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Review

Neuroevolutionary sources of laughter and social joy: Modeling primal human laughter in laboratory rats

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Abstract

Rats make abundant 50 kHz ultrasonic vocalizations (USVs) when they play and exhibit other positive social interactions. This response can be dramatically increased by tickling animals, especially when directed toward bodily areas toward which animals direct their own play solicitations (e.g., nape of the neck). The analysis of this system indicates that the response largely occurs in positive, playful social situations, and may index willingness for social engagement, similar to human infantile laughter, which may mature into productive adult socio-sexual behaviors. There are now enough formal similarities between rat 50 kHz USVs and human laughter, to realistically hypothesize that they are neurally and functionally homologous at the subcortical level of brain organization. To help contrast this behavior with human laughter, the available evidence concerning neural organization of human laughter is summarized from brain imaging and neuropsychological perspectives. Thus, a study of 50 kHz USVs in rats may offer an animal model for studying some of the fundamental properties of laughter circuitry in humans, and the brain mechanisms that facilitate positive social engagement, in the mammalian brain. It is proposed that further study of this phenomenon may provide a theoretical as well as empirical handle on the sources of social joy within the mammalian brain.

Keywords: Play; Separation distress; 50 kHz USVs; Tickling; Joy

Contents

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Joy & Woe are woven fine,
A Clothing for the Soul divine;
Under every grief & pine
Runs a joy with silken twine.
William Blake, *Auguries of Innocence*

Behavioral science has traditionally denied or ignored the possibility that animals are capable of experiencing emotions, not to mention feelings as subtle as joy and woe. Some investigators who still subscribe to an extreme variant of neural reductionism (i.e., that psychological analysis is irrelevant in a causal neural analysis) believe that even if humans have such experiences, they may not be causally effective in controlling behavior. The idea that feelings may control animal behaviors is still commonly deemed to be an unacceptable proposition (for synopsis, see [76]), since there is presumably no conceivable way such states could do neural work (i.e., how can an immaterial mind process modify neuronal activity). Of course the solution to this dilemma is straightforward. If one assumes that basic psychological processes are isomorphic with certain brain network properties, there is no casual dilemma. One only needs to recognize, following a *dual-aspect monism* strategy that certain large-scale network activities generate psychological properties. From this perspective, affect-free notions of how brains generate adaptive behaviors may be deemed incomplete. Indeed, radical neural reductionism could be deemed flawed if it does not adequately consider that one function of complex neural circuits may be to generate feelings that control behavior. Even though serious discussion of such topics has barely started in behavioral neuroscience, it is possible that poorly understood brain functions such as reinforcements and incentives, easy to define operationally by external observable events, are actually instantiated by brain mechanisms that generate various subjectively experienced feelings of goodness and badness.

Affective experiences, constructed by brain dynamics, may guide many of the behavioral choices of humans and other animals. In other words, many of the neuropsychological processes behind the psychologically neutral concept of "reinforcement" may be affective. Because of advances in neuroscience, this is now a realistic neuroscientific option for behavioral scientists to consider. Here I will pursue the idea that animals are evolutionarily designed to pursue "comfort zones" and to avoid "discomfort zones" which reflect affectively coded states of the brain that index how well animals are faring in the pursuit of survival. After briefly considering the brain substrates of the grief response (woe?), that have so far been clarified best through the use of animal models that have studied separation-distress vocalizations [64,69,74,89,91], I will consider how we could illuminate the nature of social joy by studying of vocal signals of positive affect in rats (i.e., high frequency ~50 kHz ultrasonic calls, which can vary considerably in shape and exact frequency profiles; for detailed summaries of empirical data, see [19,21]).

If, in fact, the behavioral urges of mammalian brains are organized around affective issues, we need an open discussion of what it means, in neural terms, for animal and human brains to have affective experiences. This topic becomes especially important since many psychiatric disorders in humans reflect dysregulations of emotional systems [75], and potentially no deep understanding of such brain functions in humans can be achieved until we clarify how homologous affective processes are elaborated in the brains of other mammals [70,76]. For instance, the evidence from many brain vocalization mapping studies is that the instinctual neural circuits for emotional vocalizations are situated in deep and ancient subcortical regions of the brain (for summaries, see [65]). Several mapping studies of the neural substrates from our lab – in guinea pigs [42] and domestic chicks [6] – remain to be published. Animals are typically not neutral about such artificially induced brain activations. Brain sites that yield distress-type vocalizations typically motivate animals to turn off the stimulation, and sites that yield positive vocalizations sustain self-stimulation behavior [21,47–49].

From the above perspective, it should come as no surprise that the trajectory of the separation-distress vocalization system [42,74] highlights the subcortical circuitry that mediates human sadness as estimated with PET imaging [30]. Further, one of the main neurochemical systems that reduces arousal of this circuitry, namely brain opioids that activate *mu* receptors [43,69,86,87,92] exhibit diminished activity during human sadness [117]. Other examples like this from the study of sensory pleasures (e.g., [95]) provide evidence that the basic affects in humans and other mammals arise, in part, from the same primordial brain mechanisms [31,70,76]. The amount of work on the separation-distress system is now quite large (see [65,70] as well as Newman's contribution to this issue). By comparison the study of playful–joyful vocalizations has only recently started [79], and I will summarize the substantial progress that has been made on this topic (also see [19,21]). For another recent summary of USV work in rodents, see [27].

Thus, here I will focus on one of the least explored topics in behavioral neuroscience—the possibility that our most commonly used animal subjects, laboratory rodents, may have social-joy type experiences during their playful activities and that an important communicative-affective component of that process, which invigorates social engagement, is a primordial form of laughter. In a search for cross-species homologies, I will also cover the emerging brain imaging literature on laughing mechanisms of the human brain, but mainly I will be asking: can the study of 50 kHz ultrasonic vocalizations (USVs, also designated here as "chirping") of tickled rats tell us anything scientifically useful about the origins of human laughter?

Thus the main aims of this essay will be five fold: (1) a discussion of the possibility that raw affective experience is a "real" mind-brain function in all mammals, and how we could make scientific progress on such difficult topics using a *dual-aspect monism* strategy; (2) a brief focus on the empirical findings on "rat laughter" that we have harvested, largely through the rather single-minded (and unfunded) decade-long laboratory efforts of Jeff Burgdorf and myself; (3) a brief discussion of neuropsychological homologies among mammalian species; (4) a summary of relevant human data, largely from neuropsychological brain-damage studies and the pseudo-color fruits of functional brain imaging; (5) closing with a discussion of the implications of this kind of work for enhancing behavioral neuroscience strate-

gies to understand the sources of human affective experience so as to yield new perspective for advancing basic knowledge in biological psychiatry.

