depressive disorders [e.g., 41] As we will allude to later in this section, the resident-intruder paradigm in rats may be ideally suited for analyzing differential brain gene expression in 'winners' and 'losers'. But, first we will briefly consider the scientific background for making such contrasts.

It is a commonplace observation that there are winners and losers in all forms of social competition. The idea that social defeat, which typically leads to subordination, may be a major contributory factor in the genesis of depression has recently received considerable attention within evolutionarily oriented segments of the psychiatric community [42]. In humans, at an emotional level, social defeat is accompanied by feelings such as hopelessness and helplessness, weakness and tiredness, as well as inferiority and inadequacy.

Such changes in affect are similar to those traditionally deemed to be primary characteristics of depressive disorders. Aside from pharmacological studies, where many antidepressant agents increase confidence [e.g., 43, 44], little is known about the central nervous system changes set in motion by defeat. Possible changes suggested by animal models are an initial arousal of biogenic amines [45], opiates [46], and other stress related neuropeptides, such as Corticotropin Releasing Factor (CRF) [47], and cytokines [48]. Whether alterations in these neurochemical axes are simply due to stress in general or rather to the specific social stresses described above is unknown. It has become widely accepted that stress is a major contributory factor in the etiology of depressive disorders [37, 47]. More recently, with an appreciation that all mammalian brains contain specific emotional systems that mediate social processes [10, 35], it has been recognized that social loss may be the most common type of stress that promotes the cascade of neuro-affective alterations leading to depression [49]. Furthermore, it has been proposed that such responses may reflect adaptive coping responses to a rapid diminution of available social resources [50].

In general, social stress can be categorized into two major types: (i) that which emerges from social loss, such as the loss of a loved one, and (ii) that which emerges from the loss of social status. With a growing recognition that loss in social encounters (submissiveness) can lead to depression [49], it has been increasingly theorized that social competition in animals may model certain aspects of depression in humans. Both types of social loss share certain key physiological features, such as arousal of the hypothalamic-pituitary-adrenal axis [37, 47], and activation of non-specific arousal/attentional circuits like ascending norepinephrine and acetylcholine systems [33, 52]. Use of modern gene expression technologies, such as those described above, should help unravel the neurobiological underpinnings of pathophysiological processes, and thereby offer a new understanding of both the pathogenesis of depression and the pharmacological facilitation of confidence.

Spontaneous acts of aggression commonly ensue when one adult animal intrudes on the living space of a conspecific. Such behavior patterns, which are typically more clearly evident in males than females, have the potential to be a robust animal model for social loss-induced depression. In such resident-intruder paradigms, with all other variables like weight and age controlled, the intruder routinely becomes the loser [53]. Whereas the resident (dominant) animal thrives, the intruder (subordinate) becomes unambiguously defensive and in the severest circumstances becomes physiologically compromised with a loss of weight and chronic elevation of stress indices [54]. Other severe consequences, including long-term disruptions of heart rate and body temperature regulation [55], are especially manifest when social contact with 'friendly' animals is not permitted following defeat [56]. In this last study, intruding animals had been socially housed and following defeat they were either returned to previous social housing conditions or they were kept isolated. Only the animals denied subsequent social housing (i.e., those not allowed resumption of positive social interactions) exhibited a cascade of severe physiological and psychological changes during the three weeks following defeat (e.g., loss of weight, adrenal hypertrophy, testicular regression, and increased fearfulness).

Studies employing *in situ* hybridization highlight major differences in *c-fos* gene expression between winners and losers [57]. The largest effects of losing are evident in the paraventricular nuclei of the hypothalamus, the origin of the pituitary adrenal stress response that is abnormal in depression [37, 47]. Since *c-fos* activation promotes a cascade of alterations in gene expression [e.g., 58], there are bound to be many differentially regulated genes that result from winning and losing social encounters.

