"Laughing" rats and the evolutionary antecedents of human joy?

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Abstract

Paul MacLean's concept of *epistemics*—the neuroscientific study of subjective experience—requires animal brain research that can be related to predictions concerning the internal experiences of humans. Especially robust relationships come from studies of the emotional/affective processes that arise from subcortical brain systems shared by all mammals. Recent affective neuroscience research has yielded the discovery of play- and tickle-induced ultrasonic vocalization patterns (~ 50-kHz chirps) in rats may have more than a passing resemblance to primitive human laughter. In this paper, we summarize a dozen reasons for the working hypothesis that such rat vocalizations reflect a type of positive affect that may have evolutionary relations to the joyfulness of human childhood laughter commonly accompanying social play. The neurobiological nature of human laughter is discussed, and the relevance of such ludic processes for understanding clinical disorders such as attention deficit hyperactivity disorders (ADHD), addictive urges and mood imbalances are discussed.
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1. Introduction

One of Paul MacLean's lasting insights was the recognition that subcortical regions of the mammalian brain contain a variety of evolved emotional systems for the governance of behavior. He accepted the likelihood that subjective emotional experiences arise from specifiable neural systems, and he encapsulated his interest in the fundamental nature of such psychobiological functions in the concept of *epistemics*—the study of "the subjective self and its relations to the internal and external environment" [48, p. 6]. Furthermore, he suggested that the brain regions which govern basic emotional urges exhibit an impressive functional and anatomical coherence that deserves special recognition. Thereby, his concept of the limbic system emerged as one of the great *memes* of functional neuroscience. Recently, an increasing number of neurobehaviorists have challenged the utility of this concept (e.g., Ref. [45]) albeit no neuroscientist has had adequate reason to challenge the existence of a variety of evolved emotional systems that we still share with other mammals.

That creatures as lowly as crayfish and planaria exhibit place preferences for drugs that human desire [42,71] also coaxes us to consider the utility of subtle concepts such as affect-psychological processes that are created by ancient value-encoding, neural systems of the brain. To our way of thinking, affects are the currency of the brain/mind economy that signal the survival value of objects and ways of acting in the world. Thus, there are natural categories of affective processes—some linked to sensing the fruits and dangers of the world, some related to anticipation of positive and negative events, some related to actions in the world, and some related to postconsummatory reactions. All may require some type of primitive neural structure that can be conceptualized as the "core self" [20,55,57]. Our working premise is that affects are intrinsic aspects of emotional operating systems in the brain, and thereby constitute centers of gravity around which the decision making and operational/instrumental features of the surrounding cognitive processes revolve. In the present paper, we will focus on our recent discovery of a vocal pattern in rats which may have evolutionary relationships to laughter, and hence, fundamentally to joyful social processes that are carried out by the mammalian brain.

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2. The brain systems for affective experience

During the past three decades, enormous progress has been made in characterizing the brain systems that promote reproduction (sexual and maternal nurturance systems) and related social processes that help newborn animals to signal social distress and social excitement (i.e., separation distress and playfulness) both of which promote social bonding, the development of social skills, and thereby the competence to sustain generative cycle of life [55,70]. Such evolved neurobehavioral tools, honed exquisitely and at times idiosyncratically by individual learning experiences, help establish communicative urges that support our human neurosymbolic capacities for refined forms of intersubjectivity (reflected most clearly in our abiding interest in the contents of other minds) [87]. Among the basic social signaling systems, audiovocal and presemantic forms of social communication [48] may be the antecedents to the social urges that characterize human life. However, the linkages between what we know about the human mind and what we know about animal brain functions remain a difficult and contentious topic, and the needed empirical bridges remain to be constructed with disciplinary conviction.

Those who do not work on these brain systems typically remain skeptical of the relevance of this knowledge for understanding the human condition, even though a careful analysis of the data collected during the era of psychosurgery provided some impressive data concerning the similarity of human and animal subcortical emotional functions [33]. Still, even with modern brain imaging, the details of the neural circuits that govern human emotions and motivations remain largely outside the realm of neuroscientific inquiry. The existing imaging techniques only identify regions of interest for further analyses. When it comes to the cardinal issue of identifying causal processes for mammalian emotional feelings, these techniques are susceptible to abundant false negatives as well as an indeterminate number of false positives since they highlight correlated rather than causal aspects of core emotions. Indeed, such technologies are not especially robust for visualizing brainstem functions. For instance, the widespread use of sensory stimuli to evoke emotions typically leaves open the question of how much the resulting brain arousals reflect nonaffective perceptual processes as opposed to brain functions that actively generate affective experience. Indeed, there is no unambiguous way to ascertain whether the activations that are obtained are directly reflective of the active processing of emotional feelings, as opposed to the active inhibition of mind–brain processes that accompany such experiences. Also, fMRI appears to be more sensitive to graded dentritic potentials (inputs to an area) rather than outputs from an area [47].

The dynamics of blood flow in the brain can fluctuate so rapidly that short-term "event-related" measures (as typically observed with fMRI) and longer term "state" measures (as can be monitored better with PET imaging) often do not match up, and many of the neurochemistries that are of interest (e.g., catecholamines) can have direct effects on blood flow dynamics that may be independent of neural dynamics. Still, when we look at the best brain imaging that has been done of human emotional experience [21], there is a striking correspondence to what we know about the localization of emotional circuits in the brains of other mammals [55,59,60].

Despite massive evidence suggesting conservation of principles across all mammalian species among the subcortical systems that govern basic emotions and motivations, the detailed study of neural circuits that control animal emotions remains to be generally accepted as being of fundamental importance for understanding human emotions. Partly, this simply reflects the fact that deep evolutionary considerations do not yet guide thinking in the field [68], and partly, the natural tendency of scholars to resist assimilation of the types of findings in which they have not been active participants. Thus, we are left with the dilemma that some basic neuroscientists agonize over the extent to which their empirical victories in studying the brains of animals relevant for the understanding our own species. The evolutionary perspective provides a clear answer—at a subcortical level, where anatomical and neurochemical homologies abound, there are bound to be remarkable functional similarities [68], unless, of course, these lower functions have become vestigial for human behavior. Although there has continued to be considerable evolutionary divergence in the *details* of emotional brain mechanisms across species, there is presently no empirical reason to believe such fundamental brain operating systems have become vestigial in any mammalian species, even though it is likely they can be decisively inhibited and regulated by the emergence of various higher brain functions, most dramatically the impressive cognitive capacities of humans.

Paul MacLean was one of the few who had the intellectual courage to deal directly with the implications of ancient limbic brain systems for understanding human emotions. Ultimately such neuroevolutionary perspectives must be evaluated by the new predictions they can generate, especially for the human species. For instance, the neurochemical issues have become especially tractable—there are examples of how effectively our understanding of biogenic amine systems in animal models has guided an understanding of their functions in human brains (e.g., Refs. [22,37]). Likewise, it is to be expected that advances in the study of neuropeptide systems in the regulation of emotions and motivations in animal models will soon be capable of guiding predictions at the human psychological level [55,56,58].

