

How evolutionary psychiatry can advance psychopharmacology

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The prevailing paradigm for psychopharmacology focuses on understanding brain mechanisms as the key to finding new medications and improving clinical outcomes, but frustration with slow progress has inspired many pleas for new approaches. Evolutionary psychiatry brings in an additional basic science that poses new questions about why natural selection left us vulnerable to so many mental disorders, and new insights about how drugs work. The integration of neuroscience with evolutionary psychiatry is synergistic, going beyond reductionism to provide a model like the one used by the rest of medicine. It recognizes negative emotions as symptoms, that are, like pain and cough, useful defenses whose presence should initiate a search for causes. An integrative evolutionary approach explains why agents that block useful aversive responses are usually safe, and how to anticipate when they may cause harm. More generally, an evolutionary framework suggests novel practical strategies for finding and testing new drugs.

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Introduction

During the middle of the last century, a combination of serendipity and rigorous observation led to the discovery of several new classes of psychotropic agents, including antidepressants and the antipsychotics.^{1,2} They have transformed psychiatry and improved the lives of millions of people. Subsequent neurochemical research into their mechanisms of action led to the introduction of additional agents with related mechanisms; for example, the realization that early tricyclic antidepressants inhibited noradrenergic and serotonergic reuptake prompted a search for selective serotonin reuptake inhibitors (SSRIs). These studies, in conjunction with remarkable new methods in neuroscience, encouraged hopes that we would soon discover the brain mechanisms that cause psychiatric disorders, and that these discoveries would define diagnoses objectively, and lead to new medications and better outcomes.³

These advances have not materialized. With rare exceptions, no diagnosis in the *Diagnostic and Statistical Manual of Mental Disorders (DSM)-5* is validated by a biological test, no specific brain “lesions” have been found that account for any of the major psychiatric disorders,⁴ and progress in finding new treatments has been slow. As the authors of an article in *Science* put it, “Unfortunately, there have been no major breakthroughs in the treatment of schizophrenia in the last 50 years and no major breakthroughs in the treatment of depression in the last 20 years.”⁵ The former director of NIMH concluded “Whatever we’ve been doing for five decades, it ain’t working... When I look at the numbers—the number of suicides, the number of disabilities, the mortality data—it’s abysmal, and it’s not getting any better. Maybe we just need to rethink this whole approach.”⁶

Evolutionary psychiatry is the subfield of evolutionary medicine that uses the basic science of evolutionary biology

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to better understand and treat mental disorders.⁷⁻¹⁰ It offers a framework for integrating understanding of the functions of emotion and cognition with knowledge about brain mechanisms to provide psychiatry with the same kind of conceptual and empirical foundation that physiology provides for the rest of medicine. In particular, evolutionary psychiatry recognizes that aversive negative emotions are, like pain and cough, useful responses shaped by natural selection.^{11,12} It also provides evolutionary explanations for why such symptoms are so often excessive, making it safe to block them in many instances.

Recognizing that proximate descriptions of mechanisms and evolutionary descriptions of origins and functions are both essential was a major advance in 20th-century biology that is only now being recognized in medicine.¹³⁻¹⁶ In psychopharmacology, for example, a full explanation of antidepressant actions requires not only a description of mechanisms, such as the serotonin reuptake blockade of serotonergic antidepressants, but also evolutionary explanations, of the origins and functions of serotonergic neurotransmitter systems and the emotions they influence. Evolutionary medicine takes this a step further to encourage asking why natural selection did not do a better job of regulating such responses and making organisms more resistant to disease.¹⁷ The usual answer is important—mutations happen, and genetic drift is unavoidable. However, several other kinds of explanations are also important,¹⁸ each of which we will consider in turn together with their implications for psychopharmacology.

We first summarize some core evolutionary principles that provide a foundation for psychopharmacology, then review the several kinds of explanation that evolutionary medicine offers for why natural selection has left systems vulnerable to disease. This suggests practical ways that this evolutionary framework can make psychopharmacology more effective and efficient.

Evolutionary principles

Darwin made two different discoveries. The first is that all organisms are derived from common ancestors. This

explains why similar drugs influence cognition, emotion, and motivation in similar ways in multiple species. For instance, the dopamine regulation of human motivation in humans is a derived version of octopamine regulation of mollusk and worm behavior.¹⁹ Such similarities are profound, but differences are equally important. The actions of vasopressin, for example, are different in mice and humans.²⁰

Darwin's other discovery was natural selection—the explanation for why so many aspects of organisms are so well suited to their tasks. Like every other organ, the brain was shaped by natural selection.²¹ It regulates physiology and behavior in ways that maximize reproduction.