My first goal is most difficult and controversial—to further clarify why the time may finally be ripe, because of our advances in evolutionary, neurochemical and other neuroscientific knowledge, for behavioral scientists to again openly consider the possibility that other animals do have emotional feelings as well as other affective processes (e.g., sensory affects such as pleasant and unpleasant tastes, as well as homeostatic/regulatory ones such as hunger and thirst) – states of the brain-mind that do help regulate their behavior. As already noted, the classic problem of how a supposedly immaterial process such as mind could control either human or animal behavior is easily solved through the realization that what has traditionally been called mind is, in fact, a reflection of complex neural network properties rather than something that is independent of neural function. This, of course, is a well-accepted tenet in human cognitive neuroscience, but the idea has barely penetrated epistemological and ontological discussions in modern behavioral neuroscience.

1. An affective view of brain functions in human animals

Among the greatest mysteries of human life are the emotional "energies" that captivate humans in webs of affective experiences that regulate their behavior. When we are in the throes of basic negative affective feelings (FEAR—anxiety, RAGE—anger, PANIC—grief–sadness), and their mental expansions – with the emergence of jealousy, shame, guilt – our cognitive resources are automatically channeled into obsessive grooves of ruminative reflections that powerfully influence our behavior in many directions, from retributions to abject apologies. (I use capitalizations for basic emotional system to highlight that specific neural systems are necessary for certain emotions, although these "parts" are certainly not envisioned as complete explanations of the "wholes" of either human or animal affective experiences). For details of such issues and systems, see [70,76].

When we experience primary-process positive emotions (the SEEKING of expectant-desire, CARE—nurturance, LUSTy—erotic feelings, and PLAYful—joy) our minds have broadened thoughts and cognitive associations. In affectively positive frames of mind, we are more likely to engage in abundant friendly interactions, from joking around to more penetrating social intercourse [32,98,99]. When these emotional energies combine with each other in various ways, as well as with the diversity of life experiences, various secondary (more cognitive) feelings, such as jealousy and shame, may emerge. Obviously humans, because of their symbolic–linguistic competence, are also able to have tertiary affective experiences, arising from our ability to have thoughts about thoughts (territory that simply cannot be addressed in any animal models). In any event, primary-process affective feelings may help control the behaviors of many other animals, but it has been traditionally difficult to comprehend how a seemingly insubstantial process such as experience (i.e., "mind stuff") can control behavior. To reiterate, since this is a key point, all that is needed to envision how psychological experiences participate in behavioral equations is to recognize the possibility that certain large-scale neural network functions create experienced value representations within the brain—diverse affective feelings (i.e., various types of reward and punishments) that help guide learning as well as more cognitive action plans to avoid various "discomforts" and to optimally achieve the various "comfort zones" of life. Many non-behaviorists believe this is a very sensible way to view animal life on earth. With modern neuroscience, affective concepts can finally be neurally defined in non-circular ways, and such long-neglected approaches to behavioral control can finally be empirically evaluated.

Behavioral neuroscience can finally clarify how the experienced emotional side of life, with its valuation of existence, actually arises from neural dynamics. Indeed, since the emergence of functional brain imaging technologies, these kinds of questions are being increasingly addressed in human social neuroscience research [40]. However, those technologies mainly provide rough neural correlates – regions of interest – that need to be understood in some detail before we have any deep knowledge about human and animal affective experiences. A more powerful way to get at the details of such neural systems is through affective and behavioral neuroscience strategies applied to the neurodynamics (i.e., large-scale measures of brain network activities) of our fellow animals. Interdisciplinary devotion to conceptualize animal brain functions in this way and to seek epistemological bridges to affective concerns of humans has barely begun. This is partly because of the continuing heavy weight of 20th century positivism that aspired to liberate the study of animal behavior from the shackles of subjective ambiguities.

However, brain-mind science has finally advanced to a point where remarkably fruitful bridges between basic human emotional experiences, and the corresponding neural substrates for primary process emotional behaviors and affective states can be studied in animal models. Such detailed neuroscientific inquiries can clarify the mechanisms, the neural nature, of affect. The once seemingly un-crossable chasm between rigorous behavioral analysis and the nature of primary-process brain experiential functions can finally be bridged. However, this can only be effected if one is willing to entertain that certain basic experiences (e.g., affective feelings which are completely neuronal) also guide behavioral choices in "lowly" mammals that can effectively be studied in behavioral neuroscience laboratories.

Here I will try to flesh out our working hypothesis that the common laboratory rat may in fact exhibit a laughter-type of vocalization which may be used to index their social joy [79], and which may also be used as a conditioned-instinctual indicator of expectancy/desire [52]. One of the side-benefits of studying this emotional response is that it might be especially useful for monitoring incentive salience, and hence drug craving, using spontaneously conditioned-instinctual behaviors as opposed to traditional, arbitrary operants such as lever presses [84,88]. Using this strategy, we can clarify the evolutionary sources of many other basic affective urges and feelings of the human mind by studying homologous emotional circuits in the brains of other

mammals [70,76]. As this type of theoretical view becomes more acceptable in behavioral neuroscience, we may develop new and rigorous scientific ways to envision psychological brain function that regulate behavioral dynamics. If so, the widespread belief that the scientific study of raw emotional experience in other animals is outside the realm of credible scientific inquiry should no longer be accepted as dogma. Advances in neuroscience have changed the ways we can conceptualize and analyze such issues.

Our own work in this area goes back to our analysis of brain mechanisms of separation-distress induced crying in other animals, originally conceived as a major source of experienced grief and sadness in humans [69]. Although this type of scientific-anthropormorphism has been vigorously challenged [10], it has been equally vigorously defended [74]. More recently we have advanced the idea that through the study of the brain mechanisms of playfulness in other animals, we may be able to decode a major source of positive social affect [19,77,90]. In this article, I will focus on our most extreme exemplar of this ontological–epistemological strategy: on the basis of abundant data, we have now narrowed the complexities of social play behavior down to a more easily analyzed vocal indicator of social joy, namely 50 kHz ultrasonic *chirps*, which are especially abundant during natural play (and tickling) of juvenile rats [50,77,78]. We believe the evidence supports the provisional conclusion that these *chirping* "laughter-type" of USVs do have some kind of ancestral relationship to childhood laughter that is also so prevalent during the play of our own species [101].

This radical assertion does require some explicit qualifications, especially the recognition that obviously nothing within the brain-mind is "identical" across species, except perhaps the structure of many shared neurochemicals. Diversity is a pervasive characteristic of life, and when one seeks cross-species understanding by pointing toward homologies, one can only be seeking *general principles* of operation. One can only be pursuing the evolutionary hope that clarification of processes in animal models, where the necessary neuroscientific work can be done, will at least partly highlight neurobiological aspects of human brain-mind function that cannot be approached with comparable rigor through the study of our own species. Of course, in considering evolutionary homologies, one can never neglect the possibility that one is dealing with surface analogies, which motivated my discussion of the brain substrates of human laughter at the end of this paper.

