

EXAMPLES OF APPLICATION OF THE AFFECTIVE NEUROSCIENCE STRATEGY TO CLINICAL ISSUES

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In the previous chapter, I summarized how the basic pre-clinical affective neuroscience view of emotional organization of the mammalian brain can facilitate our understanding of human emotional feelings. In this chapter, I will look at the clinical implications of this work, which are substantial, both in the arena of new medication development as well as how we conceptualize psychiatric disorders.

In 1972, it was discovered that all opioid addictions are mediated by a single receptor molecule in the brain, the mu-opioid receptor – the first neurotransmitter receptor objectively identified in the mammalian brain. If this receptor is blocked with drugs such as naloxone or naltrexone, then all the pleasurable and pain-alleviating effects of opiates from morphine to heroin are eliminated. Without this receptor, there can be no opiate addiction and the social chaos that results from abuse of powerful opiate drugs that bind to this receptor. Soon after the discovery of this receptor, it was widely recognized how the magic of opiate molecules in controlling pain, coughing and life-threatening diarrhoea was mediated. However, the widespread distribution of mu-opioid receptors throughout the brain meant that they controlled many other processes.

As soon as this receptor was discovered, we wondered whether there were neurophysiological similarities between opioid dependence and social dependence – whether social attractions and attachments were regulated by this addictive system of the brain. After all, both share a dependence phase – the remarkable affective rush that is evoked in the early phases of relationships, whether with drugs or objects of social desire. However, no matter how positive those initial feelings, they tend to fade, resembling the ‘tolerance’ phase of drug addiction, where one has to take large and larger doses to sustain the positive affect. As the power of initial social attraction, like morphine, tends to fade away, so one often tends to seek new social objects to restore the initial feelings. But even when the powerful initial affect has faded, a dependence process has set in. One cannot feel emotionally normal, or whole, when the drug or subject of dependence is suddenly taken

away. Following both opioid withdrawal and the loss of a loved one, a powerful opponent affective response emerges, consisting of similar symptoms of psychic pain, such as crying, lack of appetite, irritability and difficulty sleeping. The distress is alleviated promptly by the object or subject of affection, and a feeling of psychic normality is restored.

To evaluate whether endogenous opioids did control such social affects, we separated young animals from their mothers to see if opiate receptor stimulants would alleviate the resulting separation distress, as monitored by frequency and intensity of crying. In fact, the separation distress of young animals, whether they were puppies, guinea pigs, rats or even baby chicks, was dramatically alleviated by low doses of all the drugs and neuropeptides that stimulated mu-opioid receptors of the brain. In most of these animals, blocking the mu receptors with naloxone or naltrexone often increased separation distress. Subsequently, we evaluated hundreds of psychoactive agents, and only those that stimulated the oxytocin and prolactin receptors of the brain came close to opioids in their capacity to alleviate separation distress. All others had modest effects by comparison. If the instinctual responses of separation distress are indicative of the underlying emotional feelings, we would predict that facilitation of opioid, oxytocin and prolactin activity in the brain would symptomatically alleviate the feelings of human sadness and grief. Although little work has been done to evaluate such possibilities, recent imaging of human brain opioid activity has indicated that activity of such neurochemical systems is low during sadness (Zubieta et al., 2003).

If we consider that one of the most powerful forms of social affect is derived from the emotional power of human touch, we might expect endogenous opioids to be part of that affective equation. Early psychoanalytic work demonstrated that loving human touch was essential for the survival of human infants (Spitz 1965), and the power of social contact had been demonstrated in many other species (Harlow 1971; Panksepp et al., 1991). When we first evaluated this idea in a simple model of contact comfort (Figure 3.1), it was clear such positive social feelings were mediated, in part, by brain opioids (Panksepp et al., 1980). If young animals could not feel their endogenous opioids, because receptors were blocked with naloxone, they would not settle down (with eye closure and head nodding) as they did when administered placebos. Undrugged animals promptly stopped exhibiting distress vocalizations, and they settled down nicely, but they took two to three times as long to settle down following opioid blockade. Subsequently, we demonstrated that the abundant touch and physical activity of rough-and-tumble play also released endogenous opioids (Panksepp and Bishop 1981), and opiate-blocking agents reduced this kind of vigorous social engagement.