In the rest of this paper, we will summarize and discuss one of our most recent lines of research—a vocalization pattern in rats that we have interpreted as a laughterlike response—which can be used as an exemplar of a radical type of theorizing along these lines. Although we are not unreasonably committed to the "laughter" interpretation of the 50-kHz vocalization pattern we shall highlight here, it

provides an especially provocative and useful case study of the types of testable and falsifiable neuroevolutionary psychobiological hypotheses that the increasingly abundant behavioral neuroscience data now offers for our consideration.

Our discussion will be two pronged. First, we consider the possibility, now supported by a great deal of data, that such vocalizations (i.e., 50-kHz chirps) do reflect a laughter-type response, regardless of evolutionary relations to human laughter. Second, we entertain the possibility, which remains largely in the conceptual realm but may eventually be evaluated using neuropsychological and molecular biological approaches, namely, that the animal data will highlight some of the homologous controls that exist in human brains. Thus, we will also consider the possibility that rat "laughter" and infantile human laughter do share enough evolutionary relations for the former to be useful in decoding one of the great mysteries of human life—the deep nature of a form of joy within the brain–mind.

3. The discovery of rat "laughter"

While evaluating the sensory systems that control rough-and-tumble play in juvenile rats, we noted that deafening had a modest effect in reducing play [89]. This suggested the possibility that some type of sociovocal communication may facilitate playfulness. This problem was picked up by Brian Knutson in our lab, who first monitored the ultrasonic vocalizations of young rats in the midst of play. He promptly discovered a great abundance of 50-kHz type chirps during this type of social interaction [38]. This type of vocalization had already been studied extensively in the context of sex [1] and a much lower level of this type of vocalization had also been seen in the context aggression (Ref. [96] and *vide* infra—section 4.4, i.e., the fourth among the dozen reasons in the next section). However, in the context of play these vocalizations were much higher than ever observed in the other social contexts. Indeed, these vocalizations were especially frequent when animals were anticipating the opportunity to play, and we came to recognize that such vocal measures could be used as to measure positive affective expectancies [14,40,66].

One prong of our subsequent work on this vocalization pattern was premised on the possibility that such sounds may be used as a general index of affectively positive incentive motivation [14,39,40], perhaps even a measure of craving of various rewards, including pharmacological ones [66]. We have now extensively developed that idea and feel that it has opened up a new avenue of inquiry into the study of the positive affective experiences of another species [40,66]. It is important to emphasize that the levels of this vocalization were by far the highest in the context of playful interactions. This suggested to us that it might also index a specific type of socioemotional response related to a specific type of affectively positive social process. Thus, the other prong of our work was devoted to analyzing the special social–emotional aspects of this vocalization. We will focus on that possibility in this paper.

After we had studied play- and reward-induced 50-kHz chirping for about three years, it occurred to us that this response might reflect some type of a "laughter" type response. During the spring of 1997, the senior author came to the lab, and suggested to the junior author "Let's go tickle some rats." This was promptly done with some juvenile rats that had just finished a play experiment. We immediately discovered that the emission of 50-kHz vocalizations more than doubled over the levels we had seen during their own self-initiated play activities. To all appearances, the animals enjoyed this tickling which simulated their own playful activities. We promptly shifted our research priorities to an intensive analysis of this response. Across the subsequent years we became increasingly convinced that we had discovered a true laughter-type of responses. As a matter of principle (of the evolutionary variety), we decided to remain open to the possibility there was some type of ancestral relationship between this response, and the primitive laughter that most members of the human species exhibit in rudimentary form by the time they are three months old. This intriguing behavioral response intensifies marvelously during the next few years and is exquisitely expressed when children begin to vigorously play with each other (being especially evident when they eagerly chase each other in games such as tag).

Of course, it was hard to publish this kind of work, and it was ironic that the publication of our initial manuscript was impeded by prominent emotion researchers, some of whom take pains to deny that we can ever know whether animals have any emotional feelings. That initial manuscript (with some additional commentary) is, however, now available in the proceedings of the first major scientific conference in which this work was disseminated [61]. We parenthetically note that before any of this work was published in a scientific journal, it was shared with the public in several animal behavior documentaries (e.g., a BBC show entitled *Beyond a Joke*, and a Discovery Channel show on *Why Dogs Smile and Chimpanzees Cry*). As a result, the senior author received abundant mail from rat-fanciers who sought to replicate the phenomenon, most with considerable success (especially if they were not carriers of predatory odors, as from pet cats). We would share one letters from a fan in California who, because of her experience tickling a rat, decided to return to college to pursue graduate work in animal behavior:

After seeing the Discovery special, I decided to do a little experimenting of my own with my son's pet rat, Pinky, a young male. Within one week, Pinky was completely conditioned to playing with me and every once in a while even emits a high pitched squeak that I can hear. It's been about 4 weeks that I have been tickling him everyday and now, the second I walk into the room, he starts gnawing on the bars of his cage and bouncing around like a

kangaroo until I tickle him. He won't even eat when I feed him unless I give him a good tickle first. I had no idea that a rat could play with a person like that! He tackles my hand, nibbles, licks, rolls over onto his back to expose his tummy to be tickled [that's his favorite], and does bunny kicks when I wrestle with him. It's the funniest thing I've ever seen, even though my family thought I had lost my mind until I showed them.

In short, there was great popular interest in this discovery, although there remains some profound and *Zeitgeist* appropriate skepticism about the phenomenon among many scientists. Of course, one critical worry we all tend to have about such interpretations of animal behavior is committing the "sin of anthropomorphism." However, we would simply note that the emergence of a "critical anthropomorphism" may be essential for dealing with certain types of primitive psychobiological processes we share with the other animals [15,59]. Indeed, it may be worth noting that Morgan himself did not intend that his epistemological suggestions, which came to be known as "Morgan's Canon," (i.e., the scientifically esteemed goal of *parsimony*) would became a rationale to dogmatically deny the existence of mental life in other animals [18].

Because of the rather well-entrenched, and by now almost reflexive, antianthropomorphism stance in the neurobehaviorist community, we had already encountered similar reactions when we first started to study separation-induced distress vocalizations in puppies, guinea pigs and domestic chicks, which we hypothesized could be used as animal homologs of a form of human childhood "crying" [67,70]. Readers interested in an example of ongoing skepticism with regard to existing work on separation distress in animals, as well as related scientific issues, can find that topic debated in a series of recent articles [8,59]. We feel the neuroscience community does need to try to deal more forthrightly with the critically important affective functions of the brain. A proper neuronal conceptualization of affective processes may be essential for making sense out of many brain functions. Although all scientists can agree that affective states cannot be measured directly—that has been obvious for a long time—there are a variety of compelling indirect theoretical strategies that offer credible scientific approaches for penetrating into the nature of such mental experiences [55]. Although positive affects, such as joy, may be more difficult than the varieties of fear and anxiety, we proceeded to provisionally hypothesize that 50-kHz chirping could be used as a measure of positive social affect in rodents, and perhaps other appetitive anticipatory processes as well [40,66].

