Neural Development: Affective and Immune System Influences

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Abstract: *This paper proposes that the developmental processes of Edelman's Neural Darwinism fit together in a very coherent way with the present increasing understanding of the importance of the affective dimension in neuroscience. A synthesis of these two features, with the evolutionarily determined primary affective systems together with the immune system providing the value system required by Neural Darwinism, provides an integrative viewpoint relating psychological issues at the macro level to neurobiological processes structuring neuronal connections at the micro level. We look at the various implications of such an integrative viewpoint relating genetically determined affective systems to higher cortical functions, considering successively developmental and functional issues, primary and secondary emotions, psychological issues, evolutionary issues, language, genetic issues, neurological issues, and potential outcomes of the proposal. We suggest that the "wet-wiring" nature of neurotransmitter mediated synaptic connections may be related to this integration. We then consider the implications of molecularly based links between the brain and the immune system, showing this too might play a significant role in the processes of neural Darwinism. Indeed this could possibly relate to the evolutionary origin of affective systems.*

1: Introduction

Two recent contributions have advanced understanding of brain function: Gerald Edelman's "Neural Darwinism" (Edelman, 1989, 1992; Edelman and Tononi, 2001), dealing with how brain development and function can be well understood in terms of a process of natural selection applied to neural connections, and Jaak Panksepp's formulation of "Affective Neuroscience" (Panksepp, 1998, 2001), addressing how neurobiological systems mediate the basic emotions[3]. We point out here that these theories can complete each other in a very satisfactory way, providing a synthesis which strengthens support for each of the theories individually, and also provides an extended understanding of important interactions in the brain. In brief: on the one hand, major features of the basic value system crucial to Edelmann's neural Darwinism but not fully elucidated by him can be provided by the affective neuroscience of Panksepp. On the other hand, important aspects of the mechanism implementing Panksepp's proposal that "valenced affective feeling states provide fundamental values for the guidance of behavior" can be explicated by emphasizing neural Darwinism in a way that more fully accentuates current understanding of developmental biology.

This proposed synthesis (which might perhaps be called "Affective Neural Group Selection") then gives a useful standpoint from which to investigate the relations between affective neuroscience and neural Darwinism, and to consider aspects of developmental and evolutionary psychology. In this synthesis the emotional neural systems in the brain play an important role in selection of higher cortical connections. We present our proposal in terms of a central hypothesis which then leads to a series of conjectures that flesh it out, these in turn leading to a series of detailed questions that are susceptible to development and investigation. We indicate what some of the latter are, but do not have time or space to develop them in detail here. However this overall structure does indeed show that our central hypothesis is a fruitful one which can lead to interesting further investigations.

The second theme of this paper addresses the role of immune system-brain interactions in such neuronal selection, suggesting these links too can be interpreted as playing a significant role in neural group selection processes. It is well understood that not only are there causal links from the brain to the immune system (Sternberg, 2000; Webster et al., 2002; Kiecolt-Glaser et al., 2002) but also from the immune system to the central nervous system (Mulla & Buckingham, 1999; Maier & Watkins, 2000; Larson, 2002; Maier, 2003). In addition, it is suggested here that immune mechanisms might have been significant in the evolutionary emergence of the hierarchy of signals that result in neural Darwinism. This part of the paper takes our initial theme and extends it in a consistent way to further areas.

2: Neural Darwinism

Edelman argues that generalised principles of Darwinian natural selection ("Neural Darwinism") must apply in the developmental process controlling detailed neural connections in each individual's brain (Edelman, 1989, 1992; Edelman & Tononi, 2001)[4]. The theory[5] has three main elements:

1. Developmental selection,
2. Experiential selection,
3. Re-entry

(Edelman, 1989, pp.4-8; Edelman, 1992, pp.81-98; Edelman & Tononi, 2001, pp.79-92). The chemical gradients of molecules, which in some cases are the same as those used by the immune system, steer neurons in the generally right direction and these molecules may also prevent pre-programmed apoptosis. Competition for synapses then weeds out those which receive less use. In other words general tuning occurs by chemical gradients, but epigenetic experience provides specific tuning of those pathways.

The key feature that concerns us here is that, after developmental processes establish a great variety of connection patterns between neurons, a process of synaptic selection occurs within neuronal groups as a result of behavioural experiences that modify affective states. These changes occur because certain synapses are strengthened and others weakened without macroscopic changes in the anatomy, although there might be microscopic changes such as perforated synapses or changes in dendritic spines. "This selectional process is constrained by brain signals that arise as a result of the activity of diffusely projecting value systems, a constraint that is continually modified by successful output" (Edelman & Tononi, 2001, p.84; see also Deacon, 1997, p.202; Schore, 1994, pp.162, 253, 257)[6]. An example of a value system is the noradrenergic system, originating in the locus coeruleus and projecting diffusely to the entire brain, releasing norepinephrine. The unit of selection is neuronal groups (Edelman, 1989, pp.43-69; Edelman, 1992, pp.95-99). The "groups" that are selected experientially are those neurons which participate in ongoing, reciprocal signalling between widely separated regions of the brain (forming "re-entrant networks"). This parallel interchange allows for coordination and synchronous firing in the individual components of the neural group enabling coherent coordinated output. Edelman suggests that this re-entrant firing provides the basis for both learning and consciousness.

This argument extends the Darwinian type of understanding from the evolutionary processes that historically led to the existence of the brain and shaped the genotype to also underpinning both brain developmental processes and brain functioning, thus directly affecting the phenotype. This is in accord with the way that such processes are now understood to underlie the functioning of the immune system through clonal selection[7] (Burnet, 1959; Edelman, 1992, pp.77-78). Thus such principles are already known to occur in human physiological functioning in the immune system, giving the same benefits as discussed here: putting in place a mechanism that can deal efficiently

with conditions already encountered, but that can also deal adequately with situations that have never before been encountered by the organism. Through this mechanism, "In a very literal sense, each developing brain region adapts to the body in which it finds itself" (Deacon, 1997, p.205). Thus this provides a neural mechanism underlying traditional learning theory, also imbedding it in the broader understanding of the adaptive power of Darwinian selection processes, seen as one of the most important mechanisms in biology.

3: The Affective Connection

The key issue then is what provides the fitness characterisation determining whether particular connections are strengthened or not. In Edelman's terms, this is the value system guiding the neural Darwinism, which he relates physically to a fan of connections spreading out from a relatively small number of monoaminergic, cholinergic, and histaminergic neurons located in various brainstem and hypothalamic nuclei (see Edelman & Tononi, 2000, p.46). It is proposed in this paper that *the signals provided by the set of primitive emotional functions described by Panksepp (1998, 2001) are the key signals in the value system guiding neural selection*. This would tie brain functioning to vital capacities developed by evolutionary processes, strongly related to survival, and giving a specific set of mechanisms to implement Panksepp's hypothesis that "affect is a central organizing process for sentience" (Watt, 1999), namely diversity of the primary repertoire, selection based on epigenetic modification of synaptic connections resulting in a secondary repertoire, and re-entrant signalling based on reciprocally connected neural maps (see Edelman, 1989).

