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Emotional endophenotypes in evolutionary psychiatry

Jaak Panksepp *

Center for the Study of Animal Well-Being, College of Veterinary Medicine (VCAPP), Washington State University, Pullman, Washington, USA
Falk Center for Molecular Therapeutics, Department of Biomedical Engineering, Northwestern University, Evanston, Illinois, USA

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Abstract

Evolutionary psychiatry emerged from the conceptual successes of sociobiology and evolutionary psychology. It will need to avoid the many mistakes that biology-free Evolutionary Psychology has been prey to. It should not ignore the wealth of information that exists between the phenotypic expression of symptoms and the genotypic sources of core brain/mind processes that are disrupted in psychiatric disorders. Syndromal–conceptual thinking has become a barrier to illuminating the biological sources of psychiatric disorders. Endophenoytpic-biomarker approaches now offer robust alternatives for generating linkages between psychiatrically relevant psychological changes and the neurobiological infrastructure of disordered mentation. Here I summarize recent advances in endophenotypic thinking in biological psychiatry, and suggest that various core emotional–affective processes may be among the most important endophenotypes that need to be clarified at both neurobiological and genetic levels of analysis. To this end, I discuss strategies to link basic emotional processes that are commonly imbalanced in psychiatric disorders to neuroanatomical, neurochemical, neurophysiology, and molecular genetic levels of analysis. Conjoint animal behavioral-genetic and gene expression, microarray analyses can clarify a variety of key emotional endophenotypes and thereby provide a coherent infrastructure for psychiatric systematics. To further clarify the neurobiological dimensions of psychiatric disorders, we must also focus on psychosocial and environmental stress vectors that converge to create imbalanced emotional and motivational brain activities of psychiatric significance.

Keywords: Affect; Anger; Cognition; Depression; Endophenotypes; Emotions; Evolutionary psychology; Fear; Gene chips; Microarrays; Mind; Neuroevolutionary psychobiology; Play; Psychiatric disorders; Seeking; Separation distress; Social dominance

Contents

Abbreviations: Ach, Acetycholine; ADHD, Attention Deficit Hyperactivity Disorders; CCK, Choleocystokinin; CRF, Corticotrophin releasing factor; DBI, Diazepam binding inhibitor; EEG, Electroencephalogram; ESB, Electrical Stimulation of the Brain; fMRI, Functional Magnetic Resonance Imaging; LEAS, Levels of Emotional Awareness Scale; LH-RH, Luteinizing Hormone Release Hormone; MSH, Melanocyte Stimulating Hormone; NPY, Neuropeptide Y; PAG, Periaqueductal Gray; PET, Positron Emission Tomography; TRH, Thyrotropin Release Hormone; VTA, Ventral Tegmental Area.

* Center for the Study of Animal Well-Being, College of Veterinary Medicine (VCAPP), Washington State University, Pullman, Washington, USA. Tel.: +509 335 5803.

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1. Introduction

Psychiatric disorders are typically conceptualized as *syndromes* in which multiple brain regions and neurochemical pathways interact with environmental stressors to cause multidimensional patterns of symptoms that constitute a diagnostic category. The number of syndromes, with sub-type variants, has increased steadily with each successive Diagnostic and Statistical Manual (DSM) of the American Psychiatric Association (1994), but debates over the validity of psychiatric systematics has not abated (Wakefield, 1992). Despite many new findings about the brain changes in these syndromes that have been revealed with brain imaging (Phillips et al., 2003), our neurochemical and neurogenetic understanding of the classic psychiatric syndromes, although steadily advancing (Leboyer et al., 1998; Tandon and McGuffin, 2002), has not yet garnered any robust consensus. Major breakthroughs have been modest; replicability remains a consistent problem.

Although it has been easy to demonstrate that every psychiatric disorder has strong genetic components, yielding a host of candidate genes that may increase vulnerability to psychiatric problems (Leboyer et al., 1998), precise understanding remains modest. Perhaps the most compelling data is available for certain pervasive development disorders such as Fragile X, Rett, Williams, Prader-Willi and Angelman Syndromes (Peterson and Panksepp, 2004), even though how such genetic vulnerabilities get translated into developmental problems remain to be determined. For most adult psychiatric syndromes, the genetic linkages are more ambiguous, probably because of the pleiotropic interactions of multiple genetic dispositions with various contextual variables ranging from environmental stressors to intrapsychic processes that remain hard to monitor (see Burns, 2004 for schizophrenic conditions).

Because the syndromal approach in psychiatry, so important for diagnostic–prescriptive–socio-medical practices, has *not* promoted any robust neuroscientific understanding of the classic psychiatric disorders, investigators are seeking more productive alternatives. One promising approach is to envision psychiatric syndromes as complexes of core symptoms, with the hope that those simpler factors may be sufficiently characteristic and genetically constrained to serve as productive *endophenotypic* variables (e.g., pursuit eye movements and sensory gating in schizophrenia). Such cardinal symptoms of psychological infirmity may more easily link to brain and genetic processes than the broader conceptual syndromes. Thus, enthusiasm is mounting for reconceptualizing genetic analyses of psychiatric issues with respect to the most pervasive endophenotypes that characterize syndromes. As a result, there is diminished concern that some endophenotypes may appear in several distinct diagnostic categories (e.g., anxiety and anger), reducing the need for popular concepts such as co-morbidity.