An interesting contrast condition to the resident-intruder paradigm is the analysis of outwardly similar play behavior patterns in juvenile animals. This type of social competition is not as stressful as the resident-intruder paradigm. Under comparable conditions juvenile animals exhibit 'play fighting' which can also lead to the establishment of social dominance [59]. Such social engagements, however, are affectively positive for both animals as evaluated by place preference and other instrumental tasks [60]. In such experimental paradigms, social deprivation promotes rough-and-tumble play whereby stable, but friendly, patterns of dominance emerge [10]. Although endogenous brain opioid systems have been demonstrated to change as a result of play [61, 62], little is known about other concomitant alterations in neurochemistry. A scan of differences in gene expression may reveal that aggressive and play dominance have markedly different effects on the brain. Such an expectation stems from a recent demonstration of differential *c-fos* mRNA transcription patterns in winners and losers from adult resident-intruder paradigms [57] and during play between juveniles [63]. The precise identity of the more widespread genetic changes can be identified using gene expression microarrays.

Thus, as has been argued by several evolutionarily-oriented investigators [e.g., 49], the formation of social dominance may reveal genetic alterations that ultimately lead to depressive phenotypes in submissive animals, while the second paradigm (i.e., social play) may reveal possible differences in gene expression that lead to submission, but without negative social stress. Such gene expression patterns may carry considerably different emotional and adaptive consequences. Moreover, since both behavioral paradigms entail comparable amounts of energy use, changes in expression that are due to non-specific behavioral and general arousal processes should be filtered out of the analysis. Although no control can be perfect when it comes to such dynamic social processes, the two models are about as close as they can come to ideal mutual controls for each other. Inclusion of socially housed animals in these studies (that exhibit little robust social

interaction) can provide additional 'social-contact' controls that will permit a clearer interpretation of differences in gene expression that are observed during the two social situations.

Several other naturalistic models of animal behavior offer an opportunity to study potentially key aspects of human behavior. To be fruitful, studies of gene expression patterns must converge with other cross-species approaches, such as brain imaging technologies, the construction of behavioral phylogenies, comparative neuroanatomy, and analyzing the consequences of nucleotide polymorphisms on physiological function. Ultimately the importance of such approaches for evolutionary psychology can be directly evaluated by the development of increasingly specialized pharmacological therapies for treating psychiatric disorders.

From Brain Molecules to Mind Medicines

The most likely place where the evolutionary functions of the brain and mind will find a common, fertile ground for substantive empirical advances is in the neurochemical coding of emotional and motivational behaviors, and the affective processes and thinking tendencies associated with them. This is because homologous brain systems in humans and other animals can be studied with the same neurochemical techniques, and the underlying neurochemical systems can be linked directly to genetic issues. Neuroantomical and neurophysiological correlates are also important, but much less susceptible to such comparative genetic studies. Also, in this context, it is worth noting that the therapeutic applications that may emerge from a detailed understanding of state functions of the brain (e.g., the basic attentional, emotional, and motivational systems of the brain) are much more likely to be fruitful than that which could be achieved through a study of the channel functions of the brain (which presumably mediate the epigenetically divergent individual differences that are abundant in all species). In pursuing such neuroevolutionary psychobiological relationships, it is likely that new therapeutic principles will be discovered that will herald a new and more subtle generation of interventions in biological psychiatry.

Here we would like to briefly summarize the work of Moskal and co-workers [64] on the discovery of a new class of potential therapeutic agents that emerged from a strictly molecular approach to the brain and that furthermore highlights the remarkable power of molecular biological tools to uncover specific, evolved functions of the brain. This research was initiated in the early 1980s with the goal of discovering new brain molecules that may be important in the mediation of complex central nervous system functions, such as learning and memory formation. Since it was already well established that one of the cardinal brain areas involved in translating experiences into long-term memories was the hippocampus, the goal was to discover new memory-related molecules that may exist in tissues derived from that brain structure. Accordingly, a library of monoclonal antibodies (MAbs), directed to the developing hippocampal formation of neonatal rats was created [65]. Promising MAbs were identified first by immunocytochemical methods including identifying those that bound to the cell surfaces of live hippocampal neurons maintained in tissue culture (the assumption being that important functional events would be transpiring at the cell surface), and second by evaluation of functional effects including behavioral changes in various animal models when such antibodies were injected into the ventricular system [66, 67].