Panksepp presents in his work a careful neurologically based taxonomy of basic emotional processes, each related to specific neurotransmitters and associated with activity in specific subcortical brain areas. These are the evolutionary heritage we share with many members of the animal kingdom. They play a fundamental role in human behaviour: "the basic emotional states provide efficient ways to mediate categorical types of learned behavioural changes. ... emotional feelings not only sustain certain unconditioned behavioural tendencies but also help guide new behaviours by providing simple value coding mechanisms that provide self-referential salience, thereby allowing organisms to categorize world events efficiently so as to control future behaviours ... [they] may provide efficient ways to guide and sustain behaviour patterns, as well as to mediate certain types of learning" (Panksepp, 1998, pp.14-15). That seems just what is required to explicate in detail the value system needed by neural Darwinism (Edelman & Tononi, 2001, pp.87-90). Emotions, in this context, are then the core of pre-organized mechanisms which "help the organism classify things or events as 'good' or 'bad' because of their possible impact on survival" (Damasio, 1995, p.117).

The basic emotional systems identified by Panksepp (1998) are the following:

E1: The SEEKING system: general motivation, seeking, expectancy (pp.52-54, 144-163).
E2: The RAGE system: rage/anger (p.54 and pp.187-205).
E3: The FEAR system: fear/anxiety (p.54 and pp.206-222).
E4: The LUST systems: lust/sexuality in the male and female (p.54, pp.225-245).
E5: The CARE system: providing parental care/nurturance (p.54, pp.246-260).
E6: The PANIC system: panic/separation, need of care (p.54, pp.261-279).
E7: The PLAY system: rough-housing play/joy (pp.280-299).

Panksepp gives a detailed characterisation in each case, including associated key brain areas and neurotransmitters (for a summary, see Panksepp, 2001, p.147, and Table 1 below, developed from

Watt 1999 and Panksepp 2004). These systems – processing sensations such as heart rate, palpitations, breathing changes, vasoconstriction etc, and leading to activity in the cortical regions - embody the basic preferences or biases of the organism that guide its further behavioural development.

These basic emotional systems underlie the higher-level systems that develop in the brain (Panksepp, 1998, pp.300-323). Various inputs to the SEEKING system to do with thermal balance, hunger, thirst, sexual arousal, etc. enable it to provide the basis of maintaining homeostasis. This system also drives the basic impulse to search, investigate, and make sense of the environment. The foundation of learning is then provided by satisfaction or dissatisfaction associated with the success or failure of one's endeavours as motivated by the SEEKING system. Presumably as brain development takes place this underlies the development of systems that carry out specific tasks to aid these functions, in particular systems that anticipate what may happen by means of some kind of modelling of the external world, including anticipation of the behaviours of others.

The explicit hypothesis we make is

> ***Hypothesis:*** *The basic emotional systems E1-E7 identified by Panksepp, together with inputs from the endocrine and immune systems, are necessary and sufficient to provide the value system of neural Darwinism identified by Edelman and Tononi.*

This makes explicit the way in which emotions underlie rationality, extending the understanding of the significance of emotions beyond that recognised by Damasio, namely

(i) the production of a specific reaction to an inducing situation,
(ii) the regulation of the internal state of the organism so that it can be prepared for a specific reaction (Damasio, 2000, pp.53-56),

to also including

(iii) shaping of brain functionality, including the aspects classified as rational.

This proposal agrees with his statement that "emotions are curious adaptations that are part and parcel of the machinery with which organisms regulate survival" (Damasio, 2000, p.54). They do so both in the short term through facilitating homeostasis, and in the long term through facilitating the development of intellect (Damasio, 2003). In this way "all mammals, indeed all organisms, come into the world with a variety of abilities that do not require previous learning but which provide immediate opportunities to learn" (Panksepp, 1998, p. 25).

Thus what is proposed here can provide a neural mechanism underlying behavioural development and learning, and is therefore supported by all the body of evidence that emotion is developmentally and functionally important. In genetic terms, "the genome helps set the precise or nearly precise structure of a number of important systems and circuits in the evolutionarily old sectors of the human brain" (Damasio, 1995, p. 109); these innate circuits then "intervene not just in bodily regulation but also in the development and adult activity of the evolutionarily modern structures of the brain .... whose precise arrangement comes about under the influence of environmental circumstances complemented and constrained by the influences of the innately and precisely set circuits concerned with biological regulation" (Damasio, 1995, p. 109; Damasio, 2003, pp.30-59). It is through this process that the visual, auditory, sensory, and motor systems all contribute to the development of the central nervous system as a whole.

The present proposal is that this happens through the mechanism of Affective Neural Darwinism outlined above. Furthermore, it is suggested that apart from immune and endocrine system inputs

discussed below, the seven basic emotional systems E1-E7 together with sensory input and life-experience are *sufficient* to sculpt the developing brain; there are no other unidentified sectors of the value system. This means that when taken together with physiological needs, they are sufficient to underlie any system of "human universals" such as that proposed by Brown (1991).[8] Of course such broad concepts are hiding a vast number of essential details, and it is mainly in the explication of the details that scientific progress must be measured. It is this assumption of sufficiency that gives this proposal bite and enables it to be tested in a variety of ways discussed in the next section, and allows it to help guide the required explication of the details.

4: Implications of Affective Neural Darwinism

What are the benefits of this view? From the viewpoint of neural Darwinism, it provides a crucial link between macro-behavior and the formation of synaptic connections by identifying the macro-features of the value system in psychological terms. This system is characterised in functional terms in Edelman & Tononi, 2001 (pp.87-90), but not related there to specific macro-features of behaviour. This identification clarifies the causal nature of that system in relation to individual development and function. From the viewpoint of the affective neurosciences, it is largely unsurprising because it is just a slightly more specific version of what some already believe (e.g. Panksepp, 2001b); it emphasizes explicitly that the effects of primary affective states include adaptive selection of neuronal groups as well as their immediate effect on neuronal functioning. However although the affective viewpoint has been substantiated by recent studies (e.g. Panksepp, 2003c), it is nevertheless still contested and not gaining as much ground as one might have expected (Panksepp 2002, 2003b)[9]. The main benefit here may well be in supporting that view by indicating how naturally it fits with a neural Darwinism viewpoint.

What features might be expected and so could serve as a test of this proposal? It serves as a unifying theme that will ultimately be tested by how well it links neurological processes on the one hand and psychological issues on the other, tying them in to evolutionary and developmental processes. That is, the test is how effective it is as an integrating theme suggesting how neurological processes may be tied in to macroscopic aspects of consciousness.

On this view, the primary emotions E1 to E7 characterised above become the lynch-pin linking neurophysiology to experience and the social and physical environment. They link macro-events to neural micro-structure by top-down action from the macro to the micro scale. Consequently they are a key both to brain physiological development and to evolutionary development of secondary emotions and higher cognitive functions. This should play itself out in terms of both evolutionary psychology and developmental theory, and hence in terms of psychiatry (relating both to physical and developmental disorders) and learning theory. In particular it should manifest in terms of behavioural alterations associated with physiological changes in the primary emotional areas, and in terms of commonalities with our animal relatives. This section outlines how that might work out.