By refocusing inquiries to more discrete and easily objectified psychobehavioral processes, critical neural and genetic substrates should emerge more readily. The number of candidate endophenotypic traits for distinct syndromes are rapidly increasing, and we may soon be afloat in a flotsam of suggestions that may not really help us get to the heart of emotionally relevant mental turmoil. So far, most of the suggested endophenotypes do not seem to be of clear psychological relevance for understanding the emotional dysregulations that are among the most common presenting feature of psychiatric distress. The aim of this essay is to extend the endophenotype concept to emotional levels, and to develop the idea that certain *basic* emotional tendencies are sufficiently strongly linked to specific functional neural circuits of the mammalian brain, that emotional endophenotypes (or perhaps more appropriately, endo-psycho-phenotypes) may provide psychologically relevant sets of target variables to be studied. The assumption is that core affective processes are especially relevant for conceptualizing psychiatrically significant emotional problems. It is now clear that all mammalian brains share a large number of basic emotional systems (Panksepp, 1998a, 2005), and the cross-species manifestations of these systems may constitute among the most psychiatrically important endo-psycho-phenotypes to be clarified by neuro-genetic analyses.

Since core emotional tendencies may emerge from ancient brain processes shared by all mammals, this strategy also effectively allows one to utilize cross-species evolutionary strategies, relying on presently underutilized ethological animal brain–behavior models. With the recognition that it is highly probable that many other animals also have emotional feelings (Panksepp, 2005), we should be able to shed light into core human emotional tendencies by studying animal brains. Mammalian brains contain circuits that are critically involved in anger, fear, sexual lust, maternal care, separation distress and social bonding, as well as playfulness and a general resource acquisition system for SEEKING/wanting — *desires* in a word (Panksepp, 1998a). Each generates instinctual action tendencies that are easy to monitor in animal models, and a *dual aspect monism* approach posits that affective consciousness may have been built upon inherited instinctual response tendencies. The possibility that core emotional feelings are firmly anchored in instinctual action systems of the brain, raises the interesting possibility that the foundations of consciousness are rooted in core affective processes (Panksepp, 1998b, 2005). The fact that basic emotional tendencies may have distinct neuro-peptidergic codes (Panksepp, 1998a), also allows us to search for new psychiatric medicines that target specific types of emotional dysregulations (Panksepp and Harro, 2004).

In addition to specific neuropeptidergic controls, *all* emotional urges are modulated by generalized transmitters such as dopamine, gamma-aminobutyric acid, norepinephrine and serotonin, the targets of the first-generation of biological psychiatric interventions that regulate the intensity of information processing throughout the brain. With such specific core emotional urges and general arousal concepts, elaborated by distinct brain operating systems, one can envision new behavior

genetic studies (Burgdorf et al., 2005; Kroes et al., 2006; Panksepp et al., 2002a,b). Also, one can utilize the full strength of established transgenic approaches in animals — site-specific mutagenesis, evaluation of gene therapies, and selective breeding for emotional strengths and weakness. I will first discuss this intellectual trajectory from the perspectives of traditional evolutionary psychology and Darwinian psychiatry, and then map out specific strategies that could bridge between genetic variables and discrete behavioral/emotional ones.

2. Endophenotypes in psychiatry

Our cortico-linguistic abilities are adept at generating concepts that may have little scientific utility. This is a problem in the so-called premature sciences — ones that emerged before there was any adequate way to pursue deep causal analyses. Psychoanalysis, indeed psychology in general, represent such sciences. Psychiatry was confronted by similar problems: how to make sense of the varieties of madness and excessive emotionality at a time when there was no credible way to link them to brain processes. Although the resulting "syndromal thinking" was a useful stop-gap measure, allowing clinicians some confidence that they were talking about the same entities and eventually, with the advent of biological psychiatry, to establish standard prescription practices, syndromal concepts started to retard scientific progress once detailed neuroscientific and molecular biological approaches had matured.

Now that we realize that the whole mental apparatus (i.e., brain function) is strongly constrained by the genetically and epigenetically derived brain organizations, and we have the scientific tools to link primal mental functions to neural circuits and the underlying genetic controls, it is possible to view psychiatric disorders from the bottom-up, through an understanding of the evolved functions of the brain. The buzz-word for these natural brain functions is *endophenotype* (Gottesman and Gould, 2003a,b). Endophenotypes can be neuroanatomical, neurophysiological, neurochemical, emotional, motivational, cognitive or simple response tendencies. When they are strictly in the physiological realm, they are almost synonymous with the traditional concept of "biomarkers" and with inclusion of larger scale functional aspects, "vulnerability traits." However, with the acknowledgement that such entities have an evolutionary history which can finally be neuro-genetically analyzed, we have opportunities to take such concepts into more sophisticated psycho-behavioral realm. Here I will bring emotional markers into the analysis. In sum, the more tightly a function is linked to brain systems and genetic underpinnings, the more likely it is to be a useful endophenotype for psychiatrically relevant science. Items that are more conceptual – relying on our vast creative ability to linguistically parse brain/mind functions – will be less likely to yield equally consistent and useful scientific results.

I will not dwell on the increasing number of psychiatrically relevant endophenotypes that have been proposed in the last few years. Let it simply be said that there is an increasing list for schizophrenia (Calkins et al., 2004; Glahn et al., 2003; Palmer et al., 2003), ADHD (Heiser et al., 2004; Nigg et al., 2004; Slaats-Willemse et al., 2003) as well as biomarkers for addictions (Froehlich et al., 2000; Rangaswamy et al., 2004), but hardly any of them are devoted to neuropsychological and neuro-affective issues that may be most informative for understanding the emotional underpinnings of psychiatric disorders (Panksepp, 2004a).