This screening led to the identification of an MAb that not only bound relatively selectively to the hippocampus, but which could also facilitate learning. Pharmacological studies indicated that binding was occurring at the glycine co-agonist binding site of the NMDA receptor-ionophore complex [68, 69]. This MAb was used as a template to create, via cloning and sequencing the hypervariable regions of the antibody, a family of peptides that mimicked the antibody itself [64]. Further purification and structure-function activity studies yielded a family of small peptides we now call *Glyxins* which not only have all of the behavioral effects of the parent MAb, but also proved to be effective in inhibiting neuronal damage caused by hypoxic insult to the brain, and also proved to be effective in alleviating neuropathic pain [64, and unpublished data].

The molecular analysis of brain tissues, in conjunction with parallel behavioral studies, can yield insights into the evolved regulatory systems of the brain that cut across species barriers. We believe that with the advent of tools for the analysis of gene expression, especially micorarray technology, one can now go from the analysis of gene activation patterns in the brain to the identification of molecular targets for therapeutic interventions in psychiatry. The success of this enterprise could introduce a powerful new biological foundation for evolutionary psychological thought.

Conclusions

From the perspective of the so called 'hard' sciences, such as physics or chemistry, evolutionary psychology is an emerging discipline that will benefit immensely from a consideration of the underlying, neurobiological substrates of mental processes and behavior that can be modeled in related animals. A historical example of this can be found in the emergence of biochemistry as an independent field of inquiry. Surely biochemistry is currently accepted as a field in and of itself, but it should be remembered that not until early in the twentieth century had chemists begun to apply their knowledge and experimental methods to the study of cell function. As it were, the pioneers of biological chemistry legitimized biochemistry as a field and furthermore ushered in the present age of molecular biology by identifying the chemicals of life (e.g., glycolysis, the tricarboxylic acid pathway, essential vitamins and minerals, etc.). Later concepts such as the allosteric regulation of enzymes, energy storage and transfer in the form of adenosine triphosphate, and signal transduction via cyclic AMP solidified biochemistry as a field that had gone beyond

the mere description of the chemicals of life, to one capable of generating new hypotheses that gave important insights into cell function; concepts not intuitively obvious to chemists, but clearly grounded in basic chemical processes – emergent properties with lives of their own, if you will, but grounded by parent scientific disciplines.

Another important point to be gleaned from the history of physics and chemistry as applied to biology is how crucial model systems have been for the development of new scientific disciplines. Molecular biology would not have been possible if it were not for the use of a prokaryote, *E. coli*, which was used to generate much of the essential data that forms the backbone of the field today. The fact that the genetics of *E.coli* and the biological machinery that coordinates it differs substantially from eukaryotes has done nothing to invalidate the absolute need for having chosen a suitable model species for the investigation of fundamental processes. Moreover, nested in this approach is the key assumption that the study of less complex systems – systems that nonetheless exhibit the core properties under investigation – are the primary way in which parent sciences can lay the needed foundation for the creation of emergent disciplines. Thus, the study of basic psychological processes will benefit enormously from the neuroethological study of instinctual tendencies that all mammals share. Perhaps just as importantly, without the integration of more molar approaches with more molecular ones, newer scientific fields, such as evolutionary psychology, often fail to tap into the richness of thought that has preceded them.