4.1 Developmental and Functional Issues. The key factor underlying brain development is the fact that the stored information in the human genome is far too little to control brain development by itself. The Human Genome Project has revealed (Baltimore, 2001; Wolfsberg et al., 2001) that there are of the order of 45,000 genes in the human genome; but there are about 10^{13} cells in the human body and 10^{11} neurons in a human brain. Consequently – remembering that this genetic information has to cover development of all other bodily structure as well as the brain - there is not a fraction of the information required to structure in detail any significant brain modules, let alone the human brain as a whole (Damasio, 1995, p.108), for there is only one gene per 10^7 neurons and

per 10^9 neural connections. The fact that there may be multiple reading frames for specific genes does not alter this conclusion: the discrepancy in numbers is far too large.

Human development has to take place in the face of these genetic limitations, and this is a key reason why neural Darwinism is necessary as an effective mechanism structuring the brain and adapting it to both the local molecular and encompassing social environments. We can make this specific through the following set of conjectures that flow out of our basic hypothesis:

> ***Conjecture 1****: the only hard–wired parts of the CNS are the spinal cord, brain stem and diencephalon together with its sensory inputs while the cerebellum and telencephalic structures are genetically determined only in terms of basic neuronal structure and broad connections between different brain areas. The detailed connectivity in the cerebellum and telencephalon are determined by neuronal group selection*[10].

By *hard-wired*, we mean neuronal connections are determined largely by genes read in the local molecular context, and therefore susceptible to immune and endocrine influences during early development; however, these connections are thereafter fixed except that their strengths may vary according to use in a standard Hebbian way. The chemical milieu in which neurons find themselves early in development can play a role in organization of the brainstem emotional systems, but thereafter these connections are, relative to those in telencephalic structures, more stable and fixed. The reason for this is that it is important that the brainstem structures should not be subject to constant change, as they themselves provide the value system for later emotional development; there is no other value system, by hypothesis. Many of these structures also exhibit use-dependent plasticity, as mentioned above, but by itself this does not guide development in a way dependent on the interplay between a value system and experience; rather it plays a supporting role in such developments. The situation would become dynamically unstable, going into unbounded oscillations or exponential instability, if neural Darwinism applied to the connections determining the value system through the values implicit in that system itself. These structures must under most circumstances be fixed and unchanging in order to provide long-term stability; thus they must be relatively free of perturbation. Nevertheless extreme environmental circumstances during development may provoke dysfunctional changes in the value system.

> ***Conjecture 2:*** *Consequently, the only genetically specified brain functions are the unconscious basic regulatory capacities plus instinctive drives together with the basic emotional systems and basic sensory-motor pathways. No higher cognitive capacities are hard-wired: they are determined by developmental interaction with the internal and external environments in conjunction with the internal (self-referential) effects of the brain on itself.*

> ***Conjecture 3:*** *The secondary emotions and higher cognitive capacities develop under the guidance of the value system provided by the basic emotional systems together with broad information from the immune and endocrine systems. Consequently these higher capacities are shaped by the dimensions of the basic emotional systems, which are the filter through which environmental effects and experience are evaluated and used to guide brain development.*

On the view put here, there is a clear distinction between primary and secondary emotions. The *primary emotions* are affective states arising primarily from subcortical brain structures (the amygdala, basal forebrain, hypothalamus, and nuclei of brainstem tegmentum) that we share with other mammals. On the other hand *secondary emotions* arise through the effects of the primary

emotions on cortical regions (ventromedial prefrontal, cingulate and insular cortex) in the course of daily life and social interaction. In brief: primary emotions are hard-wired during early development, secondary emotions are soft-wired products of experience. Both may give rise to conscious awareness. In the main, secondary emotions correspond to social emotions developing out of the primary emotions with a social character (CARE and PANIC, also to some extent LUST and PLAY); this issue is discussed below. Note that some secondary emotions may also occur in other animals, developing through their social interactions.

The key question underlying these conjectures is what use is made of the very limited number of genes available for brain development. The view here is that this genetic information is used to hard-wire the brainstem and diencephalic structures, as outlined above, and to soft-wire the rest. Higher level brain development will be only generically set genetically, and then will be determined in detail by neural Darwinism in response to life experience, with the value system guiding that process provided by the less malleable primary emotional systems E1-E7 as listed above.

Intrinsic personality differences will then depend on the relative strengths of these seven affective systems, which are sufficient to determine development of higher-level aspects of the brain.[11] One can in cartoon fashion imagine a genetic genie together with the early developmental environment setting the values of the relative strengths of the systems E1-E7 for each individual on the dials of an instrument panel; these relative strengths are then fixed for life, determining that individual's basic emotional type. This is the initial material which then interacts with the physical and social environment to develop the adult personality (Donald, 2001); hence the systems E1-E7 provide the emotional palette that guides brain development.

How this works out will depend on the manner in which the social environment responds positively or negatively to these basic emotional capacities. Different personality development, in terms of secondary emotion and cognitive development, will occur according to the relative strengths of the basic systems E1-E7 on the one hand and the responsiveness and emotional tenor of the environment in each of these dimensions on the other. An analogy is helpful here: consider colour vision. Because of the genetically determined hard-wiring of the long, medium, and short wavelength photoreceptor systems, colour vision is determined by the relative sensitivities of these systems. The possible nature of colour vision disorders follows from this: there are seven possible types of colour blindness depending on which of these primary colour systems is impaired (with disorders related to non-functionality of a single colour system being more likely than those with two or three of them being dysfunctional)[12]. These can be tested for and related to genetic disorders.

If the view proposed here is correct, the pallet of primary emotions characterised above similarly determines the different kinds of emotional disorders that may occur for genetic reasons. Further, vision is determined developmentally as well as genetically: if a person or animal were kept in an environment where some colours never occurred (for example, they were kept continuously in a room illuminated only by very long wavelength light so that it avoided stimulating one set of receptors) the associated visual ability would presumably decay, and they would at later stages be unable to see the colours that had been omitted in their developmental environment. This suggests that analogous, although much more complex, emotional disorders could arise for individuals brought up in emotionally stunted environments. The possible natures of these disorders would again be determined by the pallet of primary emotions.

In functional terms, this whole setup may be regarded as a feedback control system, using genetically determined inherited goals to guide the development of the organism in accord with information implicit in those goals about survival needs in the world in which the organism lives. This kind of use of information in feedback control systems is characteristic of the way that higher level order emerges in hierarchically structured complex systems (Ellis, 2003). The information is mainly used to attain equilibrium of the organism in its environment, that is, the process is one of homeostasis. According to Milsum (1966), all human physiological systems can be regarded as means to attaining homeostasis. This theme is presented in a different way by Damasio, who emphasizes homeostatic regulation carried out by a multibranched affective tree (Damasio, 2003, pp.30-59). The bottom level consists of metabolism, basic reflexes, and immune responses. The next level is pain and pleasure behaviours associated with reward and punishment - the first stage of the "value" system. The next level is drives and motivations including play, exploration, sex: also part of the value system. Then he has "emotions-proper" such as fear, anger, shame, guilt, and at the top "feelings", a term which he reserves for qualia-like conscious awareness of emotional states, but he emphasizes that all of these levels (including emotions and feelings) are regulators of homeostasis. This is basically in accord with our view; we address the relation of these higher levels to the value system in our discussion of secondary emotions below.