An understanding of basic brain emotional systems may be among the most useful endophenotypes for evolutionary-biological psychiatry. Of course, the more complex a system is within the brain, the more complex are likely to be the genetic underpinnings. Thus, even though personality traits can be conceived of as evolutionary endophenotypes, the linkages to genetic issues are ultra-difficult (Van Gestel and Van Broeckhove, 2003). Likewise, the cognitive endophenotypes, such as emotion detection abilities (Bolte and Poustaka, 2003) are likely to be equally difficult, since many of them may be dependent on extensive epigenetic refinements. Still, animal studies affirm that remarkably complex social tendencies can be strongly influenced by single genes in creatures as diverse as flies (Demir and Dickson, 2005) and rodents (Young and Wang, 2004).

Obviously, the more any brain/mind process is an inherited "evolutionary tool," the more likely it is to be a useful construct for evolutionary psychiatry. The more derivative a process is of experience and learning, the more difficult it will be to deploy measures as neuro-genetically productive endophenotypes; they will remain syndromal concepts. To clarify this aspect of the argument, let me briefly focus on the concept of "love" without which, most may agree, the human race might be in deep trouble. However, are "loving feelings" good candidates as endophenotypic brain/mind processes?

I suspect *love*, essential as it is for human life, is rather more akin to a syndromal *concept* than a useful endophenotypic process. There is good evidence for the existence of various social emotional systems in the brain that have a genetic basis, although underlying genetic variables remain poorly understood. The evidence at the brain network level (Panksepp, 1998a, 2005) indicates that there are highly overlapping affective–emotional networks for *sexuality*, *separation-distress*, *maternal care*, and *rough-and-tumble playfulness*. These circuits appear to be homologous across all mammalian species. There may be other "social" ones (e.g., dominance and disgust), but for now, the preceding four are the only ones that have good evidence across all mammals. Strong indications are that various basic social feelings emerge from those brain dynamics, along with essential related process such as those generated by basic seeking-desire urges. Various concepts of "love" could easily supervene on those basic processes; with such core social feelings we can socially construct a variety of love concepts, as well as many other complex social emotions. Thus, loving feelings may be strongly linked to a variety of social–emotional endophenotypes, while not be an especially scientifically productive one by itself.

The preceding may highlight a general principle in future endophenotypic emotion studies: a clear taxonomy of the basic emotions may be essential for making scientific sense of the many higher-level social derived emotions as well as for the complex patterns of emotional turmoil that commonly characterizes psychiatric syndromes. If we do not get the basic systems correct, then all socially derived systems and concepts

may slip-and-slide in the conceptual realm forever. Thus, perhaps various feelings of love arise from affective intermixtures of strivings for sexual gratifications, nurturance, alleviation of separation distress and friendly playfulness, embedded in and combined with the cognitive and cultural specifics of individual lives. However, without such basic social–emotional systems, love might not exist on the face of the earth. However, "love" is not as good an endophenotype as the basic emotional tendencies from which it is constructed. This highlights a critical issue for discussing the utility of endophenotypes as well as other evolutionary psychiatric concepts. Although every thing the brain/mind does has some genetic linkages, the ones that are likely to be the most productive for solidifying psychiatric science are the ones that have the most robust genetic/neural controls.

3. Traditional evolutionary psychology and Darwinian psychiatry

Darwinian/evolutionary psychiatry seeks to explain/understand psychiatric disorders as a function of the evolved *functional* characteristics of the human mind (McGuire and Troisi, 1998; Stevens and Price, 2000). In the tradition of evolutionary psychology, this objective has typically been pursued through an adaptive explanatory framework, where various functional brain–mind 'modules' become imbalanced because of stressors. Ever increasingly, psychiatrists are interested in envisioning the nature of mental disorders through an evolutionary lens, which has led to creative theories of drug addiction (Hill and Newlin, 2002), depression (Nesse, 2000; Sloman and Gilbert, 2000), psychopathy (Mealey, 1995), obsessive compulsive disorders and a host of other psychiatric problems (Jones and Blakshaw, 2000; McGuire and Troisi, 1998; Stevens and Price, 2000). Although such approaches rarely help clarify the neural underpinnings of psychiatric disorders, they do provide new perspectives for psychiatric diagnostics. However, without stronger linkages to biology, they can be criticized for not bringing relevant cross-species psychobiological realities to bear on the presumed evolutionary underpinnings (Gardner and Wilson, 2004). The aim of the present essay is to highlight how the advantages of evolutionary approaches can be readily combined with the power of neurobiological ones.

The evolutionary psychiatry perspective must increasingly consider how psychiatric diagnostics can be related to a deeper functional understanding of the mental apparatus and its impairments. As in the rest of medicine, this aim is best achieved by clear visions of the normal functions and operations of relevant brain and body systems. Dysfunctional mentation is best illuminated by first clarifying the normal neurogenetic functions of the brain/mind. In general, an evolutionary view would suggest that normal brain emotional and motivational systems were well designed for organisms to subsist in their natural environments. Some type of "normative" utilization of such brain/mind functions defines mental health, but this can only occur if environments offer "affordances" for such brain systems to operate "normally."

Thus, evolutionary views must pay as much attention to the nature of adaptive environments as the emotional and other neuropsychological skills with which individuals are endowed. Within artificial environments that humans have constructed, psychopathology may be promoted as much by external factors as by endogenous ones. Evolutionary psychiatry brings a new view of such internal and external interactions to the table. For instance, certain drugs (e.g., opioids) maintain addictions by sustaining social–emotional homeostasis, and one may be able to diminish addictions by readjusting social environments so people are able to get more social–emotional satisfactions (Panksepp, 1981). This view corresponds well to an evolutionary view of how separation-distress arose in brain evolution: primal pain mechanisms may have been co-opted for neuro-symbolic forms of painful feelings such as those that arise from social isolation. This idea led to the finding that endogenous opioids are remarkably powerful in alleviating separation distress (Panksepp et al., 1978). Thus a psychiatrically relevant endophenotype might be the degree to which one feels psychic pain as a function of social loss, and the degree to which opioids and other key social neurochemistries (e.g., oxytocin and prolactin) can inhibit this process (Panksepp, 1998a). The animal data for opioid regulation of separation distress has recently translated nicely to human brain imaging of brain opioid dynamics during sadness (Zubietta et al., 2003).