An evolutionary framework suggests novel practical strategies for finding and testing new drugs

These two discoveries are the basis for the first two of the four questions that Nico Tinbergen, the father of modern ethology, recognized as required for a complete understanding of any biological trait: What is the evolutionary history of the trait? And how has the trait influenced fitness? The other two are “proximate” questions: How do mechanisms work? And how do they develop ontogenetically?¹⁶ Evolutionary medicine is based on recognition that all

four questions must be addressed, and that there are evolutionary explanations not only for traits that work well, but also for traits that leave us vulnerable to disease.¹⁵

All this is relevant, even crucial, for psychopharmacology because it expands the scope from looking only at mechanisms underlying attention, cognition, and emotion to looking also at their origins and functional significance. Understanding mood and anxiety requires describing how these capacities have given selective advantages that shaped them. Understanding how molecules such as serotonin interact with multiple different receptors requires an integrative description of the mechanisms, their ontogeny, their phylogeny, and their adaptive significance.

Emotions, brain loci, and neurochemicals all have adaptive functions, so it is tempting to propose a function as an evolutionary explanation: for instance, leptin has been viewed as the weight-regulating molecule, and

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serotonin as a mood regulator. However, leptin has dozens of functions,²² and serotonin influences sleep, vascular tone, and bone deposition, among other things. Emotions also have many functions. Different emotions correspond not to different functions, but to different situations in which they have been useful.²³ Genes, molecules, loci, emotions, attention, and cognition interact in tangled causal pathways very different from those in any designed system. This frustrates the understandable wish for simple models, but acknowledging the nature of organic complexity may provide a route to new advances.

Tinbergen's question about the evolutionary history of traits is especially relevant to understanding how psychotropic agents act on neural systems that have been evolutionarily conserved over tens of millions of years.²⁴ For example, opioid drugs act on opioid receptors to alter pain perception in a wide variety of species, including invertebrates.²⁵ There are differences in opioid systems across species, but this system and its role in pain perception are surprisingly consistent.^{26,27}

Another core insight is that all organisms face similar challenges: get food, avoid predation and infection, get allies and status, find mates, reproduce, and care for offspring. These behaviors all involve goal pursuit—going towards resources and away from dangers.²⁸⁻³⁰ This explains why emotional states are all positive or negative. It helps to explain the continuity between the mechanisms that regulate threat withdrawal in sea slugs and anxiety in humans. Similarly, dopaminergic reward systems that facilitate mammalian foraging, feeding, and mating, are present in evolutionarily distant species.

Evolutionary explanations for vulnerability

Evolutionary medicine builds on recognition that evolutionary explanations are essential by asking a new question. In addition to questions about how mechanisms work and what differences explain why some individuals have a disorder, it also asks why natural selection has left all members of a species vulnerable to a disorder. Why didn't natural selection do a better job? Its limitations, such as the inability to prevent all mutations, is only one of the several possible explanations for vulnerability outlined in the *Box*, and described below and in an early article about evolutionary psychopharmacology.³¹

- **Aversive emotions are useful responses shaped by natural selection that are vulnerable to excess and dysregulation for several evolutionary reasons.**
- **Natural selection shapes mental mechanisms to maximize reproduction, often at the expense of objectivity, happiness, health, and longevity.**
- **The limits to what natural selection can do are substantial**
 - Mutations are inevitable and genetic drift influences allele frequency
 - Inability to start a design from scratch constrains optimality
 - Natural selection is too slow to adapt organisms to fast changing technological and biotic environments
- **Tradeoffs make most systems suboptimal and many systems vulnerable.**

Box. Evolutionary explanations for vulnerability to mental disorders

Aversive emotions are useful, but prone to excess and dysregulation

Emotions are special states shaped by natural selection in conjunction with systems that regulate their expression. Like sweating, cough, and fever, they are normal and useful only when expressed in the situations they were shaped to cope with. A first principle is that their aversiveness is useful to motivate escape and avoidance of deleterious situations.

Another implication is that using drugs to suppress normal responses can be dangerous, as when excess suppression of cough exacerbates pneumonia. The dangers of suppressing negative emotions like anxiety and low mood are less obvious, but they need consideration for each patient.