These findings were extended by Barry Keverne's group in Cambridge, especially in their demonstration that primates would release each other's endogenous opioids when they groomed each other (Keverne et al., 1989). Presumably we humans touch each other by the way we talk to each other, and the more care and concern we detect, the more opioid activity is engendered in our brains. Indeed, the 'placebo effect' is now known to be substantially mediated, in



Figure 3.1 When held gently in human hands, newborn chicks exhibit a comfort response consisting of the cessation of vocalizations and eye closure. These effects are attenuated by opiate receptor blocking agent naloxone, indicating internal opioids help mediate contact comfort responses. Figure is adapted from photograph in Panksepp, Bean, Bishop, Vilberg, and Sahley, (1980), as reprinted from Figure 14.9 of *Affective Neuroscience* (Panksepp, 1998a) with permission of Oxford University Press.

part, by brain opioids (Petrovic et al., 2002), further highlighting the fact that many of the medical/psychiatric benefits of placebos might be derived from activation of positive social neurochemistries in the brain and body. It is possible that the healing power of religious practices, from prayer to meditation, may have similar underlying causes.

If animals do not receive enough positive social interaction, they tend to become depressed. A simplified model was generated through the study of socially isolated newborn chicks. Housed by themselves, with abundant food and water, young chicks would exhibit a depressive syndrome, capable of being alleviated by antidepressants, that was more intense in females than in males (Panksepp et al. 1991). Indeed, many animals would die from this aloneness, and simply providing a companion animal to these apparently depressed animals was completely therapeutic. It is noteworthy that human depression afflicts females more readily than males. Might depression be accompanied by low brain opioid activity, resulting from the depletion of positive social neurochemistries?

It has long been known that opioids can exert strong antidepressant effects, and some of the newer variants such as buprenorphine (that are not very addictive since they are only opiate receptor stimulants at low doses) can exert remarkable antidepressant effects in individuals that have responded to no other medications (Bodkin et al. 1995). It would seem that the use of mixed opioid agonists-antagonists, such as buprenorphine, is much under-utilized in the treatment of human depression, especially suicidal depression. It is possible that low doses of buprenorphine would

temporarily restore pleasure chemistries in the brain to such an extent that one can therapeutically work through acute suicidal crises more easily than one could with other sedatives that are more commonly used. Also, considering that oxytocin is as effective in the amelioration of separation distress as opioids, it is worth considering that such medications should be quite effective in alleviating human sadness/grief, and perhaps the more chronic conditions of melancholia, and the ensuing chronic depression.

In this context it is also worth considering that one major reason young people are attracted to opioid drugs, leading to addiction, is because they feel alienated, with inadequate positive social feelings from their interactions. They discover that opioids can alleviate their chronic distress. Considering that oxytocin tends to maintain opioid sensitivity in the brain (Kovacs et al., 1998), one wonders whether early childhood rearing practices that focus on loving interactions, with abundant physical touch/warmth, would tend to reduce the incidence of opioid addiction. However, once it (an addiction?) has started, it would seem that the utilization of mixed opioid agonists/antagonists, such as naltrexone, should have a more prominent place in early interventions provided in combination with abundant positive social support, in soothing-calming environments where confidence and desire for living can be restored. Many powerful interventions could emerge from attempts to restore potential imbalances in social neurochemistries in various disorders, especially when provided in life-affirming therapeutic environments.

Opioid dysregulation in autism

Our emerging understanding of the complex chemistries of social feelings can lead to new interventions with intractable childhood disorders of social motivation such as autism, which is characterized by deficits in socialization, communication and imagination.

It is well recognized that autism has strong biological dispositions, as highlighted by the concordance rate of up to 90 per cent for identical twins (with susceptibility loci now identified in half the chromosomes, suggesting complex epistatic genetic interactions), which is twice the level of concordance seen in schizophrenia. Many brain abnormalities have been identified in autism, characterized by larger cerebral hemispheres and often smaller and poorly organized subcortical limbic areas. For instance, the abundance of small, poorly branching neurons in the temporal lobes (amygdala and hippocampus) suggest that limbic-emotional connectivity with cortico-cognitive areas is impaired, and deficits in genes such as reelin may lead to migrational mistakes in cortical cell layering. Although there is no presently known way to restore such connections, abundant early single-trial learning as well as broad-scale sensory integration interventions are often beneficial, as should be eliminating potentially exacerbating toxins in the children's environments.