2. On the discovery of rat "laughter"

I will use the straightforward descriptor "rat laughter" in this paper for the 50 kHz ultrasonic "chirping" type vocalizations that are so readily observed during the rough-and-tumble play of juvenile rats. This vocalization is dramatically amplified by "tickling" rats with playfully dynamic and friendly sequences of hand play, which mimic the rough-and-tumble play of animals. A more behaviorally neutral descriptor for our tickling procedure might be Heterospecific Hand Play, but I will use the vernacular term "tickling" for efficiency. For this maneuver to work well, one must be adept at performing dynamic forms of inter-species interactions. With some modest training, most investigators can readily acquire the skill—it is rather similar to the dynamic hand and finger movements that one might use in tickling young human children, who can be provoked into flurries of playfulness and peals of laughter by this simple maneuver. However, I have visited several laboratories where investigators have had difficulty observing this response, although I have had no trouble obtaining the response in their animals and training the staff to tickle well, in a standardized (but hard to manualize) way. Only where labs have predators (e.g., cats) housed nearby or where animals are frequently punished (fear learning), and abundant stress odors pervade a lab, is the maneuver much less effective. This fact [77] indicates that it is not simply the physical stimulation that is essential for the response, but also an environment in which animals feel comfortable and safe.

We first discovered play-induced 50-kHz chirping when Brian Knutson came to do post-doctoral work in our laboratory in the mid 1990s. He auspiciously chose to pursue the existence of play vocalizations in rats, premised on our earlier observation that deafening young rats did mildly reduce play in rats [105]. On the day after our ultrasonic recording equipment arrived, Brian discovered that the playing-field was full 50-kHz chirping while juvenile rats indulged in their rough and tumble activities, and this vocalization became conditioned to the play chamber so that animals would also chirp in anticipation of play [50]. We first chose to focus on the idea that this vocalization may be a general measure of anticipatory, expectancy-type eagerness (namely arousal of the DA-invigorated SEEKING urge in animals). Reasonably good support for this thesis was obtained [52], but the evidence is now even more robust for a more specific social-reward hypothesis.

Chirping is not a very robust measure of anticipation in rapidly paced classical conditioning paradigms with short conditioned stimuli. Namely cues that predict small pieces of food are not especially effective in provoking chirping (abundant unpublished work in our lab, where clear signals were never found). However, if one makes the situation ecologically more realistic, namely provides an extended cue for a major anticipated feasting event, such as the signal for a forthcoming once-daily meal, there is abundant chirping during that predictive cue; scalloped anticipatory chirping also emerges when one provides rewarding brain stimulation on a free fixed-interval schedule [17]. The chirping readily conditions to environmental context where animals received rewarding drugs [51]. Conversely, elevated 22 kHz ultrasonic "complaints" are evident in contexts where animals had received aversive drugs [16].

Although contextually conditioned 50 and 22 kHz USVs can certainly be used as respective indicators of positive and negative valence changes induced by various drugs, the critical question is the natural functionality of this response in brain evolution. We now believe that the 50 kHz chirps most clearly serve to signal sustained readiness for positive social engagement. This helps explain why it is higher during play than any other social activity, even though abundant levels are also present during the appetitive phase of adult sexual activity [56] and some are emitted during aggressive encounters, but typically only just prior to the first serious fight. The existence of this response in agonistic situations may also highlight the fact that positive affect

sounds may help diffuse the tension in confrontational situations by implicitly sending messages along the lines that "I am friendly; I am not here to fight with you". A similar rationale might be offered for the observations of the chirping that is common when animals enter new environments and encounter new animals [14]. Thus, the modest chirping responses in novel and aggressive situations may have survival value by regulating or limiting conflict. Nervous laughter may serve a similar function in highly social creatures such as humans.

How did we come upon the idea that the chirpy sound of rats may have a class resemblance to laughter in humans? Having just concluded perhaps the first formal (i.e., well-controlled) ethological analysis of rough-and-tumble play in the humans species in the late 1990s, where laughter was an abundant response (i.e., [101]), I had the "insight" (perhaps delusion) that our 50 kHz chirping response in playing rats might have some ancestral relationship to human laughter. The morning after, I came to the lab, and asked Jeff Burgdorf, my undergraduate assistant at the time, to "come tickle some rats with me." We promptly discovered how powerfully and reliably "hand play" could provoke the chirping response, indeed considerably more abundantly than any condition we had yet encountered. We systematically characterized this response as a function of development, as a function of various environmental stimuli-hunger, bright light, cat smell, all of which diminished chirping even though somatosensory stimulation was kept as constant [77]. The body region that seems most sensitive to tickling is the nape area where animals normally target their own play activities [70,79], and which, when anesthetized, can dramatically reduce certain indices of play such as pinning [105].

The tickle response of rats declines more slowly than their tendency to play spontaneously, but there is an eventual decline in young adulthood. It is hard to evoke tickle induced chirping in adult animals, unless they have been tickled abundantly when young. Adult females are generally more receptive to tickling than males. The tickle response appears to generate social bonding, since animals will seek out hands that have tickled them much more than hands that have only petted them an equal amount of time. Generally, the animals that exhibited the most robust tickle response, also tended to be the most playful. After collecting the above data, and demonstrating that it exhibited robust contextual and classical conditioning, we submitted our first article to *Nature*. The resulting mixed reviews (the more critical one that torpedoed the submission asserted that "Even if this phenomenon is true, you would never be able to convince your colleagues."), led us to publish our first report elsewhere [77]. In that article, we chose to provide a historical framing of why it is so difficult for this type of research to be accepted, perhaps even acknowledged, by a positivisticallly oriented neuroscientific community. In any event, we persisted in analyzing this fascinating phenomenon, on our own dime so to speak, and the evidence suggests that this response has many of the characteristics of primary-process human laughter.

In our first peer-reviewed paper, published in this journal, we further characterized the chirping response [78]. We demonstrated how individual housing (social hunger?) was critically important for obtaining the response, and found that it took surprising long, about 48 h of isolation, to fully engage this motivational system. We evaluated the ability of tickling to motivate instrumental approach behavior, as well as contextual and more standard classical conditioning of the response. We were also surprised to find that the motivation for tickling did not extinguish in the expected way. Indeed, animals that were repeatedly presented with a now passive hand that had previously tickled them, would begin to nip on the fingers (probably social-solictation play-bites), and this response increased, rather than decreased (!) across three successive extinction days. How would classic reinforcement principles explain that, except as a gradually incrementing frustration response? We also shared our preliminary work on selective breeding for the 50 kHz USV response (a project first described in [80]) which was eventually extended in a replicate series [20] since our initial lines had died off in a laboratory fiasco. We also did a preliminary scan of pharmacological modulation of the response, finding only modest elevations of the contextually conditioned chirping with amphetamine (1 mg/kg) and reductions of both conditioned and unconditioned responses with the glutamate receptor blocker MK-801 (0.25 mg/kg). Morphine and naloxone had little effect (except in more subtle tests used later [18]), nor did antimuscarinics (scopolamine at 1 mg/kg), haloperidol (0.25 mg/kg); likewise, serotonergic facilitation with quipazine (1 mg/kg) and blockade with cyproheptadine (1 mg/kg) yielded no significant effects. In other words tickle-induced chirping was quite resistant to biogenic amine, cholinergic and opioid modulation.