A further implication is that the presence of emotional symptoms should spur a search for causes, just as the presence of fever and cough do. The situations that arouse anxiety and depression are often harder to identify, but the physician's first task is the same—try to find and deal with the cause. A careful assessment of precipitating factors might provide some of the predictive power that has been hard to get from biomarkers.

This perspective does not imply that serious anxiety and depression symptoms are adaptive—negative emotions are often expressed excessively. This perspective also does not advocate restricting access to relief from pharmacotherapy

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(so-called “psychopharmacological Calvinism”).³² Mental disorders are undertreated across the world, and relieving mental suffering is as central to the mission of medicine as relieving pain.

However, false alarms in defensive systems are common because of the smoke detector principle. When the presence of a potentially severe danger is uncertain and an inexpensive response, such as panic, provides protection, false alarms are normal, expected, and optimal, as they are for smoke detectors that shriek at burned toast.¹² This helps to explain why it is so often safe use drugs that block such symptoms.

A more subtle adaptive mechanism helps to account for the vulnerability of emotional systems to dysregulation. Repeated elicitation of a response or decreased ability to escape from danger means that avoidance and protection have been insufficient. In such situations, decreasing the threshold of stimulus required to elicit a response can be adaptive.^{33,34} Kindling in depression is a classic example,³⁵ as is the persistence of panic and agoraphobia.¹⁰ Such systems are inherently vulnerable to slipping into a positive feedback loop, and disrupting such loops offers a target for drug action.

Selection is too slow to adapt organisms to fast-changing environments

Humans evolved in environments very different from those we live in now, which has had dire consequences. For instance, junk food triggers ancient reward systems, creating the obesity epidemic.³⁶ Such a mismatch also helps to explain our vulnerability to addiction. Substances that act on reward system receptors combine with novel routes of administration to create addiction; natural selection has not had time to shape protection.³⁷ Reward systems may also be “hijacked” by a range of other modern stimuli including those found in the context of gambling and gaming—precipitating so-called behavioral addictions.³⁸

Pharmacological agents that act on reward pathways may be useful for countering addiction.³⁹ Knowledge that such drugs influence somewhat separate “wanting” and “liking” pathways is especially important to explain drug-seeking behavior that provides few rewards.^{40,41}

Vulnerability to addiction is influenced by genetic factors. An evolutionary perspective suggests that the responsible variations are likely to be genetic quirks that impose few

risks in ancestral environments where pure drugs and technological highs were unavailable. This suggests the need for studies to analyze how individuals vulnerable to addiction behave in environments without these triggers. The tendency of dopamine to increase the salience of cues would seem to predict that the foraging strategies of individuals vulnerable to addiction will be less exploratory than those of other people, but the opposite has been documented for individuals who gamble. It might well be possible to create computer foraging games that could identify children who will be especially vulnerable to drug abuse, and to find drugs that might prevent it.

Selection is too slow to provide perfect protection against infection

Conflicts between pathogens and hosts have shaped sophisticated immune systems and equally sophisticated strategies for avoiding those defenses.⁴² Streptococcal antigens similar to those in humans can arouse autoimmune responses that damage the striatum and precipitate obsessive-compulsive disorder.⁴³ Also, inflammatory mechanisms that play key roles in microbial defense may also cause a range of psychiatric disorders including depression and neurodegenerative diseases.⁴⁴⁻⁴⁶ Growing appreciation of the role of the microbiome is calling attention to the role of the gut-brain axis in the etiology of both physical and mental disorders, and to the potential value of probiotic agents.⁴⁷

Trade-offs

Too much stomach acid causes ulcers, too little increases vulnerability to infection. Too much anxiety is common, too little is the potentially fatal condition of hypophobia.⁴⁸ A more general tragic trade-off for *homo sapiens* is that some of the same characteristics that make the human brain wonderful for language, working memory, future planning, and other adaptive cognitive functions, may also make us vulnerable to conditions such as psychosis that seem to be distinctive to humans.⁴⁹⁻⁵¹

Hundreds of millions of dollars have been spent on trials of agents that disrupt amyloid β but do not slow cognitive decline. It is unlikely that natural selection would preserve a mechanism that synthesizes a molecule with no useful function and substantial dangers. Indeed, growing evidence for the antimicrobial actions of amyloid β and herpes virus remnants in plaque lesions⁵² suggests new approaches to Alzheimer’s treatment.

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Life history theory describes how natural selection shapes patterns of effort allocation in ways that maximize Darwinian fitness, that is, the number of offspring who survive to reproduce themselves. For instance, starting reproduction early increases the number of offspring, but imposes risks compared with waiting for full maturity. Several authors have suggested that early adversity may be a reliable cue of a life span that is likely to be short, making it advantageous to take risks and pursue short-term goals.⁵³ Drugs that extend an individual's time horizon could have huge benefits but we are not aware of any searches for agents with such effects.