Of course, scientifically there are two critical issues: (1) Are the empirical phenomena we have reported replicable (and so far we have heard of no major problems), and (2) Do our interpretations of the phenomena stand up to critical analysis (and so far, no one has shared an alternative perspective that is based either on evidence or clear reasoning that considers *all* the evidence)? So why are we willing to go out on this risky conceptual limb? Our first reason is that if our theoretical interpretation is basically correct, namely that these are the sounds of social joy, then we have an excellent animal model to help decipher scientifically one of the great mysteries of human emotions—the primal joyful nature of laughter and positive social interchange [58]. Another reason is simply a general ontological position that we share with Paul MacLean and other sensitive observers of animate life: The existence of affective processes in the brains of other mammals makes evolutionary sense—it could be a heuristic code of *value*. On the other hand, the assumption that the other animals are unfeeling behavioral zombies seems evolutionarily improbable, especially if many human affects emerge from subcortical circuits we share homogenously with other animals [60]. In making this last assertion, we explicitly recognize that the expansion of the human neocortex has provided the opportunity for a level of symbolic processing that is evident in no other species. Of course, if it were to turn out that experienced affect is more critically dependent on cortico–cognitive symbolic activities rather than the arousal of subcortical of emotional–instinctual action circuits as we hypothesize [55], then our position would be seriously flawed. However, there are abundant data that evolutionarily conserved subcortical systems are major "loci of control" for emotional affective processes in the mammalian brain [33,55,60,79]. In claiming this we do not deny that many perceptual affects (e.g., the qualia of sensory experiences) are heavily dependent on the ability of cortical processes to discriminate many fine *differences* of the world.

4. The weight of evidence for rat "laughter"

Before proceeding to some details, let us again affirm that our ontological position is that other mammals, and perhaps many other animals, do have affective emotional and motivational experiences which are generated by complex neurodynamics that are important for scientists to conceptualize to make progress on how the brain–mind is actually organized. This is a contentious issue, since subjective experiences cannot be directly measured in either animals or humans, and must be inferred from outwardly evident signs. This, of course, is not an uncommon problem in science, where unseen processes must be adequately conceptualized before they can be measured. In such circumstances, it is the weight of evidence and the power of new predictions, rather than the logical air-tightness of arguments that must be the basis for adjudicating the adequacy of a concept. Accordingly, we will summarize a dozen lines of evidence that coax us to consider the "laughter" interpretation of the 50-kHz chirping that is so readily evoked in young rats by providing them playful, tickling-type somatosensory stimulation (see Table 1). Be-

Table 1
Evidence that 50-kHz calls reflect a positive emotional state analogous to laughter

1. 50-kHz chirping is evoked most robustly during play and tickling	[11,13,38,77,80,88,90]
2. Existence of "tickle skin"	([61,69,70,89], Fig. 2)
3. Age related declines in tickling	([54], Fig. 2)
4. Negatively valenced stimuli reduce the tickle response	[55,61,94,97]
5. Positive relationship between playing and tickling	[38,63]
6. Tickling is rewarding for rats which exhibit high levels of 50-kHz calls	([12,61,62], Fig. 3)
7. Social isolation is an important ingredient for evocation of the tickling response	[61,62]
8. Classical conditioning of tickling	[61,62]
9. Tickle induced approach behavior is strongly correlated with rate of 50-kHz calls	([12], Fig. 4)
10. Social preferences evoked by tickling	([12], Fig. 5)
11. Low or high levels of ticklishness can be readily breed for experimental	[46,63]
12. The alternative, motor artifact explanations of the response, are not supported	([7,13,38,95], Fig. 6)

fore proceeding, let us emphasize that the two major sonographic patterns of ultrasonic vocalizations—the 22- and the 50-kHz chirps (Fig. 1)—do convey different emotional messages. The former is primarily seen in affectively negative situations, while the latter is much more evident in positive ones (for a comprehensive review of the background evidence for this and other points made in this paper, see Ref. [40]). In our experience, there is no situation where the 50-kHz chirps are more frequent than when young rats are being tickled by a human experimenter.

4.1. 50-kHz chirping is evoked most robustly by the positive social interchange of rough-and-tumble play, and even more so by human tickling

Sustained bouts of human laughter are evident in children during tickling and rough-and-tumble play, especially when they are chasing each other [80,90]. A similar type of vocal activity (chirping at about a frequency of 50 kHz, which humans cannot hear without special equipment, of course) is also evident when young rats play [38]. To our knowledge, play and tickling are by far the most robust initiators of the short 50-kHz chirps that are also common at much lower levels in other positive social situation [13]. This socially induced vocalization is highly stereotyped [11], as is human laughter [77], but there is also sufficient variability in the rodent chirps that it remains conceivable that there are several functionally distinct sounds in this type of vocalization.

Whether there are homologous play- and affect-related ultrasonic chirps in other rodents such as mice and hamsters awaits such functional analyses in those species [40]. It has

also recently been claimed that other species including primates and canids exhibit a laughter type response [77,88]. Whether these are homologous vocalizations, and to what extent there are ancestral relations to human laughter awaits a more comprehensive neural and genetic understanding of the underpinnings of this behavior than presently exists. Only when we know enough about the basic neurobiology of human laughter will we able to have an adequate database to evaluate the issue of homology in other species. The slow pace of research in this area, especially in the human species makes needed cross-species comparisons almost impossible currently, especially as far as neurological issues are concerned [13,29,73]. Indeed, it seems likely that the neurobiology of such responses in laboratory species can lead the analysis. The existence of homologies will have to be judged by the extent to which the animal data yield testable predictions in humans (e.g., identification of new neurochemistries that facilitate laughter).

4.2. On the existence of tickle skin

Tickling various areas of a rat's body is remarkably effective in generating maximal levels of this "laughter" response. Just like humans who are more ticklish on certain areas of the body (e.g., ribs), young rats have "tickle skin" concentrated at the nape of the neck where they direct their own play activities [61,89]. A developmental study of the tickling response, as a function of body area tickled, is summarized in Fig. 2 (the detailed methods are described in the legends of this and subsequent figures). Tickling at the nape of the neck consistently produced more chirping than tickling the posterior dorsal surface of the animal, but full body tickle was most effective of all. The response was significantly higher in the males during the first two test ages, but females responded significantly more than males at the oldest age. In this context, it is noteworthy that after puberty females tend to remain more playful than males ([69,70], and unpublished data).
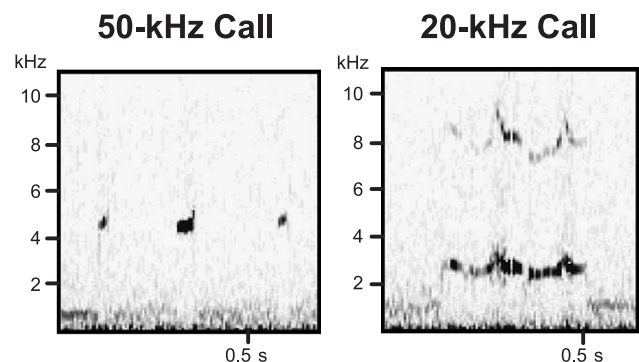