Such chemo-endophenotypic traits, may also relate to various other higher-order, cognitive-type emotional traits; for instance, feelings of sympathy and empathy. It could well be that one's ability to perceive the emotional pain of others, perhaps partly through emotional mirror-neurons, dictates their sensitivity and concern for the emotional plight of others. However, it is the underlying capacity to elaborate the pain of separation-distress that may prove to be a superb emotional endophenotype, while the capacities for sympathy and empathy that epigenetically emerge from ones experiences of separation distress, may be farther removed from the genetic underpinnings of the psychiatrically relevant feeling states.

Thus, brain-functional and ecological aspects need equal attention to understand dysregulation of emotional systems. Through their conjoint consideration can one optimize the development of new kinds of therapeutic assistance. Now, I will briefly focus on why emotional endophenotypes, which are basic concepts in evolutionary psychiatry (Gardner and Wilson, 2004; Nesse, 1990), need to move to the forefront of etiological thought. Basic brain emotional systems may serve as key endo-psycho-phenotypes for future diagnostic and therapeutic thinking in evolutionary psychiatry.

4. Types of emotional systems

The affective neuroscience approach to understanding emotional systems is based on the need to distinguish the core processes that exist in mammalian brains that are likely to have strong and coherent neural and genetic underpinnings. We can have confidence in certain processes because we can artificially activate discrete emotional patterns, with accompanying affective feelings, by electrically stimulating essentially the same brain regions in all mammalian brains. The evidence for seven basic emotional systems has been exhaustively covered elsewhere (Panksepp, 1998a) along with reasons that we can consider raw affect to reflect a neurodynamic of these system (Panksepp,

2004b, 2005). I will summarize these systems in brief synoptic ways, only highlighting one or two key references that summarize the existing neuroscience for each system. Then I will briefly sketch the neuroscience of these systems and discuss how they can be studied in humans (where higher cortical inhibition often precludes observation of the direct instinctual manifestations of these systems). I will close with a summary of how the animal research can assist us in understanding the underlying nature of these networks in all mammals. The scientific study of these systems is much easier in animal models than in human beings, where we largely have to rely on verbal self-reports. First, let us consider each of these endo-psycho-phenotypic emotional systems in action (Panksepp, 1998a for details):

1) LUST: How would mammals propagate if they did not have brain systems to feel *erotic desire*? The neural seeds of male and female sexual systems are laid down early in development, while babies are still gestating, but they do not fully germinate until puberty, when the maturing gonadal hormones begin to fertilize male and female sexual arousals (heavily centered around vasopressinergic and oxytocinergic brain systems, respectively). However, because of the way the brain and body get organized, female-type desires can also exist in male brains, and male-typical ones in female brains. Of course, learning and culture persistently add layers of control and complexity to each emotional system that cannot be disentangled through animal brain research (Pfaff, 1999).
2) CARE: How would we mammals survive if we did not have brain systems to *nurture* each other? The maternal instinct, so rich in every species of mammal (and bird too), allows us to propagate effectively (Numan and Insel, 2003). To have left this to chance, or just the vagaries of individual learning, would have assured the end of social species. These hormonally primed urges, still present in humans, condition the way we respond to newborn babies. The changing tides of peripheral estrogen, progesterone, prolactin, and brain oxytocin figure heavily in the transformation of a first time mother into a fully maternal state, through actions on extensive subneocortical systems. Because males have intrinsically weaker CARE systems, they require more emotional education to become fully engaged caretakers.
3) PANIC: When young children get lost, they exhibit intense *separation distress*. They cry out for care, and their feelings of sudden aloneness, verging on panic, may reflect the ancestral pain codes upon which adult sadness and grief are built. Brain systems yielding separation distress calls (crying) in mammals and birds have been identified using ESB techniques. They resemble each other so closely as to suggest a shared ancestral heritage. Brain chemistries that exacerbate feelings of distress (e.g., Corticotrophin Releasing Factor) and those that can powerfully alleviate distress (e.g., brain opioids, oxytocin, and prolactin) figure heavily in the genesis of social attachments (as well as sexuality and nurturance) and may ameliorate depression (Nelson and Panksepp, 1998). These chemistries help create those intersubjective spaces with others that allow organisms to learn the emotional ways of their kind, paving the way for empathy and love. An understanding of such social chemistries may eventually yield new psychiatric medicines to help those whose social emotional "energies" are more or less than they desire. This knowledge may also link up with a better understanding of childhood disorders such as autism. A subset of such children may be socially aloof because they are addicted to their own self-released social-reward chemistries as opposed to activation by significant others.
4) PLAY: Young animals *frolic* with each other in order to navigate social possibilities in joyous ways that can be easily monitored behaviorally (Fig. 1). The urge to play was also not left to chance by evolution, but is built into the instinctual action apparatus of the mammalian brain. Indeed, such systems can even promote a joyous "laughter" in other species (Panksepp and Burgdorf, 2000). These are "experience expectant" systems that bring young animals to the