From our viewpoint, we have a causal hierarchy characterised in an extremely simplified form in Figure 1. The emotional system sends information on the affective state of the organism to the cortical areas, thereby influencing the way neurons fire in the cortex and helping shape the outcome of current neuronal operations there; thus they inform the cognitive functions and modify their outputs. This is bottom-up action from the emotional system to the cortex. Similarly the higher cortical areas send information on the way the higher brain views the situation to the emotional system, thus informing it and modifying its outputs; this is top-down action from the cortex to the emotional system. However additionally, through the value system, bottom-up action by the emotional system helps shape the network of neuronal connections in the cortex; it is crucial that there is no converse downwards effect from the cortex to the emotional system.

We may summarise by saying that emotion and intellect interact with each other operationally, but emotion shapes intellect developmentally. In short: *emotion underlies intellect*. This hypothesis can be tested overall by extending the range of investigations of factors underlying human cognitive abilities (Carroll, 1993) to include the relative strengths of the primary emotional systems E1-E7 as outlined above. This may help illuminate the key unresolved issue of why some people are cleverer than others (Deary, 2001, Chapter 3).

4.2 Primary and Secondary Emotions. A key point is the relation between primary and secondary emotions (Ekman & Davidson, 1994, pp. 5-48; Damasio, 2003). On the view put forward here, secondary emotions would arise through the effects of the primary emotions on the cortex in the course of social interaction, the primary emotions based in subcortical limbic structures being our genetic heritage from our animal forbears. The secondary emotions are not part of the value system, as they don't originate in the same loci as the primary emotions. They are however indirectly able to be effective in determining neural connections through the mechanisms of neural Darwinism, because of their powerful ability to affect the state of primary emotions, which then act as the value system. In this way the secondary emotions can modulate both the immediate state of the primary emotions, and their longer-term effects through sculpting neuronal connections.

It is clearly crucial to clarify which are secondary and which are primary emotions. As an example, Damasio (2003, p.44) suggests universal primary emotions are,

P1. happiness, **P2**. sadness, **P3**. fear,
P4. anger, **P5**. surprise, **P6**. disgust,

and (pp.45 and 156) characterises developmentally emergent secondary emotions as,

S1: embarrassment, shame, guilt;
S2: contempt, indignation;
S3: sympathy, compassion;
S4: awe/wonder/elevation, gratitude, pride;
S5: jealousy, envy.

Because of animal behaviour patterns (Manning & Dawkins, 1998, pp.395-401; Slater, 1999, pp.200-204), there is a good case to add to these,

S6: social rank/dominance,
S7: belonging/exclusion.

Now these proposals may be compatible with our functional distinction between primary and secondary emotions, but this needs testing in each case; where there is a disagreement, we suggest our functional distinction should take precedence because of its grounding in neurostructure. Furthermore the classification of secondary emotions is not settled, and one can suggest that they will be universal in humanity, because of the universal nature of the developmental experiences leading to their existence. To what degree they are shared by higher primates and other animals is a fascinating subject for further study.

The point is that it isn't 100% clear which ones should be considered primary and which are derivative. Others would have different lists than those of Damasio given above[13]. The need is to come up with a coherent classification that makes sense in the light of the mechanisms proposed here and also relates sensibly to Panksepp's list E1-E7, which is not the same as the list P1-P6 above. Those listed as primary must be sufficient to underlie development of all present day intellectual and emotional capabilities, including the secondary emotions, as outlined in Conjectures 1 to 3 above, and should also be related to activity in specific subcortical structures and neurotransmitters utilized in their activation[14]. Thus a revised categorisation of primary and secondary emotions, and a characterisation of which primary emotions are most important for developing which secondary ones[15], is an important task.

The outcome of all this should be either a confirmation that Panksepp's list E1-E7 is indeed adequate to serve as the basis of higher emotional and cognitive development, or a proposal for further additions to that list in order that it is indeed sufficient. There could for example be a case for adding a basic underlying emotional system

E0: PLEASURE/PAIN, an overall "state-of -the-system" assessment, related to overall happiness/welfare/unhappiness and corresponding to Damasio's emphasis of the importance of these overall aspects of emotion (Damasio, 2003, pp. 32-34).

To make this good one would have to identify a corresponding physical locus and associated neurotransmitters. A possibility is that this dimension is related to the noradrenergic system, originating in the locus coeruleus and projecting diffusely to the entire brain (Kingsley, 2000, pp.131; Edelman and Tononi, 2001, p.84), and closely related to the SEEKING system (Panksepp, 1998). Further elucidation is needed. Pleasure/pain may just be part of the seeking system, although

the way this affective dimension is characterised by Damasio differs from Panksepp's description of E1.

Reconsideration might decide that some of the primary emotions listed by Damasio (see above) should be considered as additions to Panksepp's list. Alternatively the conclusions might be that some of them, for example **P6**: *Disgust* in which the insular cortex (Wicker, 2003) plays a major role, should rather be classified as secondary emotions. Furthermore **P5**: *Surprise* seems to be a reflex rather then an emotion (it does not convey specific values suggesting any specific actions are appropriate), and so should either be taken off the list of primary emotions, or incorporated with **E0**.

Additionally it is plausible that in view of our animal forebears' social structures, some of the social emotions may in fact be primary (i.e. hardwired through the evolutionary process and related to specific genes) because of their high survival value, suggesting a re-classification of some of the secondary emotions identified above as primary. This might specifically apply to **S6**: *social rank/ dominance*, which would then be re-classified as primary rather than secondary, and possibly also to **S1**: *embarrassment, shame, guilt.* Alternatively one would like a definite proposal as to how these can reliably emerge in each individual from the primary emotions through the processes of social interaction, for example based on **E5**: The CARE system and **E6**: The PANIC system, which are basic emotions related to sociality and so could possibly provide the basis needed for these to develop as secondary emotions.

4.3 Psychological issues. The developmental environment might be characterised in a similar way in terms of its responsiveness and depth in these emotional dimensions; the ultimately resulting personality will depend on the interaction between the environment and the intrinsic capacities in each dimension.

Two theoretically possible kinds of experiments indicate how it would in principle be possible to test the above hypotheses. They are,

> ***Experiment 1*** *(structural effects)*: surgically or chemically inactivate the various basic emotional systems E1-E7 in young children or animals, and see what the developmental results are;
>
> ***Experiment 2*** *(environmental effects)*: raise children or other mammals in a milieu where they receive only cognitive rather than emotional stimulation, and see what the developmental effects are.

In the latter case, one could have a set of four comparison groups:

E_+I_+, an emotionally and cognitively stimulating environment;
E_+I_-, an emotionally stimulating but cognitively deprived environment;
E_-I_+, an emotionally deprived but cognitively stimulating environment; and
E_-I_-, an emotionally and cognitively deprived environment.