Although no medications have been specifically approved for autism, the similarity between many of the classic symptoms of autism (e.g., pain insensitivity, lack of crying, social aloofness, various stereotypies) were sufficiently similar to

those we had observed in our animals treated with low doses of opioids, that we entertained the idea that at least a subset of autistic children may exhibit autistic aloneness, because of excessive opioid in their systems (Panksepp 1979). This idea was proposed because it had an immediate therapeutic end-point, and could be easily evaluated through the use of opioid antagonists. Of course, we did our best to evaluate the potential efficacy of such a medication first, through pre-clinical testing.

Our most compelling evidence came from analysing the social motivation of dogs given low doses of morphine or naloxone. We systematically evaluated changes in their desire to interact socially by focusing on how intensely the animals wagged their tails and how willing they were to lick our faces. Of course, we did this in a very systematic and replicable way using blind-testing procedures, and we found that low doses of morphine (0.25 and 0.5 mg/kg) made the animals more autistic-like; they would not wag their tails as much in our presence, and it took them longer to come and lick our faces. In contrast opiate receptor blockade with naltrexone led to more tail wagging and faster face licking, the kinds of pro-social effects – increases in social desire – we hoped to obtain in autistic children (Panksepp 1981).

It took an unexpectedly long time to get the clinical trials going, partly because the use of the orally effective opiate receptor antagonist naltrexone was banned from human trials for several years by the Food and Drug Administration in the United States in the mid 1980s. There was some fear that the drug was a potential carcinogen. Indeed, it was subsequently discovered that opioids do regulate tumour growth, but the low doses naltrexone (LDN) that we were hoping to use actually tend to reduce tumour growth, which is currently leading to abundant off-label use of this agent as a cancer treatment (www.lowdosenaltrexone.org).

In any event, when we first evaluated the agent in Linz, Austria, with Patrick Lensing, and in Paris, France, with Marion Leboyer, we obtained positive effects in about half the children. The optimal dosage regimen seemed to be 0.25 mg/kg given orally every other day (masked in a favourite food to hide the very bitter taste). About half the children exhibited increased social motivation, attempts to communicate, and more flexible social interactions and toy play (Panksepp et al., 1991). Often the benefits, which included increased cheerfulness, were most evident on the intervening no-drug days, but there was a lot of variability from child to child.

Our clinical impression was that only those children responded well who exhibited some opioid-withdrawal symptoms soon after the initial administration of the medication – symptoms such as tiredness, negative affect, even crying (sometime for the first time). This suggests that some children may in fact have higher than normal opioid activity in their brains. Of course, since reducing opioid tone can increase social motivation in animals, we need to advise parents of the implications of this for their child. Thus, we routinely advise the parents that this medication is not like aspirin for a fever, where one can simply get a medical response without the parents' participation. If their child turns out to be one of the lucky ones where their

social window can be nudged wider open with naltrexone, the parents need to exhibit increased social sensitivity to get the most out of the medication for their child.

Still, the present status of naltrexone in treating autistic symptoms remains ambiguous, largely because the track record of double-blind studies is mixed, with only about half exhibiting statistically significant therapeutic effects (typically studies done on quite young children, with very low doses of the medication), while the reported failures often use older children or young adults, and much higher doses of medication, administered daily. Also, our philosophy was that one should not give medications which increase social motivation, without alerting parents to the need to be attentive to increased levels of social solicitation and responsivity, so we intentionally included such a demand characteristic in our methodology, but most studies that have failed to see effects take no special measures to facilitate increased parental attention and engagement. Of course, it could be that this placebo effect is the main reason for the therapeutic effects seen in about half the children, but that is unlikely in double-blind studies (e.g., Bouvard et al. 1995).

The evidence for abnormalities in circulating opioids has remained mixed. Although Gillberg et al. (1985) originally demonstrated that opioid-like activity was elevated in the brains of about half the children, subsequent studies have failed to find elevated cerebrospinal B-endorphin levels in autistic kids. Of course, there are now many distinct types of opioids in the brain, and no thorough evaluation of all of them has yet been conducted. In studies of plasma opioids, some typical opioids have been normal while certain unusual species have been massively elevated, and normalized in children that are naltrexone responders (Bouvard et al., 1995). Although elevated opioids seems unlikely to be a primary cause of autism, it appears to be an exacerbating factor in about half the children, and a good double-blind study is needed just in those children that exhibited elevated opioid levels and/or initial positive responsivity to naltrexone.