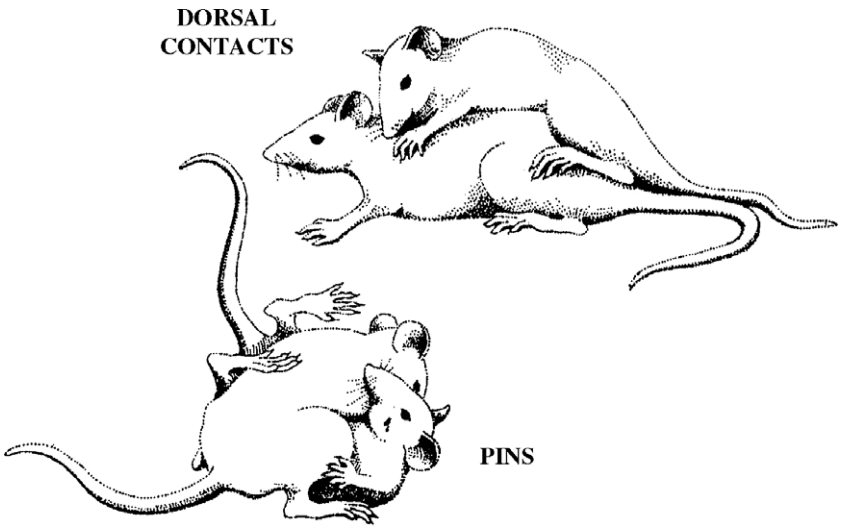

Fig. 1. Two major play postures that can be used to quantify endophenotypic behaviors of rough-and-tumble PLAY in rats (reprinted from *Affective Neuroscience* (Panksepp, 1998a), with the permission of Oxford University Press, Fig. 15.2 in the original).

perimeter of their social knowledge, to psychic places where they must pause to cognitively consider what they can or cannot do to others. Such social activities help program brain circuits essential for well-modulated social abilities, perhaps partly by activating genes that promote neuronal growth and emotional homeostasis. Children not allowed sufficient time to play may express such ancient urges in situations where they should not, thereby exhibiting symptoms of Attention Deficit Hyperactivity Disorders. Psychostimulants, which can help everyone to better attend to cognitive demands, are also strong anti-play drugs. Perhaps many of these kids would benefit from enhanced daily rations of rough-and-tumble activities.

5) FEAR: The world has abundant dangers some of which can arouse the major FEAR system of the brain. The system provokes freezing (Fig. 2) at low levels of arousal, and flight at higher levels (it is possible that the flight is precipitated by recruitment of the SEEKING system). Although stimuli that intrinsically provoke fearfulness may differ among species, the evolved core structure of aroused FEAR is similar across all mammalian species. Many other external stimuli gain access to this circuitry through learning — via cognitive–perceptual "high-roads" and more rapid, unconscious thalamic "low-roads" (LeDoux, 1996). However, it is the evolutionarily provided "Royal Road" – the unconditional FEAR circuitry that courses between the central amygdala to the periaqueductal gray of the midbrain – that concurrently controls the instinctual action apparatus and those deeply aversive feelings that intrinsically help animals avoid dangers (Panksepp, 2004c). It is more adaptive to feel anticipatory fear than to be attacked and harmed.
6) RAGE: Anger can be evoked by any of a variety of situations where there is stiff competition for resources. The RAGE system can be aroused by restraint, frustration and various other irritations, as well as directly by brain stimulation (Fig. 3). Anger is provoked when organisms do not get what they want. Just like every sub-neocortical emotional system, higher cortico-cognitive ones are able to provide inhibition, guidance, and other forms of emotional regulation. Adults can modulate their anger in ways that children and animals cannot. Individuals with frontal lobe damage exhibit more anger than those with intact brains (Berlin et al., 2004). We presently have no psychotropic medications that can specifically control pathological anger, but the neuroscientific analysis of RAGE circuitry has revealed neuropeptide controls, such as opioids and Substance P, which may eventually yield new pharmacological tools to facilitate such emotional self-regulation.
7) SEEKING: This remarkable system mediates all appetitive desire to find and harvest the fruits of the world. This dopamine facilitated SEEKING system energizes all our goal-directed urges and positive expectancies about the world (Fig. 4). Animals vigorously self-stimulate this system in addictive ways, and the neural substrates are critical for humans and other animals to obsessively self-administer all varieties of addictive drugs and to crave more and more. The underlying system is the one that mediates our intense appetitive motivation to obtain resources from the environment, and highlights how a basic state control system that mediates the primary process phenomenology of appetitive actions can readily link up with cognitive systems that mediate thoughtful awareness and appraisals (Ikemoto and Panksepp, 1999; Kapur, 2003).

Fig. 2. Endophenotypic freezing FEAR response to mild fear (reprinted from *Affective Neuroscience* (Panksepp, 1998a), with the permission of Oxford University Press, Fig. 11.2 in the original).

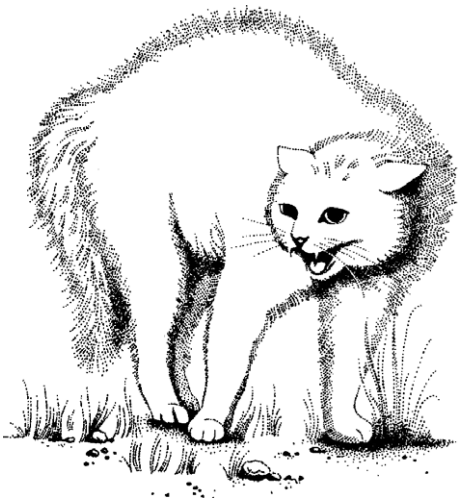

Fig. 3. Brain stimulation-induced defensive-RAGE behavior. Drawing adapted from a photograph by Walter Hess (reprinted from *Affective Neuroscience* (Panksepp, 1998a), with the permission of Oxford University Press, Fig. 10.9 in the original).