It is well known that in the latter case children will lag developmentally, will lose weight, and may even die from lack of caring attention. For example Coe and Lubach (2003) have recently reviewed the effects on the health of infant monkeys and children of the interaction of immune and psychological factors in during separation. This matrix of comparison will determine which effects are more significant, and the hypothesis will be that *it is the emotional aspect that is*

developmentally more important. One could further separate this out according to emotional category by depriving the subjects separately of stimuli/responses in each category E1-E7. Of course it might be impossible to deprive a child in just one emotional category, or even to completely separate emotional and intellectual stimuli, but still one could find environments where there were sufficient differences in these dimensions to look for such effects.

Although these variables cannot be experimentally manipulated in humans, there are situations in which this has been *effectively* what has happened, through either genetic defects or physiological trauma in the first case, and through impoverished home or environmental circumstances in the second. However this is not an all–or–nothing affair: one can create a causal matrix to test for *degrees* of such genetic and environmental effects, in particular testing for various relative strengths of the basic emotional systems on the one hand, and to what degree emotional/cognitive aspects are encouraged and responded to in particular family/school/life situations, on the other. Thus a meta-analysis could be carried out using studies already in the existing literature. (There is a great deal of relevant modern animal information on such issues, including neuroscience varieties. For an excellent review of the animal literature see Panksepp, 1998.)

The causal interactions here are of course immensely complex; nevertheless if the basic thesis proposed here is true, it should in principle be possible to characterise the relative strengths of the basic systems E1-E7 by psychological tests, and similarly to characterise the developmental environment along the same dimensions, and then to relate these two causal features to psychological tests of resulting secondary emotions and cognitive capacities, so determining a causal matrix for these primary relations. The ultimate way to test the proposed integration would be characterisation of developmental and functional disorders resulting when the various brain regions corresponding to the systems E1-E7 either suffer damage at an early age, or are developmentally defective *ab initio*. These would be contrasted with physiological damage leading to impairment of operations of the secondary emotions S1-S7, which are known to lead to a series of functional disorders (Damasio, 1995, 2003). This all clearly ties in well to the concept of emotional intelligence (Goleman, 1996) as well as the importance ascribed to emotion in design issues by Donald Norman (2003).

Примечание [GE1]: moved

This leads on naturally to studies of the relation to child developmental issues (Schore, 1994): what kinds of interactions in terms of the primary emotions E1-E7 are conducive to sound child development, and what to pathological development? What social interventions may be useful as a result? A vast amount has of course been written on this topic, and in particular Panksepp (2001b) has already developed this theme to a considerable degree in the context of affective neuroscience. Relating the sufficiency proposals made here to that literature would be a useful exercise.

It might even be possible to develop a relation of adult psychological personality categorisation schemes to the basic factors E1-E7, perhaps suggesting related psychological disorders and interventions (Panksepp, 2002). Clearly that would be a very complex and demanding project; nevertheless the hypothesis of the key developmental role of the basic emotions E1-E7 might be useful in this context too. The ***Five Factor Model*** (FFM) is viewed by most contemporary personality theorists as representing the best current model of personality structure. Developed through factor analysis, it suggests that personality can be best described in terms of five basic dimensions: *extraversion* (**E**), *emotional instability* (or *neuroticism* **N**), *openness to experience* (**O**), *agreeableness* (**A**) and *conscientiousness* (**C**). Data collected in several distinct cultures from both genders and various ages all yield five similar factors (e.g. McCrae & Costa, 1997; Costa et al., 2001; McCrae, 2001) suggesting that personality trait structure is universal. Other theorists have suggested that **E** and **A** form the axes of an interpersonal circumplex characterising interpersonal

behavior (Trapnell & Wiggins, 1990) on which they can be alternatively labeled *affiliation* and *dominance*. If these five orthogonal factors are in fact universal, they would have arisen either through genetic influence or experience common to all humans, and it would be expected that they bear some relationship to primary emotions. It might be that SEEKING provides a physiological basis for **E** for example, and PLAY for **O**. PANIC and CARE together might contribute to **A** while RAGE and FEAR provide aspects of **N**.

Примечание [GE2]: moved

The FFM may provide a mechanism to characterize different basic personality types according to the relative strengths of the basic emotional systems: the `settings on the dial' corresponding to each aspect E1-E7 of the basic emotions mentioned above[16]. In extreme cases, some of the settings might be either zero or exceptionally high, with the corresponding basic emotion either missing, with corresponding personality disorders resulting (for example E3- is an lack of emotion type E3), or pathologically dominant, with the dual emotional disorder emerging (for example $E3_+$ is over-dominance of emotion type E3). Injury might cause destruction of one or more of the basic emotional capacities, leading to similar emotional-lack disorders, the difference from the previous ones being that these problems will in this case start at some specific event in the individual's history, rather than being there *ab initio*. The FFM has already been shown in numerous studies to differentiate various personality disorders (Lynam & Widiger, 2001) and has indeed already been incorporated in the Affective Neuroscience view (Davis et al., 2003; Reuter &Hennig, 2003).

Примечание [GE3]: moved

There is a clear relation of the above to learning theory in terms of exploring emotional relations underlying learning success (in contrast to approaches based on rational aspects alone). One might suggest here for example that it is **E1**: The SEEKING system that is the primary driver in the learning of skills and abstract understanding, but with the **E7**: the PLAY system also playing a significant role, generating alternative possibilities that express creativity; and consequently that these are the ones that would be most significantly correlated with educational success; and indeed there is a large literature on the importance of play in the development of the mind (Bruner et al, 1976; Hughes, 1998; Frost et al., 2000). This proposal helps to explain why the PLAY system is important enough to be genetically determined through the evolutionary process (being a primary rather than secondary emotion).

Many schooling systems rely on **E3**: The FEAR system as a main motivational driver, which may well work in the short-term but at the expense of attaching such negative emotional tones to the relevant topics as to make probable failure of educational achievement in the long term. This would agree with what Skinner and other behaviourists pointed out: that organisms learn more readily through reward than punishment. However the implications of the present view are more than that: they are that *we should pay considerable attention to the affective climate in our educational systems as well as to the intellectual quality of activity* (c.f. Salovey and Sluyter 1997). Of course high quality intellectual activity can inspire pupils and so be a driver in the affective domain, but that cannot be taken for granted, and it is possible that *good educational outcomes may be at least as dependent on the emotional atmosphere in the classroom as on the intellectual quality of material engaged with*.

4.4 Evolutionary issues. The proposal put here has significant implications for evolutionary psychology (Barkow et al., 1992). Specific evolutionary psychology proposals should only claim to produce brain modules that have in fact been genetically implemented, and the suggestion here is that these are only the primary emotions E1-E7 plus automatic reactions. Claims of any further brain modules need solid substantiation in terms of showing they are indeed (a) physiologically existent and (b) genetically determined, taking into account the limitations on genetic information mentioned above.