Fig. 1. Sonographic analysis of a sample 50- and 20-kHz ultrasonic vocalization recorded during the third test day of the experiment depicted in Fig. 2. Ultrasonic vocalizations were recorded onto the audio channel of a VCR tape via a Petterssen D980 ultrasonic detector (Uppsala, Sweden) with a 1/10 frequency division.
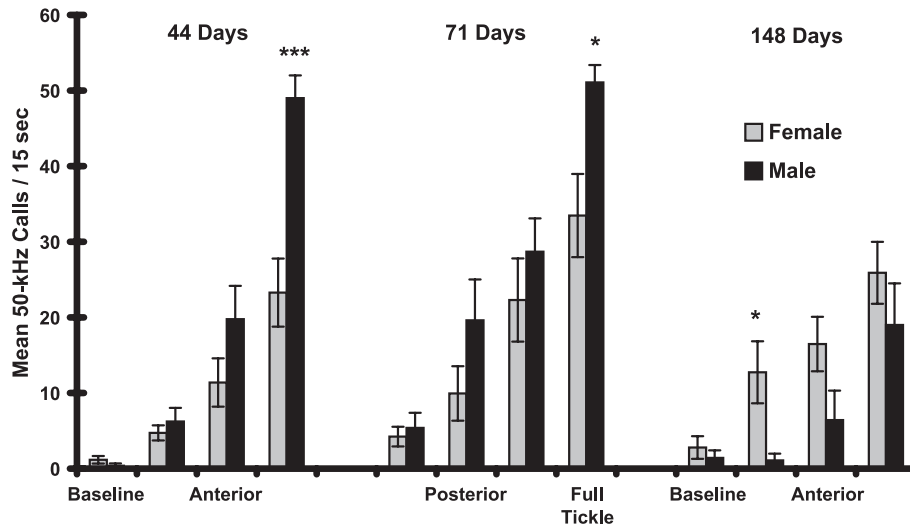
Fig. 2. Long Evans rats (13 male, 18 female) singly housed from weaning at 21 days of age were given (i) tickling stimulation of the rump of the animal (Posterior), (ii) the nape of the neck (Anterior), (iii) alternating between stimulation primarily of the nape and ventral surface of the animal when placed in a supine posture (Full Tickle) or (iv) no stimulation (Baseline) for 15-s epochs for each stimulation or baseline period. Subjects were tested using a within-subjects design at 44, 71 and 148 days of age. Methods used were identical to those previously described [61,62]. Sex differences were analyzed using two-tailed between-subjects *t* test. $P < .05$, $** P < .01$, $*** P < .001$.

4.3. Age-related declines in tickling-induced chirping

Rough and tumble play declines as a function of age [54], and so does tickling (Fig. 2, but the decline in play is much more precipitous than the decline in the tickling response. The tickling response remained stable well past puberty (at least until ~70 days of age), declining substantially only when the animals were well into full adulthood. This suggests that the reductions in natural play following puberty is probably due more to the fact that older animals do not initiate play as much as younger animals and that they (especially males) are more likely to get into intensely aggressive interactions. Although there is little data to suggest that there is a precipitous decline in positive reward from playful bodily stimulation, as animals grow older, as highlighted in section 4.6, older animals that are not accustomed to being tickled do show diminished tickle-induced place-preference as compared to younger animals.

4.4. Negatively valenced stimuli reduce the tickle response

All fearful and negative affective stimuli we have tested (cat smell, foot shock, new places, being held by the scruff of the neck, and being tested in bright light) reduce this response [61]. One of the potentially inconsistent findings is the existence of some 50-kHz chirps during aggressive encounters [51,83,96]. Indeed, Berridge [4] has questioned our "laughter" interpretation of 50-kHz chirps on the basis of this finding. However, we note that it is the intruder animal that exhibit the vast majority of the aggression-related 50-kHz vocalizations [97], and the levels are so sparse

as to be of dubious significance when contrasted to the high levels evident during play and tickling.

In a recent unpublished experiment we examined ultrasonic calls in the resident–intruder aggression protocol (e.g., Ref. [24]). Dorsal contacts, bites, freezing, as well as ultrasonic vocalizations were analyzed during either the fourth or fifth resident–intruder encounter. The 30-min test session was divided into 5-min blocks for analysis. During the first trial bock (0–5 min) animals exhibited the lowest levels of freezing behavior (Mean ± S.E.M.; 41.9 ± 34.3 s) and the fifth trial block (20–25 min) exhibited the highest level of freezing behavior (191.5 ± 64.3 s). Assuming that freezing behavior reliably indexes a negative affective state, we infer that animals exhibiting more negative affect during the fifth trial block as compared to the first. Male rats also exhibited more dorsal contacts, which index a positive affective state during play behavior [55], during the first trial block (5.1 ± 1.2 s) as compared to the fifth trial block (1.4 ± 0.9 s). Male rats exhibited significantly more 50-kHz during the first trial block (41.9 ± 34.3 s) as compared to the fifth trial block (17.7 ± 8.6 s), and significantly less 20-kHz calls during the first trial block (0.9 ± 0.9 s) as compared to the fifth trial block (128.6 ± 27.4 s). In contrast, female rats exhibited similar levels of 50-kHz and virtually no 20-kHz calls during the first and fifth trial blocks, and they exhibited very little freezing behavior. Thus, it appears that the most emotionally positive segments of aggression were associated with higher levels of 50-kHz vocalizations as compared to the more negatively valenced test periods. Just the opposite was seen for the 22-kHz calls, with more 22 kHz associated with the negatively valenced test periods as compared to the positively valenced test periods.

Even though aggression generally seems aversive, we also note that there is, in fact, an ambivalent social motivation in animals following severe social competition as measured by social choice tests. Submissive animals, given a choice to return to their home cage in a T-maze or to the home of the dominant animals, exhibited surprisingly many choices for the latter [94], while of course dominant animals would be expected to be eager for more social contact. Thus, aggressive situations still contain abundant positive social motivational features, which may help explain the modest levels of 50-kHz vocalizations evident in resident–intruder paradigms.

4.5. Positive relations between playing and tickling

Individuals that chirp the most in response to tickling, also play the most. We have observed this in two separate situations. First, in sequential daily play sessions, the amount of chirping that occurs during a session is correlated with the number of dorsal contacts (play solicitations) emitted during play testing [38]. Second, when we bred animals for high chirping, we also found that these animals exhibited significantly more play solicitations than randomly selected and low-chirp lines [63].

4.6. Tickling appears to produce a positive affective responses

Just like young children, juvenile rats find tickling to be rewarding as indicated by various approach and place preference tests [61,62]. Indeed, we have found that young rats will seek the proximity of hands that tickled them to a greater extent than they seek contact with anesthetized conspecifics [12]. Animals also exhibit a heightened attraction to other stimuli that have been associated with tickling. A replication and extension of our original place preference finding [12] is summarized in Fig. 3. Adolescent rats that exhibited abundant 50-kHz tickle-induced chirps exhibited significantly more place preference compared to adults who responded much less to the tickling.