Consider one relevant example in more detail. What is psychoneuroimmunology? In a general sense, disregard that it is a scientific field that has organized important insights into testable models, rather just think about the hybridization of terms! Psychoneuroimmunology studies the impact of psychological constructs on the unconscious aspects of the nervous system that control the immune system and its associated diseases. What was there before the concept of psychoneuroimmunology was coined? How did stress affect immune, neuronal, or mental processes? There were generally no formal hypotheses and thus there was no coherent scientific discipline addressing such questions. As parent disciplines have become progressively integrated, there was a gradual transition from some type of 'hit and miss' approach to a set of principles that allow a variety of psychosomatic abnormalities to be recognized as standard medical disorders. Currently one of the most powerful sub-notions of evolutionary theory is The Medical Model – that is diseases of the body have an organic basis that can be identified, characterized, and medical interventions can be developed based on basic chemical, physical, and biological processes. Moreover, in psychiatry emergent properties of the brain, such as basic affective responses and their accompanying emotional states, are being characterized as etiological agents that intersect with the more clearly biological features of the brain and body. No voodoo or prayer is required, unless you are at the fringes of psychoneuroimmunology!

Likewise, emotional experience and its linkage to cognitive processes is bound to figure prominently into a coherent evolutionary psychology. From this perspective, consciousness and affective experience may have arisen concurrently in neural evolution as a way to elaborate and extend the potential reach of instinctual urges, while new levels of cortico-cognitive processes that serve to increase behavioral flexibility promoted the ability of organisms to efficiently pursue goals essential to survival. Accordingly, affect could not exist independent of consciousness, since in essence it is something that exists as part and parcel of conscious perception. Even in the absence of complex intellectual function, affective experience (an apparently intrinsic brain function) appears to exert a powerful influence on behavior in all mammals, and new models have been developed which allow such issues to be addressed objectively across species [70]. It thus is essential for evolutionary psychologists to investigate how such phenomena relate to the unique human psychological traits about which they are primarily concerned. One example of how this may be achieved is through a description and subsequent dissection of the neuroscientific and molecular biological substrates that foster affective experience within all mammalian brains [10]. These issues need to be linked to the extensive data-base describing the natural behavioral tendencies of animals and humans [71]. These strategies can be directly linked to the rapidly emerging evidence that highlights the extent to which psychiatric disorders are influenced by predisposing genetic factors [72].

In conclusion, lessons from the history of science suggest the following:

(i) You must build a field of scientific inquiry using the robust tools that already exist in related disciplines and from such an approach, emergent, testable ideas can be expected;
(ii) If you are willing to embrace evolutionary theory and the Medical Model of disease, then there must be a genetic basis to many fundamental aspects of human behavior;
(iii) Many of the basic constituents of human behavior are likely to be present in animals other than humans (while at the same time not denying that many additional mental potentials arose from more recent cortico-cognitive developments); and
(iv) As such, the use of animal models to study human behavior using the tools of chemistry, physics, biology, biochemistry, and molecular biology can be fruitfully undertaken.

With the development of new molecular techniques and the subsequent collection of new data sets in model species, a more thorough understanding of the genetically promoted characteristics of human mind and behavior will gradually emerge. This, in no way, denies the special neuro-symbolic and cultural capacities that have emerged which allow humans to have thoughts about

their thoughts and feelings that seem beyond the ken of practically all other species.

This paper has argued for a relatively novel scientific framework that should be considered and debated by the current generation of evolutionary psychologists; namely, that hypotheses regarding the human mind must be tethered to a discipline we call *neuroevolutionary psychobiology*. In the final analysis, from a molecular biological perspective at least, the use of animal models should be – indeed, must be – the approach that is most valuable for unraveling the biological substrates that form the cornerstones of the human mind and behavior. In laying down such solid neuropsychological foundations, we may develop more appropriate intellectual spaces for scientifically understanding even the most subtly evolved functions of the human mind. When these foundations are more fully understood, then we will be able to better address those aspects of the human mind that are truly unique and critically dependent on our vast cortico-cognitive resources–such as our capacity to symbolize and communicate world events in linguistic terms. Such emergent capacities have permitted the emergence of spectacular cultural traditions and our profound interest in the minds of others, as each of us seeks to sustain and improve the inter-subjective fabric of our existence.

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