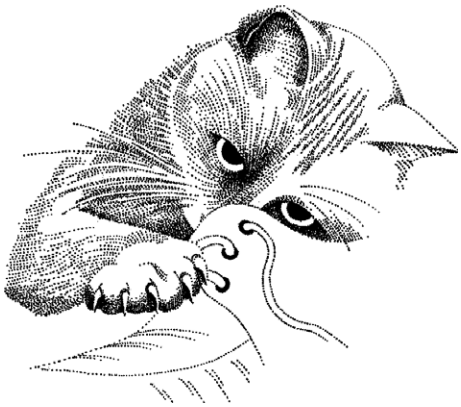

Fig. 4. The SEEKING system generates a host of investigatory–exploratory activities. This depicts a characteristic behavior that can be seen during arousal of this instinctual tendency in cats, where the system also mediates predatory intent (reprinted from *Affective Neuroscience* (Panksepp, 1998a), with the permission of Oxford University Press, Fig. 8.6 in the original).

5. Neuroscience summaries of emotion system characteristics and relations to psychiatric disorders

The underlying *dual-aspect monism* premise that motivates the current analysis is that core emotional feelings arise rather directly from the neurodynamics of these basic emotional systems (Panksepp, 2003). If so, we can begin to understand the neurologies and neurochemistries of basic affective processes by studying the emotional instinctual urges which are relatively easily studied in animal models. There is already a great deal of relevant evidence, and one approximate scheme of how these systems may relate to certain psychiatric disorders is summarized in Table 1.

A synoptic summary of the neuroanatomies and neurochemistries of these systems are summarized in Table 2. Global brain amine spritzers such as norepinepherine and serotonin are not included since the modulate all emotional and cognitive processes. Although they may nonspecifically regulate emotional arousal, there is no evidence that such systems are critical for the construction of the specific emotions noted earlier.

6. How can these systems can be studied in humans?

The problem with studying these systems in humans is that the neocortex tends to inhibit emotionality, in its role of helping cognitively parse the world and to relate affective events to real-world cognitive issues. Humans rarely act out their emotions with their instinctual action apparatus, but if the present hypothesis is on the right track, then the milder arousal of such systems in humans are critical for the way people feel. For instance, the strong modulation of separation distress by brain opioids in animals (Panksepp, 1981) has recently been identified as a vector in human sadness (Zubietta et al., 2003). Excessive or imbalanced activities of such basic emotional systems may be critical in engendering psychiatrically significant distress. Still, such imbalances cannot yet be monitored neurochemically, and for the time being, we must evaluate affective states using linguistic self-report tools.

To that end, we developed the Affective Neuroscience Personality Scale (Davis et al., 2003). Indeed, the three negative emotions on the scale (FEAR/anxiety, PANIC/separation distress, and RAGE/anger) factored together on a *negative affect* super-factor. Conversely, the three positive emotions

Table 1
Postulated relationships between basic emotional systems, common emotional processes, and major psychiatric disorders

Basic emotional system (Panksepp, 1998a)	Emergent emotions	Related emotional disorders
SEEKING (+ and −)	Interest	Obsessive compulsive
	Frustration	Paranoid schizophrenia
	Craving	Addictive personalities
RAGE (− and +)	Anger	Aggression
	Irritability	Psychopathic tendencies
	Contempt	Personality disorders
	Hatred	
FEAR (−)	Simple anxiety	Generalized anxiety disorders
	Worry	Phobias
	Psychic trauma	PTSD variants
PANIC (−)	Separation distress	Panic attacks
	Sadness	Pathological grief
	Guilt/shame	Depression
	Shyness	Agoraphobia
	Embarrassment	Social phobias, autism
PLAY (+)	Joy and glee	Mania
	Happy playfulness	ADHD
LUST (+ and −)	Erotic feelings	Fetishes
	Jealousy	Sexual addictions
CARE (+)	Nurturance	Dependency disorders
	Love	Autistic aloofness
	Attraction	Attachment disorders

The last two columns provide hypotheses of the major relationships. Obviously, multiple emotional influences contribute to each of the emergent emotions (e.g., jealousy is also tinged by separation distress and anger), and all the emotional disorders have multiple determinants. Plus and minus signs after each indicate major types of affective valence that each system can presumably generate (adapted from Panksepp, 2000). Capitalizations are used to designate the various emotional systems to highlight the fact that these are instantiated as distinct neural entities rather than simply psychological concepts. The essential neural components constitute command influences that coordinate the basic behavioral, physiological and psychological aspects of each emotional response.

Table 2
General summary of the key neuroanatomical and neurochemical factors that contribute to the construction of basic emotions within the mammalian brain

Basic emotional systems	Key brain areas	Key neuromodulators
General pos. motivation	Nucleus accumbens — VTA	Dopamine (+), Glutamate (+),
SEEKING/ expectancy	Mesolimbic and mesocortical outputs	Opioids (+), Neurotensin (+),
	Lateral hypothalamus — PAG	Many other Neuropeptides
RAGE/anger	Medial amygdala to Bed Nucleus of Stria Terminalis (BNST)	Substance P (+), ACh (+),
	Medial and glutamate (+) perifornical hypothalamic to PAG	
FEAR/anxiety	Central and lateral amygdala to medial hypothalamus and dorsal PAG CCK, alpha-MSH, NPY	Glutamate (+), DBI, CRH
LUST/ sexuality	Cortico-medial amygdala, Bed Nucleus Stria Terminalis (BNST)	Steroids (+), Vasopressin, and
	Preoptic hypothalamus, VMH, PAG	Oxytocin, LH-RH, CCK
CARE/ nurturance	Anterior cingulate, BNST	Oxytocin (+), Prolactin (+)
	Preoptic area, VTA, PAG	Dopamine (+), Opioids (+/−)
PANIC/ separation distress	Anterior cingulate, BNST and preoptic area	Opioids (−), Oxytocin (−)
	Dorsomedial thalamus, PAG	Prolactin (−), CRF (+), Glutamate (+)
PLAY/joy	Dorso-medial diencephalon	Opioids (+/−), Glutamate (+)
	Parafascicular area, PAG	ACh (+), TRH?