Tradeoffs at the level of genes contribute to many vulnerabilities. An allele that gives advantages early in life when selection is stronger will be selected for even if it causes aging later in life (antagonistic pleiotropy).⁵⁴ Multiple alleles can be maintained at a locus if they give advantages in different environments, although such balancing selection is far less common than is sometimes assumed and is unlikely to be a major factor for mental disorders. The high heritability of some mental disorders may result from a trait that is pushed up a fitness slope to near a cliff edge where fitness collapses for some individuals, in the same way that horses bred for speed are prone to break their legs.^{10,55} This undermines the assumption that all alleles associated with illness are abnormal, and it encourages searches for associated traits and benefits.

Natural selection cannot start afresh

The vertebrate eye is seen as an exemplar of perfection, but it is jury-rigged at best, with a blind spot created by the entrance of blood vessels that then run in front of the retina. Cephalopod eyes have no blind spot because their vessels and nerves penetrate the eyeball from behind, but because evolution cannot start afresh, vertebrates will never have such sensitive eyes. The mind too is a product of myriad small changes that leave it less optimal than if a fresh start could have been possible. Mechanisms that control feelings, thoughts, and behavior are mostly outside of consciousness, and many have systematic biases that we all share.⁵⁶

Selection for reproduction at the expense of health

A central principle of evolutionary science is that natural selection shapes organisms to maximize reproductive success, even if that reduces objectivity, happiness, health, or longevity. Sexual jealousy is a prime example; it increases

reproductive success at the cost of massive unhappiness and violence and the risk of pathological jealousy.⁵⁷ The three-fold higher mortality rates for young men compared with young women are another example explained by outsized mating benefits to males compared with females resulting in increased competitive tendencies and risk-taking.⁵⁸

The practical value of evolutionary psychiatry for psychopharmacology

The above principles have applications for several routine tasks in psychopharmacology:

- Describing and measuring mental disorders
- Understanding disease causes
- Understanding drug mechanisms of action and describing them to clinicians and patients
- Finding new agents
- Demonstrating efficacy and safety.

Describing and measuring mental disorders

Frustration with diagnosis has persisted and escalated to the point where the NIMH has declared the *DSM* flawed, and the first page of a leading psychiatric textbook says "There is little reason to believe that these diagnostic categories are valid."⁵⁹ The *DSM* categories are nonetheless used and useful to describe what clinicians see. The dissatisfaction arises from heterogeneity within categories, overlap between categories, and especially from the inability to find biomarkers that would define and validate specific diagnostic categories.⁶⁰

An evolutionary perspective encourages a more medical approach that recognizes many negative emotions as symptoms that are diseases themselves only when dysregulated. It also calls attention to the many disorders, such as congestive heart failure and epilepsy, that do not have one specific etiology, but result from many factors that can contribute to system failure.⁶¹

An evolutionary perspective emphasizes a comparative cross-species perspective, and dimensional and cross-diagnostic constructs⁸ in ways that are somewhat similar to the Research Domain Criteria (RDoC) framework for psychiatric research.⁶² However, an evolutionary perspective holds that dissatisfaction with psychiatric nosology may best be alleviated, not by a new diagnostic framework, but by a more realistic acknowledgment of the reality of blurry boundaries and multiple causes of medical disorders.⁶¹

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An evolutionary view also challenges the tendency to assume that depression and related disorders can be adequately measured by counts of symptom number, severity, and duration.⁶³ Different symptoms of depression are aroused by different aspects of unfavorable situations so all should be considered independently, and scales using sum scores should be viewed skeptically.⁶⁴ Psychopharmacology trials rely on a small number of “gold standard” measures such as the Hamilton Depression Rating Scale, but clinicians have long been aware of the possibility that particular psychotropics may be more useful for more limited sets of symptoms.^{65,66}

Evolutionary psychology has been criticized for just-so explanations of psychological phenomena, and for focusing on unlikely cognitive modules at the expense of appreciating the complex and messy biology of the brain-mind.⁶⁷ Psychopharmacology is open to similar criticism when it adopts an overly reductionist approach to understanding mental disorders as “chemical imbalances.” High-quality psychopharmacological treatment requires acknowledging the individuality of each patient in the full context of his or her life history, motivational structure, and psychosocial context. Simple diagnostic biomarkers are unlikely to be found for most emotional problems because most states of negative emotion do not have a single specific cause; instead, they reflect the complexity of human individuals in social environments.