In any event, this agent can provide some relief from some of the troubling symptoms of autism in some of the children, especially if it is used in the context of good social support from parents or caretakers. It is by no means clear that the main therapeutic effect is due directly to the opioid blockade, and it remains possible that the naltrexone makes certain children more socially responsive because their own internal opioid reward systems are responding more appropriately to social stimulation. Indeed, if this is the case, perhaps even lower doses of naltrexone, such as the 4 mg doses that are now common in the LDN therapies of various medical disorders, might be optimal, especially when given just before bedtime (perhaps as a trans-dermal preparation, to avoid the aversive taste). Under those conditions, one's own opioids would be expected to be higher, and perhaps more responsive, when one awakens.

Although many variables remain to be evaluated in LDN therapy, it can be quite a benefit to family life when it works. Responders who have good verbal skills can provide some insight into what is happening psychologically. For instance, I asked a very high-functioning 16-year-old autistic girl, who was very self-centred

and obsessive, but had good language skills, what she was experiencing from the benefits that were apparent on the medication. Soon after starting 0.25 mg/kg naltrexone, she started to participate more in family activities, would be more willing to go out shopping with her mother, and would be considerably more social and even talk about what was happening on the TV shows she was now watching with her parents. During a visit, I asked Jennifer, ‘You seem so different after the medication. How has the medication changed you?’ She looked at me, a bit perplexed and said: ‘Medication hasn’t changed me. The world has changed!’ This is a profound statement about how we project our feelings into the world. When our emotions change, often the world appears very different to all of us.

The larger lesson of the above work is that the study of basic emotions in animal models is a robust strategy for asking important psychological questions that we could ask in no other way. In animals we can

- 1 evaluate the role of genetic vulnerability in detail (e.g., via the use of knockout mice)
- 2 systematically study environmental toxic factors, since they can be directly manipulated
- 3 study the relevant underlying brain and body systems in detail
- 4 isolate the developmental processes more rigorously
- 5 evaluate biological therapies before considering their use in humans.

In any event such a strategy first coaxed us to evaluate the efficacy of naltrexone in the treatment of young autistic children. However, all psychiatric problems are not medical problems, and now I would like to share one childhood problem that may be more of a social-developmental problem than a neurobiological one.

Play and Attention Deficit Hyperactivity Disorders

We have now been studying the basic mechanisms of rough-and-tumble play in a laboratory rat model for a quarter of a century. This is one of the easiest and most enjoyable emotional processes to study systematically, since all young rats have a strong intrinsic urge to play. Early work has been summarized in Panksepp et al. (1984) and in various more recent reviews (Vanderschuren et al., 1997; Panksepp 1998a; Siviy 1998). This is an important experient-expectant process that has important implications for brain and psychological development (Spinka et al. 2001; Gordon et al. 2003), as well as the understanding of the nature of social-joy within the mammalian brain. Most recently we have been focusing on play vocalizations as a direct measure of this positive emotional experience, and have garnered considerable evidence about the nature of social joy, perhaps even the evolutionary nature of our childhood laughter (Panksepp and Burgdorf 2003).

A fuller understanding of mammalian play systems may offer new and practical therapeutic ideas for various developmental disorders, but most especially for the millions of American children diagnosed with Attention Deficit Hyperactivity

Disorder, who are being treated with potential drugs of abuse, which may have long-term developmental effects on the brain and mind.

Psycho-stimulants like Ritalin (methylphenidate) are among the most powerful play-reducing drugs ever discovered through the use of animal models. Might it be that so many children are given Ritalin these days partly because it reduces disorderly behaviours that arise from poorly regulated playful urges? If so, adequate research should be conducted to determine how play and psycho-stimulants influence long-term brain organization. Troublesome facts have already arisen from animal research. These drugs easily 'sensitize' animal brains making them hyper-responsive to similar drugs throughout the lifespan. Typically young animals do not sensitize as readily as older animals, but some sensitization has been observed in young animals.

Our past work with animal models has demonstrated that play 'therapy' reduces impulsive behaviours resembling ADHD (Panksepp et al., 2003). Might play also be therapeutic for children diagnosed with ADHD? We may shed light on such issues if the deep sources of play in animal brains are, in fact, evolutionarily similar to those that motivate our own children to romp with each other. Using animal models, we have shown that playfulness arises from ancient, subcortical brain systems we probably share with other animals. Play is certainly a fundamental source of joy, but it probably also helps organize the brain/mind in pro-social ways. It may, along with separation-distress and social-bonding systems, be one of the fundamental tools that nature provides for the epigenetic construction of the social brain.