The monoamines serotonin and norepinephrine are not indicated since they participate in non-specific ways in all emotions. The higher cortical zones devoted to emotionality, mostly in frontal, cingulate, insular, and temporal areas, are not indicated. Key: CCK = choleocystokinin, CRF = corticotrophin releasing factor, DBI = diazepam binding inhibitor, ACh = acetylcholine, MSH = Melanocyte Stimulating Hormone, NPY = Neuropeptide Y. − inhibits prototype, + activates prototype (data adapted from Panksepp, 1998a and Watt, 1999).

(SEEKING/interest, CARE/nurturance, and PLAY/joy) loaded on a *positive affect* super-factor. There is already data that some of these emotional traits can be linked to human single nucleotide polymorphisms (Reuter et al., submitted for publication), but a great deal more work is needed to evaluate such linkages. In addition to such *trait* scales of emotional strengths and weaknesses, the corresponding *state* variables also need attention, especially as a function of various environmental and neurochemical challenges.

It is also important to try to develop more direct behavioral measures of emotional endophenotypes, but one can only suggest potentially promising approaches along those lines. For instance, for fearfulness, one could monitor potentiated startle responses, which are easily implemented at behavioral levels (Lang, 1995). One could envision that bodily postures and facial expressions, along with autonomic measures, in structured dyadic interactions as well as when individuals are exposed to potential emotional stimuli of various sorts might yield good indicators (Levenson, 2003). Measurement of prosodic voice quality should be a promising line of inquiry (Knutson et al., 2002). Unfortunately, the bottom line right now is that such measures, except for potentiated startle, are not sufficiently well standardized for routine use. Thus, these approaches need extensive research before they could be linked to the relevant genetic and neuroscience research. Indeed, it is hard to imagine how the sensitivity and responsivity of the distinct emotional processes in humans could be linked routinely to the analysis of the sub-neocortical emotional operating systems that have been so well studied in animals (Panksepp, 1998a, 2005).

Despite great advances in human brain imaging, there are yet no routine direct brain measures of affective states in the brain. At present it appears that PET approaches may yield more robust and clear differential affective signals than fMRI, and the locus of affective controls appears to be largely sub-neocortical (Damasio et al., 2000; Liotti and Panksepp, 2004). On the other hand, because of its temporal resolution characteristics, fMRI is better suited to envision emotional information processing in the brain (Murphy et al., 2003; Phan et al., 2002). Also, EEG measures provide a more direct estimate of neural activities, and it may be recruited to analyze higher brain substrates of emotionality (Lewis, in press) but it seems that surface recordings are rather far from affect source generators in sub-neocortical regions of the brain, which will require more signal processing than has yet yielded compelling routine measure of the discrete emotions (Panksepp, 2000).

For the time being, the most likely routine approaches will be the development of new emotion scales, perhaps open-ended narrative approaches, such as the Levels of Emotional Awareness Scales (LEAS) developed by Lane and colleagues (1990), may be especially useful. They could allow each of the basic emotions to be evaluated in the context of more cognitive responses that people generate to prototypic emotional situations. Such scales also need to be studied in the context of depth-psychological approaches where one evaluates manipulation of the various neurochemical factors (Table 2) that have been revealed through animal research (Panksepp, 1999).

7. How animal research assists us in understanding these systems

In contrast to the difficulty of evaluating the status of these systems in humans, it is considerably easier to study them systematically in animal models. We can place electrodes directly into the trajectories of these systems, and monitor circuit sensitivities by determining how much current is needed to activate emotional responses, and how various environmental challenges modify those sensitivities.

Likewise, there is the reverse-engineering approach of knockout animals. There are now a large number of lines available that have characteristic emotional strengths and weaknesses (Crawley, 2000). In breeding experiments, we can select animals for a large number of emotional traits, even though it is hard to track down the allelic patterns that mediate the selection effects. Also, we can genetically "type" animals and observe how their brains' gene expression patterns change in response to archetypal emotional challenges (Kroes et al., 2006; Panksepp et al., 2002b).

Thus, assuming that the genetic controls of basic emotional systems are remarkably similar in all mammals, the animal models provide a host of candidate genes that then can be evaluated in human psychiatric populations. For instance, we already know that allelic variants that lead to anxiety, aggression, and social insecurities seem to be similar in mice, monkeys and men (Crawley, 2000). However, research in this field is just beginning to blossom. Unfortunately, one of the most interesting aspects of the genetic controls – how gene expression profiles in the brain responds to emotional environmental challenges – can only be studied in animals. Such techniques require brain samples, often from precise sub-regions of the brain. Thus, some of the most interesting endophenotypic changes simply cannot be easily harvested in humans, highlighting how essential it is to integrate the animal and human work to make optimal progress on the most interesting variables in such analyses.