4.7. Social isolation as an important ingredient for evocation of the tickling response

One may wonder why young rats, who might be threatened by large humans, exhibit a desire for the types of playful interactions we have employed. Clearly, this type of receptivity is primed by prior social isolation. Young animals taken immediately from their family groups do not exhibit a robust chirping response to being tickled. It takes about two days of prior social isolation to obtain the full response [62]. The fact that social isolation is so potent in opening a "doorway" to this type of interaction suggests that the response is regulated by social-need processes within the brain. In contrast, food deprivation does not significantly elevate the response [61]. In this context, it is
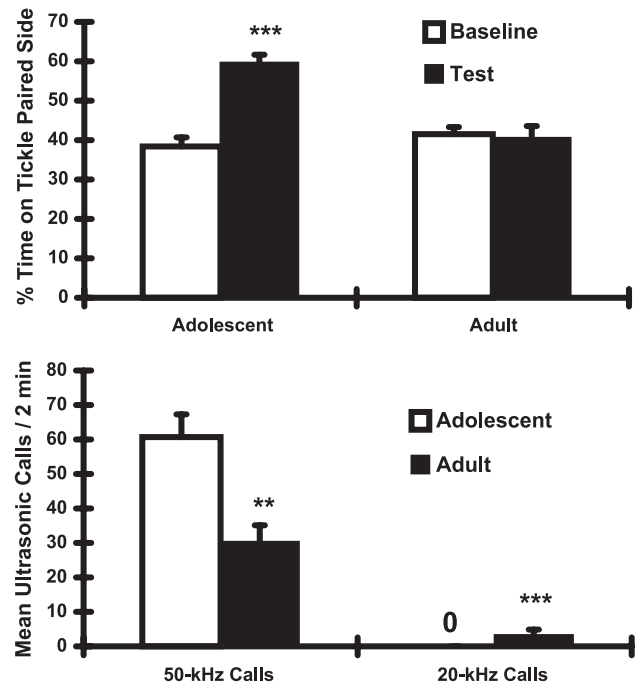

Fig. 3. Long–Evans rats singly housed from weaning at either 21 or 40–41 days of age were used in this study. Adolescent animals ($n = 29$) began testing at 41–42 days of age and adult animals ($n = 19$) were between 2 and 9 months of age at the start of testing. Subjects received 2 min of tickling stimulation consisting of four successive blocks of 15 s of no stimulation followed by 15-s period of full body tickle [62] for three consecutive days in the white side of a white–black conditioned place preference box [14]. Ultrasonic vocalizations were analyzed for the 2-min tickling session on the third test day. Subjects were also placed in the black side of the place preference box without tickling stimulation for each of the three test days. On the fourth day subjects were allowed free access to both the white and black side of the place preference box for 5 min. Conditioned place preference was analyzed with a two-tailed within-subject t test. 50-kHz calls were analyzed with a two-tailed between-subject t test, and 20-kHz calls with a Mann–Whitney U. $P < .05$, ** $P < .01$, *** $P < .001$.

also noteworthy that it is rather difficult for strangers to provoke young children into tickle games until they have been adequately familiarized with the adult and perceive them to be friendly (Panksepp and Reddy, 2002, unpublished observations).

4.8. Classical conditioning of tickling

It is well known that in human children one can very rapidly condition a laughter response. If one has successfully tickled a young child, then one can evoke peals of laughter simply by threatening with a "Coochi-coochi-coo" type of "I-will-get-you" provocation. A very similar conditioned response can be seen in juvenile rats, by waving one's hand as a conditional stimulus prior to each tickling bout [61,62]. Not only does the tickling response classically conditions rapidly to cues that predict tickling, but during extinction, social solicitations [play-bites] actually go up during successive test days (see Fig. 5 and Ref. [62]), as opposed to down as might be expected from classical ex-
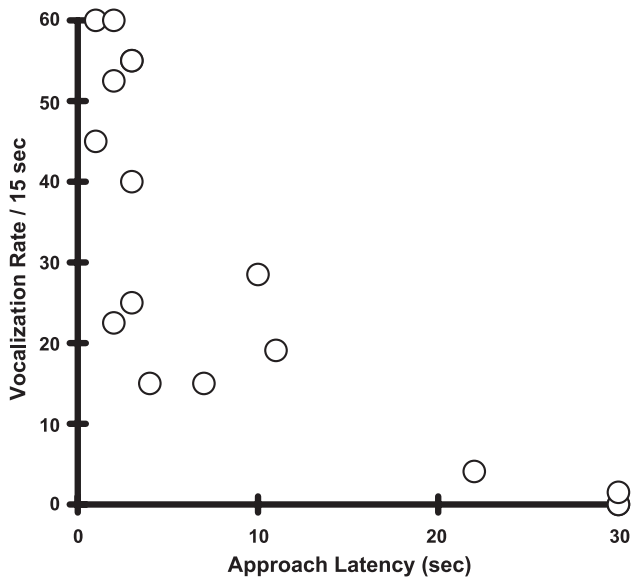
Fig. 4. Long–Evans rats ($n = 4$) age 32 days of age were singly housed from weaning at 21 days of age were used in this study. Subjects were given 15 s of full tickle stimulation which was made contingent on the animals approaching and touching the experimenters hand or after 30 s without contact. A total of 4–5 trials were given per animal. 50-kHz calls while the animals were approaching the experimenters hand was used for analysis. Methods were virtually identical to experiment 2 of Burgdorf and Panksepp [12]. Pearson Correlation $r = .80$, $P < .001$.

tinction processes. It is fascinating that the play biting is further elevated in these animals across successive extinction days (see Fig. 5 and Ref. [62]). Our interpretation is that the animals are in a central state of "play desire" and that their behavior reflects an instrumental attempt to elicit playful engagement from their only available partner (the experimenter's hand). This solicitation response may have more than a passing resemblance to the pestering that children and pets commonly exhibit when they want more social attention from individuals to whom they are attached. Thus, we believe the various social appetitive responses observed in these studies may also be used as measures of degree of social attachment in rats. For instance, individually housed young rats readily learn to follow a hand that has tickled them around a large test arena.

4.9. Instrumental conditioning with tickling as reward

Animals will run mazes and press levers to get tickled [12]. This indicates that the experience is a positive reinforcement from a behaviorist perspective, and a positive affective experience from a psychobiological perspective. Indeed, in a simple "approach-to-hand" paradigm, animals that chirp the most in response to tickling exhibit the fastest approach speeds [12]. Vocalization rate while animals are approaching the experimenter's hand is also highly correlated with approach latency, as depicted in Fig. 4. Indeed, play and tickling are highly rewarding interactions, and animals that emit high numbers of 50-kHz vocalizations

can generally be classified as being more gregarious, and more desirable social companions, than those emitting low numbers of 50-kHz vocalizations.

4.10. Social preferences evoked by tickling

Young animals more readily approach a hand that has tickled them, yielding many chirps, than to a hand that has only petted them, which yields comparatively few chips [12]. Also, young animals like to spend more time with older animals that chirp a lot rather than with those that chirp infrequently. As summarized in Fig. 5, when juvenile rats were placed individually into a modified T-maze that gave them access to two adults, one that still exhibited abundant 50-kHz vocalizations and one that did not, the young animals overwhelmingly selected to spend most of their time with adults that still chirped a lot. These data could be interpreted to mean that animals prefer to spend time with other animals that express positive affect.