We subsequently demonstrated that ticking could be used as a reward for the acquisition of lever-press responding [18], and that the contextually-conditioned response sensitized to repeated administration of play-reducing doses of methylphenidate [81]. It is now clear that this response systems is intimately related to the mesolimbic dopamine energized brain "reward" system [15,19,21], and that one can easily evoke many 50 kHz USVs by direct administration of amphetamine into the ventral striatum, especially the most rewarding zones of the accumbens shell [15,110]. As noted earlier, we believe 50 kHz USVs can be used as valence or affective "self" report measures for drug cravings, and hence may be a "natural" indicator of the abuse potential of drugs [84,88].

In sum, so far the evidence strongly suggests rat chirping is evolutionarily related to the joyful laughter of our own species [19,72,79]. Since humans gravitate toward laughter, we were pleased to find that young rats, given a choice between an adult who still spontaneously chirped a lot and one that did not, spent substantially more time with the apparently happier adults [79].

We realize that the "laughter" interpretation of this response is a major conceptual challenge for many in the field of behavioral neuroscience, but we encourage behaviorally oriented investigators to have open minds about such issues. We have tried to negate our view over and over, and have failed to do so. Accordingly, we feel justified in cautiously advancing and empirically cultivating the theoretical possibility that there is some kind of an ancestral relationship between the playful chirps of juvenile rats and primary-process infantile human laughter. This hypothesis has caused great consternation for many colleagues in the behavioral neuroscience community; they see no reason for any-

one to go so far out on the ontological limb. Several colleagues have discouraged this kind of theorizing, suggesting that this is fundamentally inappropriate, even embarrassing, for members of our discipline to speak about animal brain functions in such blatantly anthropomorphic ways [10,74]. We, on the other hand, think that the traditional conceptual conservatism in our field, which served us well before the advent of modern functional neuroscience, may now be impeding progress since it may not be envisioning certain evolutionarily reasonable survival adaptations (i.e., network properties that generate mental states). From this vantage, the prevailing preference for a extreme neural reductionism may be misguided.

It is certainly reasonable to consider that ancient forms of affective experience, shared by all mammals, do serve a functional role in the guidance of animal behavior. Anthropomorphism can be a valid and productive concept if the underlying mechanisms for a psychobehavioral process are homologous across mammalian species. Thus, the time may be ripe to empirically cultivate, more vigorously than ever before, the possibility that our studies of animal brain–behavior relationships have a real possibility of clarifying basic affective processes of the human species. I believe such studies can clarify brain-mind issues of first-rate importance for biological psychiatry [75,76].

3. Primary-process neuro-mental homologies across mammalian species

The above findings could help reverse the long-standing silence that has pervaded functional discussions in behavioral neuroscience ever since Jacques Loeb and his protégés John Watson and B.F. Skinner, brought us the methodological rigor and ontological mischief of "never-mind" behaviorism. Through their pervasive influence on 20th century physiological psychology and then behavioral neuroscience, the sensible early concept that rewards were fundamentally affective (i.e., the original Thorndikian [111] "Law of Affect" which relied on concepts such as "satisfactions" and "discomforts") was discarded. It was replaced with the non-affective, phlogiston-like concepts of *reinforcement* theory [76]. It is now time to evaluate whether the functional relationship between the neurology of basic instinctual emotional behaviors and primary-process affective states is empirically productive. Are there deep neuropsychological homologies across all mammalian species?

There is little doubt among neurogeneticists, neuroanatomists, neurochemists and neurophysiologists that basic neurophysiological mechanisms are remarkably similar in all mammals, and that many of the functional controls can be traced much further down in phylogeny (e.g., just consider Eric Kandel's seminal work on the learning and memory mechanisms of the Aplysia). In accepting this as a valid general statement of the empirically established state of knowledge in the field, no one would deny that such underlying cross-species principles – such neuro-mechanistic ancestral homologies – may also have yielded a kaleidoscopic variety of distinct forms through the evolutionary diversifications. Indeed, there will always be massive diversity in the fine details of brain structures and functions across species as well as different individuals of a single species. Thus, the evolutionary and epigenetic refinements of global brain functions that control behavioral and psychological tendencies might be so vast as to reduce, toward the vanishing point, any useful functional translations across species. I doubt if anyone in the present era would wish to be that skeptical, for then the practical utility of our work would indeed be rather modest and of little value for helping solve human problems. Thus, the question that needs to be evaluated is whether there are *basic* neuropsychological homologies in the primary-process emotional operating systems of mammals. It is time to openly consider whether animal models of emotionality can be used to shed some light on subtle mental issues such as the nature of affects, without necessarily worrying about the associated cognitions, a much more difficult problem that concerns human mind-scientists most. I think we now have the epistemological strength to clarify more primitive functions like homeostatic, sensory, and emotional affects [31,70].

Because of the potential psychiatric importance of such translational research [75], I have advocated that certain basic affective states are reflections of the instinctual brain mechanisms that can be objectively studied by analyzing various unconditioned emotional and motivational behaviors of other organisms. This has led me to accept, as a guiding paradigm, the *dual-aspect monism* strategy, where the working hypothesis is that the brain mechanisms that generate instinctual emotional behaviors generate the corresponding affects, e.g., rage behaviors (as evoked by stimulus bound affective attack [70]) are of critical importance for the generation of angry feelings. Because of advances in psychopharmacology, based on homologous neurochemical systems in all mammalian species, many cross-species emotional predictions can now be generated from animal brain research to human psychological responses [85]. Let us briefly consider these issues in the context of social joy, before moving on to what we know about human laughter.