8. The future of evolutionary psychiatry

Evolutionary Psychiatry is motivating investigators of the human mind to consider the ancient cross-mammalian foundational principles of the mental apparatus. Most scholars are beginning to concede the existence of a core human psyche that is largely a product of biological evolution (specifically a result of natural selection). However, there has been little consensus on what criteria should constitute an adequate weight of evidence for identifying evolutionary adaptations. Thus, understanding precisely how various evolutionary perspectives fit into a comprehensive framework for studying the human brain and mind remains a major challenge for evolutionary psychiatry. So far, rigorous neurobiological and genetic evidence have not been among the standard criteria for hypothesis generation. There needs to be less simplistic talk about "modules" that is still common in evolutionary psychology, and more psychobiological work with the relevant brain systems. Obviously, there are many specialized systems in our brains, especially within the sub-neocortical foundations, but they are networks of interacting circuits and not

encapsulated "modules." As long as the interests of evolutionary psychologists remain riveted on the higher brain systems that may be unique to humans, they will probably continue to ignore the most important evolutionary adaptations on which our minds are built — ranging from homeostatic systems, to attentional, emotional, and motivational ones (Panksepp and Panksepp, 2000).

Evolutionary psychiatrists are beginning to agree that much of human mental activity is driven by the ancient affective emotional and motivational brain systems shared with other animals (Gardner and Wilson, 2004). The most productive findings will emerge when we begin 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. Evolutionary psychiatry will benefit immensely from a rigorous analysis of the neurobiological underpinnings of basic psychological traits. Most of this work must be done using animal models.

Identifying homologous brain emotional functions will help us understand how mental differences between individuals and species are associated with differences in brain structure, connectivity, neurochemistry, patterns of neuronal activation and analysis of DNA polymorphisms and RNA expression patterns. However, such levels of organization will be difficult to translate to human research. Still, such interdisciplinary paradigms can be facilitated by promoting two general strategies: (i) investing in carefully selected animal models of basic behavior patterns that can also be studied in terms of human psychological constructs and (ii) taking these phases of investigation into the realm of modern neurochemistry and molecular biology. Such approaches can extend the scope of evolutionary psychiatry to include levels of organization essential for understanding the evolution of the emotional and motivational foundations of the mental apparatus. Ultimately the importance of such approaches for evolutionary psychiatry can be directly evaluated by the development of increasingly specialized pharmacological therapies for treating psychiatric disorders (Panksepp and Harro, 2004).

9. From brain molecules to mind medicines

The most likely place where the evolutionary functions of the brain and mind will find 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 neuroscience techniques, and the underlying neurochemical systems can be linked directly to genetic issues. 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 more likely to be fruitful than what can be achieved through a study of the information *channel functions* of the brain (which presumably mediate the epigenetically divergent individual differences that are abundant in all species). In pursuing such neuroevolutionary psychobiological understanding of the basic substrates for mentality, shared by all mammals, new therapeutic principles may be discovered that can herald new and more subtle generations of interventions in biological psychiatry. Future mind medicines may be quite specific to more discrete emotional traits, and may work optimally in the context of therapeutic environments that enhance emotional education (Panksepp and Harro, 2004).

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. With the advent of tools for the analysis of gene expression, especially microrarray 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 (Panksepp et al., 2002b). Such approaches will promote emergence of powerful neurobiological foundation for evolutionary psychiatric thought.

10. Conclusions

The appeal of evolutionary theory in modern psychiatry is that diseases of the brain/mind have an organic basis that can be identified, characterized, and medical interventions can be developed based on basic chemical, physical, and biological processes. The emergent properties of large brain ensembles, such as basic affective states emerging from emotional action systems, can be characterized as etiological agents that interact with environments and biological features of brains and bodies. The reason this type of evolutionary dual-aspect monism strategy has not been more widely entertained in the brain/mind sciences is because the sub-neocortical emotional systems in humans are not as open to causal inquiries as they are in other mammals.

Likewise, emotional experience and its linkage to cognitive processes is bound to figure prominently in a coherent evolutionary psychiatry. From this perspective, consciousness and affective experience may have arisen concurrently in neural evolution as ways to elaborate and extend the potential reach of instinctual urges to generate adaptive responses to the environment. In a sense, the raw evolutionary function of affect is to rapidly encode life sustaining and life detracting features of the world, and to promote adaptive instinctual responses as a first-line of defense to such challenges. More recent levels of cortico-cognitive information processing – the parsing of the world into increasingly detailed and well resolved perceptions along with the resulting emotional *awareness* – serve to increase behavioral flexibility. Cognitions promote the ability of organisms to learn how the instinctual adaptive responses can be refined, as indexed by affective changes. Indeed, it is possible the behaviorist concept of "reinforcement" is intimately intertwined with the neural nature of affective processes that allow animals to efficiently pursue goals essential for survival (Panksepp, 2005).

In conclusion, relevant lessons from the history of science suggest that: (i) we must build new fields of scientific inquiry using the robust tools that already exist in related disciplines and from such approaches, emergent, testable ideas can be expected. (ii) If we are willing to embrace evolutionary theory and neurobiological models of endophenotypic brain traits that lead to psychiatric disease, then there must be a decipherable genetic basis for the fundamental aspects of both the normal and psychically imbalanced mental apparatus. (iii) Many of the foundational aspects and constituents of human consciousness, and its disturbances, are likely to be present, homologously, in animals other than humans (while many additional mental capacities have arisen from more recent cortico-cognitive developments that vary more dramatically across mammalian species). (iv) Finally, the use of animal models to help clarify the foundational nature of human mind using the tools of neuroscience and molecular biology can be fruitfully undertaken. With the development and maturation of such integrative approaches, a more thorough understanding of the natural fracture lines of human mind and behavior will emerge.

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