If we are willing to assume that such "laughter" responses and preferences reflect the basic neuronal infrastructure of joy within the mammalian brain, these data suggest that a positive form of social affect may be fundamental to mammalian brain organization. Although the social facilitation and social bonding associated with joint laughter remain to be empirically evaluated, laughter certainly is infectious [49], and may transmit moods of positive social solidarity, thereby promoting cooperative forms of social engagement.
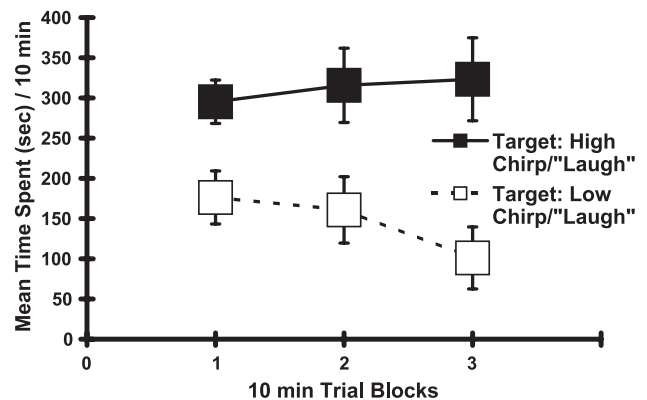

Fig. 5. Long–Evans rats ($n = 7$) which were 30 days of age at testing had been singly housed from weaning at 21 days of age were used in this study. On the test day, they were given the opportunity to shuttle between three compartments via two 4 cm in diameter tunnels during a 30-min session. In one compartment a young adult rat (56 days of age) that had shown high levels of 50-kHz ultrasonic vocalizations in response to manual tickling by the experimenter (high tickle group). In a second compartment, another young adult who had shown low levels of 50-kHz ultrasonic vocalizations in response to manual tickling by the experimenter (low tickle group). The third middle compartment was left empty. Due to the small diameter of the tunnels, only the adolescent rats could shuttle between the three compartments. Data were analyzed with a two-way repeated measures ANOVA. Adolescent rats spent significantly more time with the high tickle animal that exhibited abundant chirps in response to tickling then with the low tickle animal [$F(1,12) = 26.6$, $P < .0005$].

Presumably one ultimate evolutionary function of such states is to help organize social dynamics in support of reproductive fitness. Thus, it will be very important to determine empirically whether shared laughter in humans and chirping in rats are potent factors in establishing friendships and social bonds. Likewise, we have not formally evaluated the infectiousness of rat 50-kHz calls yet, but preliminary observations suggest that animals that can hear other animal playing also become playful as indicated by increased activity and jumpiness (personal observations and Kelly Lambert, personal communication, 2002). Of course, in making these assertions, we recognize that excessive tickling and too much rough-and-tumble can become aversive. In unpublished work we often observe 22-kHz calls at the end of prolonged test sessions.

4.11. Breeding for tickling

The chirping response is a temperamental characteristic of animals, for it can be successfully selected for and against within four generations of selective breeding [63]. Since there has to be brain circuitry for this response, there have to be genes that are involved in the construction and neurochemical support of such circuits. Accordingly, we believe that the search for the genes that control the rat "laughter/chirping" response with modern molecular biology approaches may be one relevant way to analyze the nature of the underlying neurobiological systems. Such work may eventually provide evidence to allow us to judge whether cross-species homologies in such a joy response do, in fact, exist across various species, including humans. Clearly, different individuals and species differ greatly in their capacity for fun and laugher, but we presently know essentially nothing about the underlying psychobiological causes. Parenthetically, we would note there are some data for the existence of heritable factors in human laughter [46].

4.12. The alternative, motor artifact explanations of the response, are not supported

50-kHz calls have been hypothesized to be an artifact of thoracic compression caused by forepaw impact normally exhibited during locomotor activity [7] based primarily on evidence of a locomotor-dependent vocalizations in gerbils [95]. In a series of studies we have shown that 50-kHz calls can be disassociated from locomotor behavior, with increases of 50-kHz calls being associated with a decrease [38] as well as no change [13] in locomotor behavior. As summarized in Fig. 6, we found that only 9% of a total of two hundred two 50-kHz calls recorded occurred either coincident or within 0.5 s after the automated detection of a movement. In fact, there was a nonsignificant trend ($P = .06$) for a greater rate of 50-kHz calls 0.5 s before abrupt locomotor actions then rates within 0.5 s after such events.
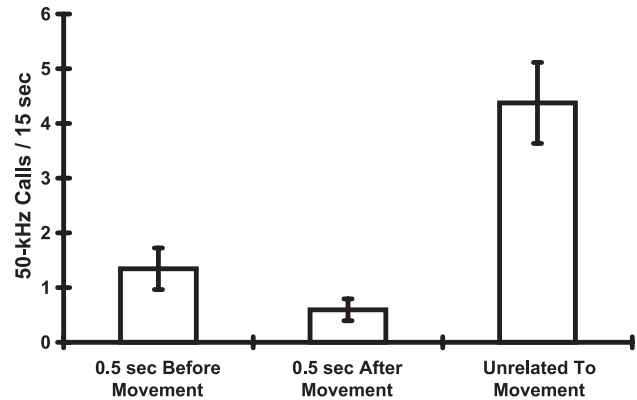

Fig. 6. Long–Evans rats ($n = 4$) were singly housed from weaning at 21 days of age were used in this study. At 54 days of age, subjects were placed on a magnetic stabilimeter, which converted movement into an audible signal. Animals received 5 min of testing consisting of successive blocks of 15 s of full tickling followed by 15 s no stimulation in which the experimenter moved their finger above the animal to elicit 50-kHz calls [61]. The sound produced by the stabilimeter did not mask 50-kHz calls. Sonographic analysis was performed comparing the temporal relationship between 50-kHz calls and sonic artifacts produced by the stabilimeter (indicating a movement had occurred). Paired t tests (two-tailed) revealed that subjects exhibit significantly ($P < .001$) more 50-kHz calls at time points that were not clearly related to the sounds that were coincident with the indices of locomotor activity. There was also a nonsignificant ($P = .06$) trend for more vocalizations to occur during the half second before movement as compared to the half second after the movement.

In sum, even though there is a great deal of data that coaxes us to posit a positive affective dimensions of this response tendency in rats, we must wonder why many other mammals do not seem to exhibit this type of a vocal response. Perhaps vocal components of this emotional state only survived in species whose lives were not threatened by such sounds alerting predators. Ultrasonic calls of rats do not carry far and are hard to detect. Accordingly, the survival of young rats may not have been compromised by the joyful emissions of ultrasonic chirps during their playful activities. Of course, even if there are relations between human laughter and rat "laughter" there are also bound to be many differences, simply because of the long (~ 70–90 million year) divergence since they shared a common ancestor.

5. On the nature of human laughter

Are any of the above data relevant for understanding the mystery of human laughter? As discussed elsewhere [58], the stereotyped vocal pattern of human laughter that first appears in rudimentary form at 2–3 months of age [80,92] suggests an ancient heritage. Of course, the subtleties of human adult laughter, so abundantly expressed during the cognitive delights of humor, may highlight how certain ancient emotional processes interact with refined cognitions within higher reaches of the brain–mind [25]. Since laughter is best understood in our own species, the human phenomenon

must remain the criterion against which work on the "laughter" of other animals must be judged. Unfortunately, there has been remarkably little breakthrough empirical work on human laughter since the insightful observations of Joubert in 1579 [36]. Accordingly, much of what can be said about human laughter must come from the realm of folk knowledge, with all its potential flaws, rather than from the archives of well-established scientific facts.