How might play facilitate normal brain development? Our pet hypothesis is that it 'fertilizes' brain functions by promoting genetic activation of neurotrophin-type molecules, such as brain derived neurotrophic factor (BDNF), which help brains mature in beneficial ways. For example, Gordon and colleagues (Gordon et al., 2003) have collected data suggesting that gene-expression of BDNF in the frontal cortex and amygdala is facilitated by playful activities. However, there are many other fertilizers from GDNF to FGT (Glial Derived Neurotrophic Factor and Fibroblast Growth Factors) to be analysed (Riva et al., 2005). If play is an experience-expectant process for the construction of the social brain, there may be serious consequences for brain maturation in children who have little chance to play normally, as happens in many families today. Since the urge to play is a neurological 'drive' or urge, we suspect that if it is left unfulfilled then symptoms of ADHD may readily emerge in social situations where rough-and-tumble activities are restricted, such as classrooms. Surprisingly, the rough-and-tumble play of our species was not formally studied until quite recently (Scott and Panksepp 2003), and we were surprised that boys and girls generally exhibited the same number (frequency) of specific play gestures, even though the roughness of the play, which is difficult to measure objectively, was probably higher in boys, who are generally bigger and stronger. Eric Scott and I have now completed a feasibility study of a play-intervention programme for pre-kindergarten classes within our local public school system and the children liked it very much even if some of the teachers did

not. We have not yet been able to pursue such a study with ADHD-type children.

There are a variety of compelling issues to be considered: what if it turned out that a substantial percentage of ADHD kids receiving psycho-stimulants are simply normal kids who have strong, unsatisfied desires to play? What if these medications sensitize their brains? It is disturbing to contemplate these issues, especially since some animal research already suggests that early experiences with such drugs can promote addiction later in life (Panksepp et al., 2002), although there are also other studies that suggest such drugs may reduce addictions (Andersen 2005). For the time being, our research goal is to determine how access to rough-and-tumble play modifies the long-term organization of the mammalian brain (Panksepp et al., 2003), and to see how psycho-stimulants either facilitate or impede such processes in animal models.

We are also already probing the genetic code with micro-array (gene chip) technologies, and wish to determine which genes are tuned up or down in animals permitted to play. We want to evaluate differences between animals that play a lot and those that do not. We are eager to know if differences may exist between boys and girls, by studying male and female rats at various ages. We want to know whether patterns are different between winners and losers, not only as they emerge during joyous playground activities but also on the embittered battlefields of adult life (which should provide data relevant to the types of social loss that often promote depression: Kroes et al., 2006). And, of course, we want to know how psycho-stimulants modify genetic expression profiles in young brains.

Some may believe that it is premature (even presumptuous) to suggest that such animal data may have important implications for human clinical practice. This is bound to remain a controversial issue until robust predictions are generated for humans. For starters, our predictions are that

- 1 when properly evaluated, we will find that psycho-stimulants reduce the urge of human children to play;
- 2 a regular diet of physical play, each and every day during childhood, will be able to alleviate ADHD type symptoms in many children that would otherwise be on that 'clinical' track;
- 3 play will have long-term benefits for children's brains and minds, benefits that are not obtained with psycho-stimulants;
- 4 under some conditions, psycho-stimulants may sensitize young brains and intensify internally experienced urges that may, if socio-environmental opportunities are available, be manifested as elevated desires to seek drugs;

if and when we finally get to the genetic studies, we anticipate that the profiles of gene-activation resulting from lots of play and lots of psycho-stimulants will be quite different in the brain.

In short, we suspect the data will show that different genetic tunes can be strummed in various regions of the brain by the relevant pharmacological and socio-environmental factors. We anticipate that the bottom line of such research

will be in accord with what Plato asserted in *The Republic* (section IV) when he insisted that

our children from their earliest years must take part in all the more lawful forms of play, for if they are not surrounded with such an atmosphere they can never grow up to be well conducted and virtuous citizens.

(Plato 2000: 573a)

At present we are devoting much research effort to figure out the nature of social joy within the mammalian brain. Our main model, rough-and-tumble play in juvenile rats, has now been refined to one exquisite indicator of the underlying affective processes, a 50 kHz chirpy vocalization that is abundant during play (Knutson et al., 2002). When we discovered that we could obtain this vocalization simply by tickling young rats (Panksepp and Burgdorf 2003), we initiated an intense research programme to characterize this simplified model of joy (Panksepp and Burgdorf 2003), and we are narrowing our search to specific systems of the brain (Burgdorf and Panksepp 2006), which may yield new neurochemical control systems that may help us think about much better medications for social-emotional problems of our own species.