Thus this proposal should enable a re-visiting of the specific claims of evolutionary psychology, seeing if one can relate them to the primary emotions E1-E7 and subsequent reliable development of secondary emotions S1-S7, without supposing any other genetically determined systems. Here, as indicated above, we define basic emotions as those that are genetically determined in the context of the developmental environment and secondary emotions as those that then are developmentally determined.

One task would be to show *why each of the genetically determined primary emotions E1-E7 plays such an important role in individual functioning in the face of threats to survival, that it became hard-wired into the species.* This re-visitation might result in postulation of specific further basic genetically determined modules needed for explanatory completeness, that could then be searched for physiologically and psychologically, for example (as noted above) checking if some of the social emotions are hard wired. In terms of evolutionary game theory, the idea would be to determine what might be an *evolutionary stable set of emotions* that could underlie evolutionary stable strategies. There is a clear relation of this proposal to studies of primates and our other close animal relations who share a large part of our genetic heritage, so ethology is also very relevant (Panksepp, 2003a).

Apart from looking at our close relatives such as apes for the corresponding emotional systems and their developmental effects, for example looking at the role of the amygdala in such animals (Aggleton & Young, 2002), relevant tests could be carried out on animals such as mice, lab rats, and naked mole rats, the latter being of particular interest in this regard because of their eusociality. By doing so one might be able to establish the kind of link envisaged here between emotional systems and behavior in those animals, and so establish relevant aspects of the path of its evolutionary development (Panksepp, 2002). One could also look for its precursor traces in much simpler animals such as *C. elegans* and *Drosophila*, thereby tracing even earlier parts of this evolutionary history.

4.5 Language. The key issue of language and symbolism separates humans from all other animals (Deacon, 1997; Hauser et al., 2002). There may be a significant difference in the way the seeking system operates in humans as opposed to in all other animals in order to allow language development in conjunction with the vocal apparatus allowing speech. This mechanism must provide the basis for brain-language-culture co-evolution (Deacon, 1997; Donald, 1991). As argued above there is not sufficient genetic information available to specifically determine construction of language modules (Pinker, 1994), but rather the mechanisms to develop such modules must evolve; see Edelman (1992), Deacon (1997), Panksepp (1998). Similar issues arise in relation to mathematics and numeracy (Butterworth, 1999; Devlin, 2000).

It may well be that language develops in response to strong emotional pressures related to development of culture and social interaction between ever more conscious beings in a social context (Bonner, 1980; Donald, 1991, 2001; Tomasello, 2003). Thus apart from **E1**: The SEEKING system, one might expect that together with **E7:** the PLAY system (important in all cognitive development as discussed above, and known to be important in language development, see e.g. Bruner 1985, Rinaldi et al., 2000), it is **E5**: The CARE system that is crucial in language development in the individual, because it is the mother-child dyad that is crucial in early mental development (Schore, 1994) and communication between them must be the essential foundation of individual language development; this will be strongly driven by parent-child bonding. Hence one can look at these basic emotional capacities in those with language disorders both in terms of psychological tests of those basic capacities, and checking for structural or chemical variations in areas important

to these emotional systems. One might also include the proposed emotions **S6**: *social rank/ dominance* and **S7:** *belonging/exclusion* as drivers of language ability, whether these are in fact primary or secondary emotions.

Furthermore in evolutionary terms one would look for some substantial change in these systems at the time that language arose, subsequently seen as a difference between us and our closest primate relatives. One could compare such possibilities of a change in the SEEKING or CARE system with the claim that the sudden expansion of the cortex, based on the number of times the neural precursor cells divide, might have been enough to lead to language, given that other apes have already well developed emotional responses including curiosity and nurturance. However that scenario fails to explain why the expansion of the cortex took place. It makes sense to ask if some other change took place first, that then led to the need for greatly increased memory and/or computational capacity.

The further challenge here will be to explain from this perspective the kinds of developmental issues that have led Pinker and others to postulate a specific intrinsic language module (Pinker, 1994). These apparent in-built grammatical propensities should arise out of the way the generic pattern-seeking apparatus of the cortex interacts with the seeking system in response to environmental stimuli. Showing how this happens is an intriguing and substantial challenge; Tomasello (2003) may have already done what is needed here, but his proposal, based on *intention-reading* and *pattern-finding* on the one hand, and on *usage based linguistics* (emphasizing that language structure emerges from language use) on the other, could usefully be revisited in the light of the affective connection (which he does not emphasize). The CARE system will plausibly play a major role in intention reading; while pattern-finding (and associated world modelling) would seem to be central to the SEEKING system's functioning.

4.6 Genetic issues. Given the claim that the basic emotional faculties are genetically determined, clearly one could try to locate the specific genes related to each such capacity E1-E7 (functionally based in the limbic system). One can in principle determine which sets of genes or quantitative-trait loci (QTL) are related to which basic emotional system by looking for correlations between disorders in development in the corresponding brain areas and the characteristics of the individual's genome. These disorders should lead to developmental consequences as indicated above, so those can be looked for also, realizing however that many disorders are complicated by complexity of interactions in several pathways. For example Fullerton et al., (2003) have recently reported a genetic linkage scan identifying QTLs that influence variation in the personality trait of neuroticism.

In particular, genetic studies of families showing inherited language disabilities should be particularly informative in relation to the development of language, as briefly mentioned above. Lai et al. (2001) have recently reported finding a mutation on chromosome 7 which severely disrupts language but not other abilities. One could presumably try to trace the developmental pathways associated with the relevant genes, and compare the human genome with animal genomes in this context in order to search for differences associated with the rise of language. We mention this possibility of what would be immensely complex studies, without attempting to give any details at this point, because they would be an important part of the overall project and our proposal would be incomplete without indicating this link.

4.7 Neurological issues. We have not attempted here any detailed characterisation of the brain areas and neural connections underlying the above proposals, and of course a vast amount is known about these connections (see e.g. Schore, 1994 and references therein) and in particular about the

regions and neurotransmitters associated with specific primary emotional systems (see Panksepp, 1998; and Chapter 4 of Solms and Turnbull, 2001, partially summarised in Table 1 below). The final requirement to pull the present proposal together is to pursue those neural connections in detail and see how the connectivity between the various parts of the limbic system and the various areas in the cortex might implement the suggested neural Darwinism mechanisms based on the primary emotions.

Thus we need to relate this proposal to a much more detailed characterisation of how the different affective systems connect to different brain regions. This will not be attempted in this brief paper, for it is a large task whose elucidation will require much further endeavour. However the overall point is that *the different primary emotions E1-E7 are of primary significance for the different secondary emotions and cognitive powers, and the major neural connectivities should reflect this set of functional relations*. Two further comments are as follows:

First, the emotions listed above are valenced: many are negative emotions suggesting either avoidance or confrontation (`fight or flee'), but some are positive emotions suggesting reinforcement. These two valences (to some degree depending on the context) must presumably be handled in a different way through the effects of their associated neurotransmitters, which may either strengthen or weaken neural connections (but not in simple overall correlation to the valence of the emotion). Explicating this would seem a worthwhile exercise.