Clearly, feelings of mirth and funniness are energized by positively valenced emotional systems of the human brain. However, until the advent of modern neuroscience, investigators could not discuss these issues in anything more than conceptual terms (from [46] to [98], so to speak). There seemed to be little hope that animal research could ever inform us of the deep neural nature of social joy and laughter. That has changed dramatically in the past few decades, as we have realized that most mammalian brains contain social play circuits [22], and that many species make abundant happy-type sounds, outwardly resembling laughter, in the midst of their rough-housing and carousing, as has also been studied systematically in chimpanzees by Matsusaka [58], with preliminary work in dogs by Simonet et al. [104]. Play vocalizations have been noted during the rough and tumble play of squirrel monkeys [5], and the brain circuits for emotional vocalizations have been extensively studied in this species [47–49,65]. However, no homology relationship has yet been envisioned to laughter. Considering that the young of our species begin to exhibit their social joy with laughter at a very young age [108], and the basic foundations for human laughter are found in very ancient regions of the brain [114], it probably should have been anticipated that various other species may have similar systems in their brains. The finding that rats make chirpy

sounds when playing and being tickled, and that they seem to enjoy this kind of stimulation, has now opened up the possibility of detailed neuroscientific inquiries of such propositions.

Young rats certainly find human hand play highly rewarding [79], perhaps in ways little different than their own playful activities. Rats seem to get many of the same functional effects from human hand play as from their own intra-species play. Soon after we initiated the systematic laboratory analysis of rat play [91], we envisioned the rat play paradigm as one that is optimal for informing us about the foundational substrates of human play. Long before we discovered play-induced and tickle-induced chirping, we evaluated whether human hand-play would emulate the satisfactions of rats' own play. It did, as analyzed through the lens of the play "satiation" curve that is evident across half-hour play sessions. If one restricted ludic activity of young rats to human hand-play during the first 15 min of a half-hour play session, juvenile rats played much less among each other during the second 15 min of the play period. In other words, the hand play appeared to have satisfied (satiated) them as much as play with a partner of their own species (Panksepp and Normansell, 1986, Unpublished data). This cross-species play suggests that basic play mechanisms are conserved among mammalian species. It led us to consider that the play urge is one of the major genetically provided tools for facilitating the epigenetic construction of social brain [73], an effect already observed by varying the quality of maternal care [59].

It is doubtful that the human genome has enough informational resolution to construct a fully social human brain. Perhaps one of the most emotionally painful genetically provided "tools" instantiated in emotional circuits of the brain are separation-distress states, accompanied by crying. Such emotional feelings assure that young infants will value the company of others, especially those willing to invest in their welfare. An even more wonderful tool provided to achieve the fuller socialization of the brain is rough-and-tumble play. Play allows young animals to learn about social dynamics in an affectively positive environment, and many behavioral and mental functions may be refined during play. Although there are many other functional possibilities to be considered [107], the play urge may be one of the few innate emotional tools of nature that evolution provided for the epigenetic construction of fully social brains in mammalian species. Although all emotional systems surely help contribute to that (especially the quality of maternal care), a case can be made that strong and flexible prosocial strategies are critically molded through the living dynamics of play and separation-distress circuitry. It is through the use of these systems in social contexts, that animals come to understand what they can do to others and what they want others to do to them—it is through these few comparatively "simple" genetically provided emotional urges that animals may get woven naturally into their social structures. Such epigenetic effects that help refine neuronal circuits for social conduct [59,73], might be achieved through arrays of brain gene activational effects instigated by playful activities [36,37].

We also agree with the ideas that some human psychologists have advanced (e.g., [32]), that positive social affect can broaden one's thinking, and deepen and strengthen one's psychological resilience and options. Based on the fact that all drugs used to treat Attention Deficit, Hyperactivity Disorders (ADHD) in our children are powerful play reducing agents in rat models [81], it is possible that, in the long run, provisioning abundant daily access to happy rough-and-tumble play for very young children (between the "terrible twos" and the time they enter school) may be an optimal social strategy for helping our kids get the full cerebral benefits of their early playful years, certainly better than giving them attention-promoting psychostimulant drugs that reduce their impulsivity [71]. Indeed, our evaluation of such possibilities in a rat neurological model of ADHD (i.e., frontal cortical damage) has affirmed the benefits of abundant early play [82]. Of course, the utility of such ideas is critically dependent on the degree of homology in the underlying emotional systems between animals and humans. To get a better handle on possible relations of human and rat "laughter" let's delve into the rapidly growing human brain imaging literature on the topic.

4. The brain correlates and mechanisms of human laughter

The study of human laughter has largely focused on how people respond to humorous cognitive stimuli, namely cartoons and jokes. Human humor is generally deemed to have three components [94]— (i) the motor act of laughter, most easily evoked by tickling, with its abundant autonomic accompaniments (first strikingly described by [46]), which, as we have seen, can now be studied in other animals; (ii) the wonderful emotional feeling of mirth that commonly accompanies laughter, which makes it especially important for emotion studies; (iii) the cognitive process of *getting a joke*, which is likely to be a fool's errand if sought in animal models, especially on lissencephalic mammals such as rodents, most commonly used in behavioral neuroscience research.

My reading of the evidence is that the mechanisms of raw emotional feelings are very closely linked to the emotional-instinctual action systems of the brain [70,76]. If so, the feeling of mirth might be closely linked to brain systems that generate the full and sincere pattern of laugher within the brain. This is not to deny that at low level of the neuroaxis one cannot provoke laughter responses that are not accompanied by positively valenced ludic feelings [7,97], but to assert that the executive structures that coordinate laughter further up in the brainstem (for instance, the mesolimbic trajectory of the chirping circuitry; see [15,21]) may mediate the neurodynamics of social joy that most humans experience during a good belly laugh.

One line of evidence for this is that the motor actions of laughter may be sufficient to make people feel good. This phenomenon probably helps explain the existence of laughing clubs in some areas of the world, where people simply come to share the good feelings engendered by laughing together (without any need for joke-telling). Indeed, humans who voluntarily generate the whole-body motor action dynamics of laughter often experience increased positive feelings [26]. This has now been documented in college students who were simply asked to internally generate the motor imagery of laughter mentally. For instance, we first trained college students to voluntarily generate the instinctual

actions of laughter and crying, and then asked them to simply envision these actions in their minds. The students reported selective increases of happiness and sadness as a result of voluntary generation of such instinctual-action imagery [83], leading to some fMRI brain imaging of such processes [38]. Since there exists no scientific evidence for any kind of humor (obviously no joke-telling) in animals, we cannot focus our cross-species scientific lens on the third dimension of laughter highlighted at the beginning of this section. However, because of our discovery of "rat laughter" we may now focus empirically on the other two.

4.1. The motor aspects of laughter

The existence of laughter mechanisms in the human brain have been long recognized [116], with abundant examples of how brain damage can release pathological laughter, typically with no feelings of mirth. Disinhibitory damage to corticobulbar tracts in the brainstem are especially effective in doing this [7,45,97]. More recently Wild et al. [114] have noted that: "Nearly all authors agree that there must exist in the brainstem a final common pathway for laughter, integrating facial expression, respiration, and autonomic reactions" and "Such a laughter-coordinating centre must lie in the dorsal area of the upper pontine mesencephalon and is connected to the periaqueductal gray (PAG) and the reticular formation (RF)" (p. 21). Parvizi et al., have emphasized cerebellar participation in the triggering of laughter episodes [93]. Others have focused on striatal and pallidal contributions [39] and as summarized in Burgdorf et al. [21], we have recently found the associated mesolimbic dopamine pathways exert powerful control over the emissions of tickle-induced chirping in rats (also see, [16] and [19]). We can also anticipate that the robust GABAergic and glutamatergic circuits that control motor movements in these brain regions will also have corresponding influences on laughter. For instance, laughter may surge when GABA inhibition in basal ganglia (striato-pallidal) circuits is reduced, perhaps partly by dopaminergic enjoyment signals coursing through this circuitry.