Development of new medications

Once we understand the neurochemical details of the various core emotional systems, we will have the basic knowledge needed to think about how we might best seek to alleviate the affective burdens of people in emotional distress. We can finally be certain that many of our passions and our hungers and all variety of delights and agonies of the soul have chemical codes. Some of the chemical messengers cut across many species of feelings (i.e., the biogenic amines such as norepinephrine and serotonin), while others are unique to one or another motivation.

Many of these *specific* carriers of the affective life will be molecules of the neuropeptide class (short protein sequences), which can control neuronal system sensitivities and responsivities for extended periods of time. This not only helps explain why many feelings linger, but also provides new ways to think about how we might coax them to linger in different ways. I have discussed these possibilities more extensively elsewhere (Panksepp 1993, 1998a; Panksepp and Harro 2004). However, I would reaffirm my belief that the subtle mind medicines that we can create from this knowledge will be best used with a new sensitivity for those who need such help. Many of these molecules will work best when combined with sensitive psychological care offered in environments that support the ability of people to see their lives from different affective perspectives. In this vision, people with deep emotional needs and disturbances, will have to be full participants in professional attempts to restore affective balance (Panksepp 1999). They should not just be given pills and sent on their way.

The battle over whether psychological or biological therapies are better for

psychiatric disturbances finally shows signs of abating. Modern brain imaging has demonstrated, time and again, that psychotherapy has demonstrable and beneficial effects on the brain. This is creating a sea-change in our conception of who we are and what we are seeking to accomplish in therapeutic interventions (Cozolino 2002). Dan Siegel said it well in the Foreword to Louis Cozolino's penetrating book: clinicians immerse themselves

in the stories of individuals who come for help in feeling better. . . . Whatever the approach, lasting change in therapy occurs as a result of changes in the human mind . . . which involve changes in the functions of the brain. Exactly how the mind changes during the therapeutic process is the fundamental puzzle that the synthesis of neuroscience and psychotherapy seeks to solve.

The all pervasive cognitive-emotion interactions

Since emotional states are so effective in channelling perceptual and cognitive processes, an increasing number of investigators seem eager to conflate cognitive and affective processes during the current 'emotion revolution' that is captivating cognitive science (e.g., Lane and Nadel 2000). Although it is essential eventually to understand how emotional and cognitive processes interact at the neuronal level, for their interchange is intimate at the psychological level, little progress, aside from some coarse localized brain regions of interest, little deep understanding can be achieved until we better understand the basic core emotions. I suspect the current attempt to see both affect and thought as two sides of the same cognitive coin hinders a solid scientific confrontation with one of the most important and most neglected issues of mind/brain science – the fundamental nature of affect. As already noted, it is possible that the many socially constructed emotions rely on the more basic ones for their affective impact, and their cognitive distinctiveness to the core relational themes they represent. Hence, emotions such as abhorrence, contempt, empathy, loathing, scorn, smugness, even disgust, guilt and shame, may require certain types of cognitive framings in order for several concurrently aroused basic affects to coalesce into a new emotional entity. To understand these emotions, we must truly consider cognitive and affective processes conjointly.

The fact that most everyday cognitions are deeply embedded in affective structures (yielding an abundance of socially constructed emotions) should not lead us to neglect the even deeper evolutionary nature of affective experience. For instance, human infants come into the world as profoundly affective creatures. Their initial cognitive limitations are erased gradually by experiences in loving intersubjective spaces where they can be potent actors on the world stage that now envelops them. Their first explorations are not devoted to the inanimate world, but the eyes, the voice, the touch of the caregiver – who is, we hope, a mother whose brain affective systems have been well prepared not only by culture but also by the loving touch of

neurochemical systems that can make engagement with an infant a special delight. It is from the rich intersubjective dance of mother and child from which future possibilities are woven, in both humans (Trevvarthen 2001; Reddy 2003) and other mammals (Meaney 2001). To believe that these infants, in their first engagements with life, are unconscious packages of reflexes as opposed to affectively engaged human beings is an intellectual travesty that is not yet erased from the sad ongoing history of the behavioural sciences. It has been even worse when scientists have considered the lives of other animals (Panksepp 2005a).