Second, we note that it is possible for neurons to be directly wired to each other, rather than so often using the rather odd mechanism of sending neurotransmitters across a synaptic gap to convey information from an axon to a dendrite. Why has this strange soup-based mechanism evolved, instead of the simpler use of direct wiring?[17] One possible answer is that *this mechanism is needed in order that neural Darwinism can take place*. By using neurotransmitters to convey information across synapses, one enables non-local modulation of synaptic effects by neurotransmitters from the value system that are conveyed to all the neurons in a cortical region, the catecholamine neurotransmitters sometimes diffusing from their source to fill a volume rather than being transmitted to precisely chosen synaptic connections. Those synapses in this region that are currently active may then be affected by these diffuse neurotransmitters[18] but those that are inactive will not, and this may be presumed to be a key aspect of neural Darwinism.

Thus the strange "wet-wiring" across synapses may be needed to enable neuronal group selection to function. If this is correct, one might make the following tentative hypothesis:

> ***Conjecture 4:*** *Those neuronal connections that are genetically hard-wired (for example in the eye, the synapses within the retina itself i.e. between bipolar cells, horizontal, amacrine and ganglion cells) will often be directly wired electrical synapses; but all those whose detail is determined by neural Darwinism will be neurotransmitter-based chemical synapses. This difference would then be reflected in some appropriate way in the genes determining the neural structuring.*

This would be supported by noting the increased efficiency that direct wiring will allow, but on the other hand evolution often does not attain maximal efficiency, and rather cobbles together solutions based on the material at hand; in which case chemical synapses might be used in these cases too, even though that is relatively inefficient.

An interesting point is that chemical synapses may also be needed to enable memory to function, apparently providing a different rationale for their use. But the issue then is, Who chooses what to

remember? Information is thrown away by the billions of bits each day, with only the important remembered out of the flood of information arriving in our brain; but determining what is important requires a value system to provide a decision, so this may in fact be related to the proposal here: wet connections are required both for neural Darwinism and for memory.

4.8 Potential Outcomes. The above characterisation of relations that might follow from our overall hypothesis provides a variety of ways of checking its validity. On pursuing them, we should be able to check the adequacy of the main hypothesis by developing implications of the relation of the value system identified (the basic emotional systems E1-E7) to neuroscience on the one hand and the integrated package of genetics, evolution, and development on the other. This is in principle doable as outlined above. This serves as a test of the outlined proposal and may suggest areas where it is deficient. In particular, we can consider

> *(a) Are the basic emotions plus the immune and endocrine systems sufficient to characterise the value system, or should there be other kinds of components added? If so what are they and how would one test for them?*

The point here is that whatever such extra components might be, because of their developmental importance (which would follow precisely because they are part of the value system), in turn leading to evolutionary significance (else they would not be genetically determined), they must have determinable psychological effects which can be searched for. The suggestion here is that the basic emotions E1-E7, with a possible addition of **E0** as characterised above, are sufficient as well as necessary to determine the value system. But that can be tested as a hypothesis. If there are other factors needed they should be characterisable; any such proposal will then lead to a revision of all the aspects outlined above.

> *(b) Is the list of basic emotions E1-E7 complete or does it need supplementation?*

Apart from seeking for omissions of basic emotions needed for causal completeness, such as **E0**, the main issue here is separating primary and secondary emotions as discussed above, with the former genetically determined but the latter developmentally determined. For example, should there be recognised a primary emotion corresponding to social status or rank ("pecking order")? Various studies of animal behavior might suggest some such system exists in our animal relatives, and has strong survival value so that it is embodied in our genetic structure. But then its physical correlates should be determinable. We note here that play may be a substrate for the epigenetic emergence of adult dominance, especially when combined with anger and fear systems. Alternatively, as dominance is one axis of the interpersonal circumplex, perhaps it is indeed a primary emotion.

Any such understandings will in principle have implications for child psychology/ psychiatry on the one hand and learning/teaching theory on the other, as briefly indicated above. In essence such implications then form the platform for further testing of the basic hypothesis, either confirming it, or showing its inadequacy and the need for further development of the basic idea.

5: Relation to the Immune System

One might also speculate on conceivable implications regarding the interaction between the immune system and the brain. It is known that these two systems interact with each other at multiple levels and in a bi-directional manner (see Sternberg, 2000 and references therein). If the conjecture proposed here were correct, similar Darwinian processes would underlie both neural and

clonal selection in the nervous system and the immune system (for the immune system case, see Burnett, 1959). One could therefore consider whether the immune system might, through similar mechanisms, also be engaged in shaping the brain at a sub-emotional level (see Figure 1).

In evolutionary terms, if one accepts the notion proposed by Edelman, described above, that the emotional neurocircuitry of the brain, including noradrenergic systems activated during fear or stress, play a role in shaping higher order brain functions as discussed in the first part of this paper, then it is not unreasonable to propose that the immune system may have evolutionarily played a similar role in setting emotional brain systems. There is much evidence that cells and molecules of the immune system play an essential role in shaping neuronal connections, synapse formation and even neuronal cell death and survival in health, during development, throughout life, during learning, and in the course of inflammatory and infectious diseases of the brain. Furthermore, immune molecules also alter the emotional circuitry of the brain at a systems level (e.g. Maier & Watkins, 1998; Mulla & Buckingham, 1999; Maier & Watkins, 2000; Larson, 2002; Davidson et al., 2002; Maier, 2003).

There are an immense variety of immune molecules, with many used both in the immune and nervous systems. It is known that some affect neuronal function at the cellular level and may also modify structural relationships between neurons. Thus, the immune molecule interleukin 1 (IL-1) plays a role in memory consolidation, especially certain types of memory that depend on place recognition in the hippocampus (Watkins & Maier, 2000). Maier et al., (2003) have shown that IL-1 treatment of mice during context dependent conditioning interferes with the establishment of contextual memory for the aversive stimulus. The same immune molecule, IL-1, affects an immediate electrical/cellular event important in establishment of memory, long-term potentiation. Schneider et al., (1998) have shown that just as neurotransmitters do, IL-1 itself can induce long-term potentiation. There are also structural parallels between molecules expressed in the immune and central nervous systems, which play an important role in the establishment of connections and signalling between immune cells on the one hand and neurons on the other. Thus a molecule usually expressed on immune cells, MHC class 1, which in the immune system is critical for lymphocyte-macrophage interactions with antigen and subsequent lymphocyte maturation, is also expressed on neurons and is important in synapse plasticity (Huh et al., 2002).

Immune molecules act as growth factors in the CNS (Benveniste, 1998), and immune molecules and cells also play an important role in neuronal cell death and survival (Bajetto et al., 2002). It is now clear that interleukins are produced by some non-neuronal cells of the nervous system - including microglia and astrocytes - some of which are derived from or closely related to the immune cells, macrophages. Immune molecules released from these cells within the nervous system act in many ways like growth factors, either enhancing neuronal survival under some conditions, or promoting cell death, or apoptosis, under other conditions. Immune molecules can affect neuronal cell death and survival whether they are released from resident non-neuronal cells of the nervous system, or from immune cells that enter the nervous system in the course of inflammation (Schwartz & Cohen, 2000; Rothwell et al., 1997; Rothwell & Luheshi, 2000). The role that these cells and molecules play in neuronal cell death, survival and synapse formation can thus be thought of as shaping brain development in much the same way that pruning may shape a tree by stimulating some branches to grow and removing others. That is another way of saying they participate in neuronal group selection, but in this case based on immunological rather than affective states.