In general these findings are consistent with data from other primates. Jürgens [49], although not commenting how his superb brain mapping of emotional vocalization circuits might illuminate human affective feelings, has detailed the brain regions that generates a large variety of emotional vocalizations that courses from higher brain regions to the periaqueducatal gray, and then via medullary reticular pathways to the vocal motor apparatus of the nucleus retroambiguus and the nuclei of the tractus solitarius (also see his chapter in this issue). The lower aspects of this circuitry are regulated by frontal brain regions, especially those emanating from the anterior cingulate cortex, a brain area long known to regulate social emotions [57].

Localized brain stimulation of certain basal temporal and frontal lobes sites (especially the supplementary motor area) can provoke mirthful laughter, and a few sites have also been identified in the globus pallidus and putamen which also control facial expressions of laughing and smiling [33,41,45,54,61]. These systems also participate in the laughter that often accompanies several other neurological conditions, including epileptic fits—i.e., gelastic seizures [1,25]. Yet other sites in the parahippocampal gyrus and fusiform gyrus [1], as well as anterior cingulate and orbitorfrontal cortices [102] have also occasionally been found to evoke laughter with feelings of mirth. The functions of these areas in facilitation of joy are not clear, but clarity may be emerging through the recognition that the hippocampus, which is so intimately involved in memory formation, may facilitate humor appreciation. The anterior cingulate cortex is intimately involved in detection of incongruity, a common ingredient of humor, and hence perhaps various kinds of humor-related emotional perceptions and decision-making [23,112].

4.2. Laughter and the feeling of mirth

Iwase et al. [45], in their PET studies, have contrasted laughing and smiling expressions generated spontaneously (in response to comic videos) with the same expressions generated volitionally. The frontal cortical areas implicated in mirthful laughter (e.g., [33]) were highly responsive during such voluntary emotional expressions. However, the left putamen was selectively involved in mirthful laughter, again implicating the subcortical structures in the generation of affect, as affirmed by many human brain imaging studies (e.g., [30]; for summaries see [55,66]). A subcortical locus of control for affect generation has been long supported by animal studies [70,76]. Thus, it would seem that in order for cognitive stimuli to provoke laughter, they must interact with critical subcortical circuits, where homologies across mammalian species are more abundant than in cortical regions, especially the association cortices such as the massive frontal and parietal cortical expansions of humans.

Of course, this does not mean that there will not also be non-affective motor areas for laughter subcortically. Laughter without mirth has been evoked by localized electrical stimulation of the brain (ESB) of globus pallidus [41], indicating that this brain region also elaborates some strictly motor components of laughter. However, these inter-digitate with nearby circuitry that also promotes mirth, as seems evident from the use of deep brain stimulation (DBS) to alleviate Parkinsonian symptoms [68].

Perhaps mesolimbic dopamine circuitry that has been implicated in the regulation of rat "laughter" using pharmacological, brain stimulation and lesion techniques [19,21] and correspond to homologous brain regions that commonly "light up" in human brain imaging studies. For instance, Mobbs et al. [61] observed arousal of the mesolimbic "reward" (or in our terms SEEKING) system from the ventral tegmental area (VTA) to the nucleus accumbens. This brain system, as well as the more anterior frontal cortical regions implicated in laughter (*vide supra*), are richly innervated by dopamine circuits that have already been implicated in the regulation of rat "laughter". Since burst firing in brain dopamine neurons is a critically important aspect of anticipatory eagerness and seeking-exploratory urges in the pursuit of pleasures/rewards, one could suggest that the anticipatory pleasure and eventual gratifications of funny punch-lines of jokes may reflect sudden engagement of this circuit. Indeed, Okun et

al. [68] report that DBS in the vicinity of the nucleus accumbens can evoke smiling with feelings of euphoria. Of course, this same brain region has recently been implicated in many euphoric delights, from anticipation of monetary rewards [53] to intensely moving music, especially those that produce peak emotional experiences such as chills [9]. In short, the mesolimbic continuum may be important in both human mirth and rat "laughter". Indeed, it is noteworthy that every electrode site in rats that evokes chirping, is close to classic brain "reward" systems and supports self-stimulation behavior [21]. This raises the possibility that emotional vocalizations may be employed as unconditional "self-reports" of affective state in animals, with implications for the study of drug craving [84].

Let me re-emphasize that the ancestral roots of human laughter seem to exist among the brain mechanisms of playful social joy rather than simply humor appreciation. Children first laugh in the midst of play, and peek-a-boo and tickle games, long before they have any appreciation of semantic-cognitive humor (which must clearly be a neocortical function). However, long before young children appreciate cognitive humor, they have a strong sense of fun (more clearly sub-neocortical), and they laugh especially robustly in the midst of play [101], a behavior that is widely assumed to be foundational for competent adult socio-sexual behavior. In other words, positive social states may be signaled by play sounds that can facilitate reproductive success. Indeed, we should not forget that most of adult human laughter also occurs is in the context of friendly social interactions rather than the telling of jokes [98,106]. Perhaps only through experience-dependent higher cortical functions do we humans come to enjoy unusual verbal associations (puns) as well as getting the point of various unusual associations of ideas (jokes).

4.3. Humor and the cognitive dimensions of laughter

The higher reaches of the human brain are surely essential for our species to get the point of a joke—to be tickled and "ribbed" by words. Those kinds of cognitive humor, built perhaps on the more basic theme of friendly social-engagement induced bantering and playful laughter, are not directly relevant to our analysis of rat "laughter". However, for the sake of completion, let's briefly focus on what we know about those cognitive aspects. Norm Holland [44] has recently provided a fine summary as well as a novel theoretical vision of these higher cognitive and self-identity related aspects of human laughter. I follow his lead in the following synopsis.

4.4. The cognitive aspects of humor

Brain researchers are increasingly probing the cognitive aspect of laughter, and currently there is abundant disagreement about the brain systems involved. In an fMRI study, Mobbs et al. [61] compared responses to funny and not-funny cartoons. The largest cortical activations occurred in the left lateral inferior frontal gyrus, including Broca's area. Similar left lateralized trends have been found for verbal humor when contrasted with sight gags [113]. In other words, comprehension of verbal jokes and cartoons draw on left hemispheric language comprehension abilities. Indeed, understanding the meaning within the wording of jokes and the comprehension of cartoons may call upon similar brain abilities. By contrast, neuroimaging data [35] and data from patients with right hemisphere damage [12,103,109] indicate that the right hemisphere also participates in joke comprehension. In general, right frontal lobe lesions appear to disrupt the ability to appreciate humor. Various explanations are being considered.