It is of the utmost importance for our society to promote a new and deeper level of emotional education – an affective intelligence that can abort the emotional neglectful ‘sins’ of parents being passed on to children in cycles of child abuse that are more commonly mental than physical. Every emotional system that has been studied exhibits use-dependent plasticity. This means that if one has been exposed to too many horrible experiences, then the brain systems that mediate the resulting feelings will have been strengthened. Infants that have lived at the centre of caregivers’ positive emotional engagements, and have been offered manageable life challenges with which they become engaged, have been given a precious gift of life. When we begin to understand how the solidification of emotional habits occurs at the neuronal level, which is much deeper than simple learning of phobias, then we may also learn how to partly disentangle the damage that has been wrought by emotional misfortunes (Panksepp 2001; Sunderland 2006). We remain far from such knowledge at the present time, largely because of a lack of will in our culture to pursue such questions in our fellow animals. Without emotionally informed animal brain research, it is to be hoped done with utmost inter-species sensitivity, that kind of knowledge will never be ours.

In sum

The understanding of the foundations of human and animal nature, and the recognition that we are inheritors of core emotional-affective systems that are remarkably similar to those of other mammals, will, we hope, eventually penetrate our culture. If that is achieved, without marginalizing the best of our cultural achievements, it can be a very beneficial cultural achievement for the human race. There is a primitive affective consciousness built into the infrastructure of our brains that is the birthright of every mammal, bird and perhaps some other animals as well. Considering the fact that emotional feelings are so important in guiding cognitive and social decision-making (Damasio 1994; Adolphs et al. 2003), we must certainly wonder whether the existence of cool rationality in the human mind has been overrated.

The acceptance of this possibility – that the lower sub-neocortical region of our brain may have a consciousness of its own, has yet to be accepted by the neuroscience community. Most scholars of emotions are still committed to the view that affective feelings, to be experienced, need to be ‘read-out’ into the higher regions of the brain. Some would place the read-out in the somatosensory regions of the

neocortex (Damasio 1994, 2003). Some would place the read-out in the working memory regions of the dorsolateral frontal cortex (LeDoux 1996). Yet others suggest that all forms of consciousness are critically dependent on our linguistic abilities, and hence mostly on the language regions of our left hemispheres (Rolls 1999). How this magical 'read-out' might occur has not been clarified by anyone. I personally do not believe it exists, even though those higher areas are very important in regulating emotions by generating attributions and all the cultural dimensions of emotional life. Abundant evidence already shows that the sub-neocortical regions have the neural sophistication to construct certain emotional aspects of our mental lives, the parts we share with many other animals – raw affective experiences. The key areas which are critical for this achievement may be very deep and ancient brainstem structures such as the PAG and surrounding tectal areas, which help elaborate a core self (Panksepp 1998a, 1998b; Damasio 1999).

None of us really needs higher order thoughts to achieve a coarse affective level of awareness (pain is an excellent example). Yes, our cognitive apparatus is remarkably important in resolving our affective experience into all manner of subtle nuances. Crucial as those attributional contents are for our mental life, the energetic engines to achieve the intensity of felt emotions are sub-neocortically situated. Infants emerge into our cognitive worlds by seeing how their feelings relate to the world into which they were born. And, of course, our understanding of the world is critically dependent on the emergence of those cortico-cognitive abilities. This gradually emerging cognitive apparatus adds an enormous cognitive richness to our lives, but without our inborn, fully embodied, neuronally energized capacity to feel good and bad about the world – those basic tools for living that we inherit – we and the other animals would be zombies.

A major challenge of twenty-first century neuroscience is to confront the deep evolutionary nature of human emotional response systems and the affective feelings they help create. Most psychiatric problems ultimately reflect difficulties individuals encounter in regulating their feelings, whether precipitated by environmental and organic problems or, most commonly, by interactions of the two.

Most of my own scientific career has been devoted to deciphering the fundamental sources of emotions in human and animal brains. This project is based on the recognition that the foundations of our emotions are shared, in principle, with other mammals. Through animal brain research, we may shed more light on the neuro-evolutionary sources of our human emotions than by studying members of our own species. Obviously, we cannot evaluate deep neuroscience issues in humans the way that we can in other animals, just as we cannot easily evaluate cognitive contents in animals with anything like the efficiency we can in humans. On the other hand, a mountain of evidence suggests that the essential neural substrates for a multitude of emotional-affective processes are concentrated in those sub-neocortical regions of the brain, commonly known as the limbic system (MacLean 1990), that we share homologously with other mammals.