Here, after a summary of the phenomenology of human laughter, we summarize what little that we know about the evolutionary and psychobiological sources and consequences of human laughter. Because of the dearth of basic research in the area, we will also highlight some key questions that remain to be empirically evaluated.

6. Laughter in infancy and adulthood: from tickling to humor?

Human laughter is fundamentally a social phenomenon, and in young children, it is most easily evoked by playful tickling. Indeed, if one seeks to become friends with a young child, there is no better way to negotiate the social terrain than mutually joyous, escalating tickle games (an obvious fact that remains to be experimentally well documented, although it is easily observed by any sensitive adult who wishes to do so). The perennial childhood puzzle of why one cannot tickle themselves, may be due to the fact that the underlying neural systems are controlled by social cues and interactions—the perception of being wanted/chased as well as the predictability/unpredictability of the resulting social interactions. These are factors that help weave individuals into the social fabric in which they reside, reflecting various hues of position and dominance. Being tickled by another arouses the brain more than being "tickled" by oneself [6]. This fact highlights how subtly our brains have been honed, in part by evolution, to be mindful of social priorities.

During infancy and early childhood, the most abundant laughter occurs in the midst of self-movements during rough-and-tumble play and as a result of friendly tickling by others [80,92]. The response conditions so rapidly that after only a few tickles; one can evoke laughter simply through hand and verbal gestures that imply threats of tickling (e.g., "coochi-coochi-coo"). The fact that certain parts of the body are more ticklish than others, both in humans [32] and animals (Fig. 2), highlights the potential existence of specialized receptor organs in the skin and pathways in the brain to specifically mediate this response.

Infant's engagements with joyful tickling seems to pave the way for peek-a-boo games where the anticipation of certain social dynamics can rivet their delighted attentions [72]. These antecedents gradually lead to children's enjoyment of the many forms of unpredictability in the games, the mischievous pranks and practical jokes they cherish. However, most laughter eventually occurs in the midst of every-

day interactions. Throughout childhood, laughter occurs most commonly and most intensely in the midst of vigorous social engagements, such as the chasing and running activities of rough-and-tumble play [90].

It is a reasonable but not a scientifically established view that the human taste for humor is based, in some fundamental way, on the existence of infantile and childhood joy and laughter [27,28,78]. According to this view, the intrinsic ability of the nervous system to laugh and experience social joy is an essential precondition for the emergence of the type of mental sophistication that is able to find joy and laughter among the slapstick incongruence of life and the interplay of unpredictable cognitive events. How far back play, joy, laughter and smiling go in brain evolution is presently anyone's guess. Some key questions are as follows:

> What we need to determine now is when does laughter occur precisely in the midst of rough-and-tumble play and other social interactions? What behaviors does it predict? What behaviors does it follow? How does tickling laughter become conditioned in a child and other young organisms? How does laughter come to be used for subsidiary social goals? Is shared laughter a potent factor in establishing friendships and social bonds? What is the precise relationship between natural laughter and feelings of mirth? Can laughter and feelings of mirth really change bodily functions and promote health? Where are the neural circuits for laughter and what are their cardinal neurochemistries?" [58, pp. 185–186].

7. The neural substrates of laughter in humans

Since smiling and laughter are the quintessential indicators of joyful affect across human cultures [84], a study of the underlying neurobiological substrates may help us decode the fundamental nature of joy within the brain. As already noted, laboratory rats also exhibit a laughter type response [61], raising the possibility that some aspects of the neural substrates that control human laughter may be clarified through this animal model.

At present, the neuroanatomy, neurophysiology and neurochemistry of laughter remain poorly defined. Although certain neuropathologies (including certain epilepsies) are accompanied by uncontrollable bouts of laughter, often with no accompanying feelings of mirth, they provide only marginal clues to the underlying brain substrates of joy [5]. It has long been known that the progressive diseases in which the insulation around nerve cells (i.e., myelin) begins to degenerate, such as multiple sclerosis and amyotrophic lateral sclerosis, are commonly accompanied by fits of crying and laughter [23]. Often the crying bouts set in first, followed by laughter, but typically, neither is accompanied by the appropriate affect [74]. They are often motor displays, which reflect release from inhibition of deep subcortical motor circuits situated in the brainstem [73].

It is generally believed that feelings of mirth may require higher brain systems. Recent evidence suggests that the frontal lobes help instigate laughter, and the right frontal lobes may be especially important for the appreciation of humor [85]. A remarkable recent discovery is the induction of hearty laughter, accompanied by true mirth, during presurgical stimulation of a frontal cortical area (i.e., the supplementary motor cortex), that has long been recognized as important in the initiation of movement. One 16-year-old girl undergoing brain stimulation for localization of intractable seizures exhibited bouts of vigorous laughter that intensified as brain stimulation intensity increased. A striking feature was that this type of brain arousal led to the projection of mirthful feelings onto "whatever external stimulus was present" [26, p. 650]. A recent PET study of laughter and smiling response to humorous video clips also found activation of the supplementary motor cortex as well as other cortical and subcortical structures during hedonic laughter and smiling [35]. These studies dramatically confirmed that arousal of frontal areas of the brain, which have long been recognized as being more important in the generation of emotions than posterior sensory–perceptual area, are able to trigger feelings of mirth.

What a brain analysis can yield are credible hypotheses about the specific mechanisms through which laughter may operate. At the lowest level of organization there appears to be a response integration system for laughter, the arousal of which may establish an essential precondition for mirth. This system is evolutionarily prepared to respond to certain environmental events, such as tickle and friendly surprising stimuli, so as to facilitate social interactions and to take them in positive directions in ways that promote bonding and cooperative activities. If one tries to envision such processes in dynamic terms, one might imagine laughter and mirth to be global attractor processes that captivate widely reverberating ensembles of neural networks within the brain of one individual that can spread infectiously among interacting individuals. Perhaps such activities release growth promoting molecules of the brain such as neurotrophins, which may help condition the brain in positive and lasting ways that have barely started to be evaluated [30].

8. And the dark side of laughter

Of course there is a dark side to laughter that has not been emphasized here: the "sudden glory" that philosopher Thomas Hobbes saw as the heart of laughter that emerged from a "conception of some eminency in ourselves" (see Ref. [31]). Usually the children that prevail in play tend to laugh the most [9,98], suggesting that to some extent laughter may reflect a social dominance-seeking response, which may pave the way for laughter to stigmatize and degrade others through such behavior. All too often, especially in children, laughter tends to become a psychological tool for teasing and taunting—the establishment of exclu-

sionary group identities that can set the stage for finding mirth in the misfortunes of others. These tendencies may arise rather naturally from the fact that within-group laughter promotes group solidarity, which can then be used to ostracize and exhibit scorn toward those outside the group. We doubt if most other animals are capable of exhibiting such psychological tendencies, but such possibilities certainly need to be considered in future research, especially on other primates. Likewise, the role of such vocalization in the emergence of friendliness and social bonding deserves our attention.