Coulson and Williams [28,29], using an EEG event-related potential analysis, have confirmed a right hemispheric locus of control when contrasting brain responses to joke and non-joke sentences. For example, they compared items such as "The last time a guy in a mask took all my money, I was in surgery" with the less humorous "The last time a guy in a mask took all my money, I was in shock." They envision right hemispheric language networks (using perhaps a "coarse coding" function) to generate oddball meanings for words, meanings that the left hemisphere tends to ignore, except perhaps when one needs to comprehend metaphors or jokes. After transhemispheric processing, allowing right hemisphere global processing to transpire, left hemisphere language networks may come to appreciate the sense or nonsense of the sentence being processed. In this context, it is worth noting that the right hemisphere is generally more emotional, indeed to the extent that after damage to the right convexity (leading to left handed paralysis), patients often deny their paralysis, which suggests that the speaking hemisphere is often dissociated (defensively protected?) from psychological trauma. In any event, Coulson and Williams [28] concluded that the right hemisphere, because of its more holistic association networks and increased access to alternative meanings, may more readily decode surprising meanings in joke endings than the left hemisphere which operate in a more linear fashion.

Goel and Dolan [35] have contrasted non-jokes with two other types of jokes, semantic ones relying on the meanings of words – for example, "What do engineers use for birth control? Their personalities" – with jokes where humor arises from the sounds of words – for example, "Why did the golfer wear two sets of pants? He got a hole in one." Puns activated left temporal phonological systems and nearby speech production regions (left inferior frontal gyrus) more than non-jokes. Semantic jokes activated additional left temporal regions along with similar regions in the right hemisphere, suggesting the need for bilateral semantic processing for the decoding of the linguistically more sophisticated semantic humor. Anterior cingulate and frontoinsular cortical arousals have been envisioned to serve similar functions [113].

Such correlational studies are not completely consistent with all brain damage evidence: Wild et al. [115] report no studies implicating the right frontal regions in humor perception, but do report reduced arousal of right orbitofrontal cortex during the perception of humor. This may be consistent with the widely held view that right frontal arousal is related to negative affect. The abundant variability in human studies may arise from variables not controlled in many studies, including gender differences in humor [2] and various personality variables [62]. Clearly more research is needed for any definitive conclusions.

4.5. The emotional aspect

Wild et al. [115] summarize how humor and laughter may be organized within the brain. Humor has many components, and recently investigators have sought to distinguish humor detection and appreciation regions of the brain [63,113]. Generally, higher brain regions (frontal and temporal cortices) are important for humor detection while lower brain regions (insular cortices, amygdalar as well as midline diencephalic and mesencephalic regions) facilitate humor appreciation by promoting appropriate affects. Those regions are aroused simply by hearing laughter [100], perhaps in a mirror-neuron fashion, which may help illuminate the pervasive social infectiousness of laughter, especially evident in everyday human social interactions [98].

Preliminary evidence exists for which brain regions mediate feelings of mirth. Several brain imaging studies have found clusters of cortical arousals to funny as compared to non-funny cartoons; also, as with the animal play and tickling data, various subcortical networks are aroused including prominently the meoslimbic dopamine systems (from ventral tegmental area, through hypothalamus, to ventral striatum/nucleus accumbens); lower midbrain regions such as the PAG may also be important for feelings of mirth [61,113]. At present these are the regions most implicated in tickle induced 50 kHz chirping in rats [21], suggesting that the happy feelings evoked by human joking around are potentially homologous to those that mediate joyful social engagement in rats. We look forward to comparable investigations in mice, which are known to have a rich ultrasonic repertoire, and perhaps because of their smaller body size, their ∼70 kHz USVs may be homologous to rat ∼50 kHz USVs (for a excellent recent summary of mouse USVs, see Constantini and D'Amato, [27]). However, we can anticipate one dilemma for such analyzes in mice—juvenile domesticated mice typically do not exhibit clear rough-and-tumble play (personal observations for BALB and Swiss Webster mice). However, Pellis and Pasztor [96] have observed rudimentary play fighting in the highly social C57 strain of mice, suggesting that may be the optimal species for utilizing the power of mouse-genome data bases for guiding molecular-biological studies.

The highest frontal brain regions also contribute to feelings of mirth. For instance, Goel and Dolan [35] observed mirthful feelings correlating with increased activity of ventro-medial prefrontal regions. Indeed, this is a dopamine rich reward zone of the brain [67], and one where mirthful laughter has been evoked by localized electrical stimulation of the brain [1]. These regions can sustain strong self-stimulation behavior in animals. Thus, a case can be made, both from human and animal studies, that the positive affect of humor does recruit the dopamine-based euphoria inducing SEEKING-expectancy (meaning creating) systems of the brain [19,21,70]. Perhaps laughter arises when tonic frontal inhibition of such systems suddenly diminishes [114].

Thus social play, especially the experience of being tickled, may be the foundation on which the mirth of human humor is based. Consider the structural similarities between jokes and rough and tumble play. Both are characterized by mild (non-serious) social threats, whether instigated through the cognitive complexity of jokes or physically in the midst of play attacks and chasing. Both are characterized by complex social-behavioral and psychological dynamics that may be needed to navigate complex social space. These threats are resolved by comprehending a joke or finding that the tickling or rough-and-tumble activity is really not a serious threat. Both yield to a mirthful companionship feelings, signaled by laughter, which facilitates continuation of fun. The foiled anticipations and lack of predictability of jokes and play may help explain why one cannot easily tickle themselves, except perhaps among schizophrenics [8] who may have a disconnection syndrome where lower affective and higher cognitive processes are no longer coordinated. Most of the rest of us cannot really threaten or surprise ourselves.

5. Cross-species predictions

Because of evolutionary divergences, animal models of emotions can only be approximations of how similar processes are elaborated in humans, but general organizational principles may be conserved. There is little evidence to support the skeptical view that the basic neuroanatomical and neurochemical controls of basic emotions are so different that useful cross-species heuristics cannot be identified. Of course, the success of such modeling of human emotions depends on the degree to which findings from animals can be successfully translated back to the human condition through novel predictions. Since there are enough variables that can be used as translational bridges, especially neurochemical manipulations [85], cross-species hypotheses are capable of being supported or falsified. There is always danger that the inferences drawn will be erroneous, but ultimately that decision must be based on disconfirmations that destroy working hypotheses. So let us consider a few.