The overriding premise of my work has been that if we study the shared neural foundations of human and animal nature, especially through a study of the various

evolved *state-functions* of the mammalian nervous system, we will gradually reveal one of the great mysteries of life – the fundamental neuro-evolutionary sources of affective experiences in all mammals. Again, this is not to suggest that the *channel-functions*, which reflect specific types of information processing (e.g. cognitions), can yield any comparably robust cross-species knowledge. However, if we pursue the neuro-emotional work well, we may gain a profound understanding of the nature of affective life in all mammals, which may even promote a new, and deeply appropriate and needed, sensitivity toward both wild and domestic animals.

Because obvious ethical concerns forbid such research on humans, only animal brain research can reveal how the specific circuits and molecules of the brain generate the miracle of affective consciousness. A careful reading of the evidence garnered from other animals demonstrates that our basic emotional feelings may arise substantially from evolutionary processes that evolved to generate ‘instinctual’ emotional behaviours. In other words, affective feelings appear to be closely linked to the ‘action neurodynamics’ that generate instinctual emotional displays within the animal brain. Whether this requires read-out by higher neocortical systems is unresolved, but it does not appear to be essential from what we presently know about these systems. If anything, emotional behaviour in animals is increased by removal of neocortical tissues, and these behaviours do not appear to be affectively vacuous. One of the most dramatic and intriguing positive emotional urges is that for rough-and-tumble play in young animals. The joyous feelings underlying such action patterns do not have to be learned, even though they probably guide both behavioural choices and a great deal of subsequent learning. Indeed, the instinctual nature of affects within human brains makes them one of the major factors upon which all of us base our life decisions.

To derive useful knowledge from such animal studies (e.g., novel therapeutic agents as well as novel non-organic approaches), we will have to understand the molecular underpinnings and psychobehavioural consequences of these systems better than we presently do. Fortunately, the neuroscience and molecular biology revolutions have now provided the essential tools for a penetrating pursuit of such questions. The work has already yielded potential neurochemical codes for various emotions, drives and appetites – the many state-control systems of the deeply SELF-referential brain – that may be the primal sources of our biological values and possibly a major source process for consciousness itself.

My own long-term aim is to take the type of analysis described in this chapter to a genetic level. New genetic methods are capable of probing how the DNA ‘orchestra’ plays its tunes under different environmental circumstances. ‘Gene chip’ technologies, which monitor the changing activities of tens of thousands of genes simultaneously, are among the most promising ways to clarify such issues. However, utilization of such difficult techniques requires communication and collaboration among scientific subcultures not well acquainted with each other’s views. My short-term hope is to characterize, with the help of skilled colleagues, the molecular-genetic consequences of playfulness (Panksepp et al., 2002).

In concluding this chapter, I want to add a few comments about an issue that

may be of considerable concern – the ethical issues associated with the study of affect in animal models. Many will justifiably feel both emotional discomfort and cognitive concern about such work on which our neural knowledge of emotions is based. These are appropriate and difficult issues: as soon as we accept that other animals have emotional lives, the ethics of such research must become a key issue. This is one reason I dealt with such issues at the very outset of my text on *Affective Neuroscience* (Panksepp 1998a). Since we have no reasonable alternative way to obtain this knowledge, ethical compromises may need to be made by investigators willing to seek this knowledge. The pursuit of such investigations puts special responsibilities upon investigators to pursue their inquiries with the least amount of stress to their animal subjects. Indeed, many of the issues I have described can be pursued in such a way that critical studies concerning emotional circuits can be conducted under full anaesthesia.

Such concerns have convinced me to pursue positive emotions more than aversive ones. Still, the bottom line is that we will never obtain this important knowledge unless we are willing to pursue certain lines of experimental inquiry, without denying that there are ethical sacrifices that must be made in order to obtain this knowledge. There is also the likelihood that most laboratory animals do not have the cognitive depths to consider such issues from human perspectives, and that if we take special additional efforts to assure that our experimental animals are allowed to live within their ‘comfort zones’ that perhaps we have not offended them as much as we would have if they had had the capacity cognitively to conceptualize their place in the living order. Obviously, if we do not pursue detailed animal brain research on such issues, we will forever remain ignorant of the deep neurobiological nature of those affective processes that guide human and animal lives.

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