In adults, most laughter occurs in the midst of simple friendly social interactions while greeting and "ribbing" each other rather than in response to explicit verbal jokes [75–77]. The two are brought together in our institution of "roasting" those we love and admire: The more dominant the targets of the roast, the more mirth there is to be had at their good-humored expense. Surely our appreciation of such subtle types of humor arises from fully matured comico–cognitive developments of the brain. There is no evidence that other species partake of such high shenanigans. Indeed, only gradually do children appreciate those foolish social dynamics (e.g., often highlighting self-other disparities and similarities) that we cherish as the essence of jokes and humor, but which can also serve as the basis for social ridicule.

Although it is to be expected that social preferences in humans would be strongly related to amounts of laughter experienced in social encounters, we must leave considerable leeway for perceived reciprocity issues and cultural display rules in such predictions. Certain cultures do not encourage laughter and smiling among strangers [84], and well-enculturated adults are probably sensitized to maintain a balance of laughter among social participants. One-sided laughter can certainly become an irritant, perhaps because it signals high dominance seeking. At a depth psychological level, perhaps we should also suspect excessive self-involvement in those who laugh persistently at their own remarks.

9. Clinical implications of this work with a focus on ADHD, addictions and mood disorders

It is noteworthy that Joubert [36] discussed a variety of still unresolved medical topics in various chapters of his magnificent monograph, such as: "Why It Is That Great Laughers Easily Become Fat," (Third Book, Chapter XIII) and "What Good Accompanies Laughter, and Whether a Sick Person Can Be Healed By Dint of Laughing" (Third Book, Chapter XIV). A relationship between the amount of positive affect and health benefits has also been suggested by more recent pioneers like Cousins [19] who made "the joyous discovery that ten minutes of genuine belly laughter had an anesthetic effect" that allowed him hours of relief from chronic pain (p. 39). Since then, some evidence indi-

cates that laughter can ameliorate certain types of pain (e.g., Ref. [99]), may promote immune functions [43] and reduce some physiological and psychological stress responses [3,100], while enhancing feelings of well-being, in part by counteracting negative affects [41,93]. Some of these effects could be due to the release of endogenous opioids and oxytocin–neuropeptides that are known to be important in mediating social affect [16,34,55], but many other brain and body chemistries are likely to be involved [3].

It is hard to imagine that mirth would fully elaborate in the brain without the accompanying expressive act of laughter. It will be most interesting to know how the readiness to laugh and play are related to the development of psychological resilience as well as to many other dimensions of personality. A more thorough scientific understanding of these psychological birthrights of the human brain may give us new insights on how to better treat various psychiatric and medical problems, and to better regulate the emotional economy of everyday life. Work on such problems may also shed some new light on a variety of classic psychiatric problems.

10. Attention deficit hyperactivity disorders (ADHD)

We have suggested that the preceding data on animal play and laughter may be of considerable relevance for understanding certain psychiatric syndromes, especially attention deficit hyperactivity disorders (ADHD). Psychostimulants like methylphenidate (e.g., Ritalin) are remarkably powerful play-reducing drugs in animal models [2]. It is certainly possible that many children are given such drugs partly because they reduce disorderly behaviors, and at time bladder control problems, that arise from playful urges [58,86], but we must be concerned whether such long-term drug treatments have deleterious consequences on brain development [52]. One major concern is the issue of psychostimulant sensitization, which can lead to long-term behavioral changes in animals which might not be deemed desirable [53,91], including increased drug seeking tendencies [10,44]. Indeed, using our 50-kHz laughter measure, we have found evidence for sensitization. Namely, animals that had been treated with methylphenidate at levels that dramatically reduced play, led to heightened 50-kHz vocalizations in response to subsequent exposures to the play chamber [64]. The potential benefits of play therapy in the treatment of ADHD are supported by preclinical data [30,65].

Although young animals typically do not sensitize as readily as older animals, it does emerge as a function of chronic psychostimulant use. This work also suggests that the neural systems that regulate play and 50-kHz vocalizations can also be dissociated: Namely, psychostimulants reduce rough and tumble play, but if anything, they mildly increase the 50-kHz chirps [13,39]. This allows us to use these vocalizations to potentially monitor drug cra-

ving, using a "self-report" measure of appetitive eagerness [40,66].

11. Chirping as a craving measure in drug addiction studies

Briefly, we have found that the 50-kHz chirping measure can be used effectively to study drugs of abuse which presumably sustain intake partly by the positive affective responses they generate [12,66]. The measure may be a useful supplement to conditioned place preference and drug self-administration procedures [39], and since it is response that could be easily interfaced with neuroethological studies, it provides an potentially useful entry point for analyzing the neural substrates of desire and craving. We will not elaborate on this issue here, since recently it has been extensively discussed elsewhere [40].

12. Laughter, joy and depression

Clearly, further work on the joy evoked by laughter could have implications for the treatment of various psychiatric disorders, especially depression. Indeed, it has been proposed that merely simulating the motor rhythms of laughter can promote positive feelings [17], and laughter has been clinically utilized to promote relaxation and acceptance of one's circumstances [93]. Certain societies already have "laughing clubs" which assume that laughter, even without any explicit humorous stimuli, is a pleasant way to spend time with others and to obtain apparent emotional benefits.

Our hope is that if we ever identify specific chemistries that regulate the tickle-induced 50-kHz chirping response, we may have new ideas for development of new classes of antidepressants that can elevate positive social moods as opposed to simply dampening the influence of negative moods. That, of course, is all that most existing antidepressants do. Now that the potential health benefits of positive emotions are being increasingly recognized [81], we can only hope that solid empirical studies will follow. In sum, it will be most interesting to establish the relationships between the tendency to laugh and mental health outcomes, especially in children. Can the tendency for mirth and laugh be established as an emotional trait variable early in childhood, and will this trait have some predictive validity in reflecting the developmental progression of a child? We anticipate that the utilization of animal models for this may be especially instructive.

The mind–body dichotomy that has characterized much of modern psychological thought is eroding as we increasingly appreciate the powerful relationships between emotional states and bodily functions [50]. Although neurobiological work on laughter and joy remains in its preliminary stages, we can anticipate that future work along such lines will have important implications for mental and perhaps bodily

health issues, both at diagnostic and therapeutic levels [30, 64,65,82].

13. Summary

Whether there are fundamental neural homologies to be found between the "laughing" response of rodents and the playful laughter of human children remains to be assessed using neurological and genetic tools. Such issues may eventually be capable of being evaluated through the cross species contrasting of pharmacological manipulations. For instance, if we find a brain chemical that provokes rodent chirping, we will be most interested to see if it promotes human mirth. At present, we only have preliminary data on that issue which suggests a role for glutamatergic and dopaminergic stimulation in the control of the 50-kHz response [13,29,62,101], but no comparable data is yet available at the human level. If the basic neural substrates for social joy are, in fact, similar in rats and humans, animal experimentation should help us elucidate of the underlying neural details more readily than any conceivable studies in humans. Until data to the contrary emerges, we plan to keep an open mind to the possibility that a detailed analysis of the underlying neurobiological controls may highlight important commonalties between tickle-induced chirping in young rodents and youthful laughter in the human species. In any event, we anticipate that the further study of this and related emotional measures offer powerful new approaches for understanding some of the general principles which mediate positive social affects and motivations within mammalian brains. Through such pursuits, the neuroscience of *epistemics,* as first conceptualized by Paul MacLean, may be substantially advanced.

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