From the present analysis, we would predict that (i) human laughter will diminish with dopamine blockade, (ii) that in brain imaging the mesolimbic trajectory of brain dopamine systems will be especially active during fully mirthful laughter (perhaps best evaluated with PET imaging), and (iii) that glutamatergic blockade will tend to reduce laughter. Overall, it would be predicted that as new neurochemical variables are identified that modulate rat play and tickle-induced 50 kHz chirping, comparable effects would be obtained in juvenile human laughter. Since comparable predictions are not readily generated from any other intellectual trajectory, it is important to keep an open mind to the animal modeling efforts. We should remember there is no other robust strategy to get at the neurochemical infrastructure of basic human emotions, which makes animal modeling one of the few entry points into the neuronal infrastructure of primary-process feelings that may be shared by all mammals.

In any event, the inference that animals also experience their emotional states is an empirical issue, and one that can be evaluated with a host of behavioral predictions [76]. Overall, this type of animal modeling, although still not widely accepted as a strategy for generating some lasting understanding about basic aspects of the human condition, and the nature of the animal mind, needs to be judged not by the relatively rigid pre-neuroscientific "never-mind" approaches to behavior, but by the

degree to which novel predictions promote the harvesting of new types of knowledge that can have important consequences for our understanding of mental health and disease in both animals and humans. As the work proceeds, shortcomings will be identified, but it is wiser for us to remain open to the affective nature of animal minds than to deny such possibilities. That is an optimal way to identify the general principles by which similar processes control the basic human feelings which have long been neglected in behavior-only analyses.

6. Conclusions

Although some of our colleagues are bound to feel we have gone too far out on the theoretical limb in our suggestion that the "lowly" rat may have positive emotions such as social joy, capable of being indexed by their chirpy play sounds that may have some ancestral relationship to human laughter, we feel the idea deserves open consideration and discussion. Modern neuroscience and molecular biology, with their revelation of profound evolutionary continuities (homologies) among all mammalian species, suggest ways we may finally begin to understand the affective nature of animal minds. Since no comparably detailed functional neuroscience work can be done in our own species, such inquiries could provide working hypotheses and solid evidence for homologous processes in humans. This is not to say that evolutionary divergences and convergent evolution, generating analogous processes, can be disregarded. The varieties of explanatory possibilities need to be sifted through the generation of differential predictions.

Still, affective-behavioral neuroscience is the most intellectually robust scientific approach to understanding the psychological infrastructure of mammalian minds. In order to use such strategies well, we must entertain the existence of a variety of "instinctual" brain processes that are not easily envisioned simply by an environmentally guided reinforcement-learning approaches. Traditional behavioral neuroscience has yet to exhibit the intellectual courage to consider all credible possibilities about how the mammalian brain is organized, especially the diversity of mental processes woven into brain functions through evolutionary selection. One reason we have pushed the "rat laughter" idea to the limit is not only to foster such a discussion, but to also highlight the fact that so far we have not been able to falsify the radical hypothesis that we introduced. Until someone can offer us some data that falsifies our hypothesis, we believe our theoretical approach better reveals the true nature of the underlying processes than any intellectual scheme that simply constrains itself simply to the accurate description of the environmental and neural control of behavioral acts. It seems that certain evolutionary "tools" of the brain, such as the instinctual-emotional operating systems that course through the higher brainstem of all mammals, are ripe for fruitful cross-species psychological interpretations.

From an evolutionary perspective, human laughter may have arisen from primordial social play and joy responses of ancestral species [24,70]. Traditional behavioristic pre-conceptions about the impenetrability of mental processes in animals coax us to be skeptical about such possibilities, but there are few empirical reasons for us to remain timid about such issues. The evidence so far is remarkably consistent with the possibility that human laughter and rat 50 kHz chirping are rewarding and share an executive infrastructure that at the very least, has homologous components. We have empirically evaluated this relationship from many perspectives; we have encountered no major disconfirmations that compel us to change our minds on the hypothesis that they are evolutionarily related [19,79].

In proposing that rats exhibit an ancestral form of laughter, we are not suggesting that they have any refined sense of humor. Obviously, ancestral joy responses such a rat laughter will not illuminate the mystery of how jokes tickle members of our own species, but it could provide a major avenue for understanding the neuranatomical, neurochemical and neurogenetic underpinnings of our own laughter response. The issue of humor and jokes in other animals must, for the time being, remain in the realm of anecdotes. No one has developed any credible experimental paradigms to evaluate such issues. If rudiments of such processes do exist in other animals, they are bound to be of the lowest variety found in humans, namely slapstick. For instance, if a cat or some other animal had been a persistently troublesome feature of a rat's life, might that rat show a few happy chirps if something bad happened to its nemesis? Would a rat chirp if the cat fell into a trap, or was whisked up into the air by its tail? We would not recommend such mean-spirited experiments to be conducted, but would encourage anyone who wishes to go in that direction to find more benign ways to evaluate those issues. Interesting anecdotes that can guide thinking are available in Balcombe [3] and Bekoff [4].

It will be a long time before there is any coherent science of humor in other animals, and if that ever does emerge, it may have few practical implications. However, we think an understanding of the play-joy-laughter and separation-distress processes already have important implications for biological psychiatry, including new ideas on how to promote positive feelings, by directly facilitating positive affect and diminishing negative affect, that can provide new testable ideas on how to counteract depression. For instance, we would suggest that opioids, which dramatically reduce separation-distress, could be developed into effective anti-depressants. Indeed opioids were commonly used for such purposes prior to the modern era of biological psychiatry, and new hardly addictive agents such as buprenorphine are likely to be very effective in treating depressions that have not responded to the more well-accepted medications [11]. Also, the fact that muscarinic cholinergics can provoke 22 kHz USVs throughout the basal forebrain [13] would suggest that blocking those receptors in human brains could also alleviate depression, a prediction that has recently been affirmed [34].

As already noted, the study of play has suggested better ways to facilitate the construction of social brains in our children as well as the potential alleviation of the increasing prevalent ADHD symptomology in our society. For such reasons we are currently pursuing behavioral genetics experiments where the target behavior has been the degree of chirping in response to a standard tickling stimulation [20] and also evaluating the gene expression consequences of ludic activities within the rodent brain [21]. We hope this work will eventually reveal the psy-

chobiological benefits of playful activities and feelings of mirth, much valued by our species down through the ages.

Social play and humor seem to share common neural substrates. Not only does their emotional impact depend on similar subcortical brain regions [15,21], but functionally they may both be adaptations which allow animals to "navigate through a shifting and complex social space" [113]. We encourage others to become involved in this work. It may be of first-rate importance, if the basic play processes of the brain, along with the playful laughter sounds that accompany play, are ancient psychobehavioral tools that promote the epigenetic development of fully social brains in both rodents and men. Such findings may have useful cultural and biomedical impact [71,72].

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