Understanding disease causes

The best way to find a new treatment is to identify the cause of a disorder but hopes of finding specific genetic or brain abnormalities have faded even as a mountain of evidence demonstrates small average differences between people who do and do not have a mental disorder. Attempts to map specific disorders to excesses or deficiencies of dopamine, serotonin, and other neuroactive molecules have collapsed, even as evidence for the relevance of these molecules grows. The wish to describe systems in reductionist terms is understandable as is the hope that simple excesses or deficits can explain disorders. The search for causes will progress faster if it is recognized that organic complexity is different from complexity in designed systems. This perspective may be particularly useful in psychopharmacological psychoeducation.^{68,69}

Understanding drug mechanisms of action

Psychotropic drugs are often thought to replace neurotrans-

mitter deficiencies or otherwise normalize brain systems. Recognition of the functions of emotions suggests, however, that most drugs for anxiety and depression disrupt the normal functions of adaptive systems in the same way that aspirin, ibuprofen, acetaminophen, and opiates all relieve pain via disrupting different aspects of inflammation and nociception.

Discussions with patients can be especially helpful when informed by evolutionary principles. Patients who feel defective after being told that they have a “brain disorder” often feel affirmed and validated when they learn that anxiety and low mood have useful functions, and that people who lack those responses have a serious disorder.

Finding new agents

Assessing potential new agents by their similarity to known effective molecules is a tried and true method that is being augmented by new data analytic methods, but it rarely leads to fundamentally different drugs. Animal models have also been useful, especially the forced swim test that is now the basis for an average of about one new publication each day.⁷⁰ The standard view of the test assumes that persistence is good. However, when rats stop swimming they don’t drown, they float with their noses just out of the water. In the natural environment, this strategy is often superior to useless struggle, as demonstrated by increased rates of drowning in rats treated with antidepressants compared with those treated with placebo.⁷¹

Such insights should suggest better animal models. In particular, studies that examine persistence time in pursuit of scarce food may identify new antidepressants, as may studies of persistence in mate pursuit and studies of social defeat.⁷² Given advances in our understanding of the multiple causes of depression, such models may benefit from integrating data from genomics with data from the environment (eg, the situations that shift mood, including early exposure to stressors and different styles of parenting). More generally, better results may come from ecologically valid models that measure changes in behavior in response to situations that normally influence motivation systems. Meetings that convene behavioral ecologists with psychopharmacologists may pay big dividends.

Demonstrating efficacy and safety

It has been hard to confirm the efficacy of many psychotropic

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agents believed to be useful, especially antidepressants. Part of the problem is the large magnitude of placebo responses in mood, anxiety, and pain disorders. Symptom profiles and genetic data have been used to identify subgroups of drug responders, but effect sizes tend to be small.

An alternative approach is to create diagnostic subgroups based on the situations and causal pathways that arouse low mood. Depression arising from loss is different from that arising from being trapped in a bad situation, and both are different from depression arising from a medication or inflammation. Larger effect sizes might emerge if subgroups of patients are based on individual causal pathways and social context, and if symptoms are analyzed individually instead of as sum scores. Also, recognition of the function of emotions encourages measuring functional improvement as well as symptom relief.

Conclusion

Modern psychopharmacology originated from serendipitous discoveries and has progressed thanks to better understanding of brain mechanisms. Hopes remain high that neuroscience will deliver discoveries of specific biomarkers and specific causal abnormalities, but they have been slow in coming and few advances have been translated from the bench to

the bedside. An evolutionary perspective synergizes with growing advances in understanding neural mechanisms in several ways. It explains why diagnosis has been so problematic, and how subcategories of disorders based on the functions of emotions and the life situations of patients may increase the ability to demonstrate efficacy. It suggests that many agents act by disrupting normal defensive systems, and that study of these systems in context may provide a new route to drug discovery. It also suggests looking for positive feedback loops that create and sustain disorders, as a possible foundation for finding ways to stop them.

A single article about applications of an additional basic science to psychopharmacology can only sketch a few basic principles and examples that illustrate the opportunity. Interested psychopharmacologists are encouraged to join the International Society for Evolution, Medicine and Public Health, and to organize meetings where evolutionary biologists, behavioral ecologists, and pharmacologists can collaborate to find new ways that evolutionary biology can advance psychopharmacology. ■

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