In addition to this effect of immune molecules on neurons and neuronal function at a molecular and cellular level, immune molecules also have important effects on brain function at a systems level.

Thus, immune molecules produced outside the nervous system, at sites of inflammation, in immune organs, or during infection, can alter a variety of brain functions. Interleukins in this sense act like hormones, molecules that are produced at one site in the body and affect the function of an organ distal to their site of origin. Many immune molecules, including interleukins and interferons, have been shown to activate the brain's hormonal stress response (reviewed in Webster et al., 2002), alter mood and cognition, induce sleep and fever (Krueger & Majde, 1994), and induce a set of behaviours called sickness behavior (Dantzer et al., 1998: Watkins & Maier, 2000). The latter are conserved across species and consist of decreased locomotion, loss of appetite, social isolation, loss of interest in sex – i.e. a pattern of behaviours that causes the organism to turn in upon itself rather than focusing on the outside world. At the same time, interleukins also cause a profound change in mood, with induction of symptoms in many ways overlapping with those of depression (Davidson et al., 2002; Dantzer et al., 1998; Miller, 1998).

Thus at molecular, cellular and functional levels, immune cells and molecules have profound immediate and long-lasting effects on the nervous system in general, and on emotional sub-systems within the nervous system, in particular. Thus *the immune system acts in a functional way on the CNS, in particular activating affective states;* we are suggesting that additionally, *part of this function can be seen as adding to the value system that guides neuronal group selection,* in this case conveying danger signals implied by homeostatic disequilibrium.

Interestingly, while the amygdala-based fear system is amongst those proposed to mediate selection of adaptive pathways of higher brain functions, it is the parasympathetic vagal system, originating in the brainstem nucleus of the tractus solitarius, which mediates incoming immune signals to the emotional systems of the brain. One could question the evolutionary advantage of these two opposing arms of the autonomic nervous system in selection of adaptive pathways at two sequential levels of this hierarchy. One possible answer might be that the inhibitory effects of the parasympathetic nervous system on the adrenergic sympathetic nervous system, could serve as a natural negative feedback loop, protecting the overall system from spiralling out of control[19].

There are two points that arise. The first is what specific effects might arise through long-term programming of emotional systems by immune system molecules during the life of an individual. It might extend to affecting the way the primary systems are activated: attaching negative emotional valence to specific kinds of conditions and hence developing avoidance reactions to such situations, and perhaps playing a role in depression.

The second is, what role could this have played in evolution? We propose

> ***Conjecture 5****: The immune system could have played a selective and survival role in setting emotional systems in the first place during evolutionary history.*

The issue here is not how the different emotional systems became differentiated but rather how any emotional system at all came into being. This is a crucial step on the way to full consciousness. Once the basic capacity was there it could evolve to respond to the major environmental issues confronting the individuals in a population, resulting in the basic affective reactions. That capacity would then evolve to the present primary emotional systems that are indeed genetically laid down and realised in response to the local environment during embryonic development. Once they have come into being, the immune system would still help guide neural development but not in as specific a way as the primary emotions.

The proposal here is that in the causal hierarchy shown in Figure 1, immune signals to the emotional subsystems of the nervous system, and in turn, neurotransmitter signals from emotional systems to cortical areas of higher brain function, could represent not only a current functional hierarchy but also an evolutionary developmental sequence. Consider early animal development where a rudimentary CNS is in operation but no affective system has yet been formed; the animal is unable to consciously "feel" (it behaves as if it is emotional though; it shows what might be called emotional behaviours, but on a reflexive level). But later animals can feel; the issue is how the possibility of affective states first arose. Now we have seen that the immune system can signal to and affect the CNS, conveying the information of health-threatening states to the CNS; this is a possible rudimentary form of value system as discussed above. It is then natural to suggest an evolutionary sequence whereby

(i) the innate immune system was there even before any neural cells; then
(ii) a primitive CNS came into being, allowing complex behavior including learning and neural plasticity,
(iii) the clonal adaptive immune system next came into being,
(iv) the adaptive immune system started functioning as a value system for the CNS, enabling the first animals to come into existence with a primitive form of neural Darwinism operative in the CNS.

The common molecules would have facilitated the development of synapses that are reliant on neurotransmitters, because of the survival value of recognising the threats to life from the events and environments associated with infectious attack. As consciousness developed, in whatever way that happened, it might be natural for this immune system interaction with the CNS to provide the first affective states, essentially the feeling of "being ill".[20] The immune system also provided the first differentiation of "self" from "non-self", an ability which reaches its highest level in human consciousness.

Once a first set of such affective states had come into existence, presumably corresponding to the suggested basic affective dimension **E0**: PLEASURE/PAIN suggested above, they could have been adapted and developed into the full set E1-E7 identified by Panksepp and additionally become genetically determined, because of the evolutionary advantage they provided through acting as a value system. Neural Darwinism in the individual would have proved itself to be a winning strategy and hence could have developed further affective capacities in an efficient way, through the usual evolutionary process of natural selection acting on the developing brain in a sequence of animal species.

> ***Conjecture 6****: It was through this process of immune system interaction with the CNS that neural Darwinism came into being as a brain-structuring mechanism in the course of evolutionary history.*

This suggestion has the potential to explain *why some molecules are both immune system molecules and also neurotransmitters*. It could conceivably even help explain how chemical synapses came into being in the first place, or at least why they are so common.

6: Implications of the Immune System Link

The proposal here suggests an evolutionary sequence that can be searched for through its survival in present day animals: first the basic immune system came into being, then neurons connected together to form a CNS developing a simple response capacity, then the basic immune system

developed into a clonal selection system, and only then the major emotional neural systems coming into being. Hence one can test the proposal made here by looking at the levels of primary emotions and immune system development in simpler animals (for example nematodes and insects, as well as more complex animals such as birds and mammals), using this to trace the evolutionary sequence and hence see if it is in accord with the idea proposed here or not. This investigation could also clearly be related to the study of the genomes of these animals and their developmental pathways.

Our proposal also suggests that infectious attacks may develop not only immediate feelings of ill-health but also *longer term emotional aversion to the kinds of conditions that lead to those infections*. Presumably one could test that kind of effect in animals such as mice, finding corresponding behavioural effects. One could then try to trace how far down the scale of complexity such effects existed: for example could snails be shown to behave in this way? This would clearly relate to the evolutionary issue just mentioned.

7: Conclusion

There is an immense and complex literature on neuronal development and function. Our suggestion is that the overall causal linkages we have sketched here might represent significant organising principles applying within that complex reality. We would not be so bold as to make such a proposal *ab initio*; rather we gain some confidence because our proposal is based on unifying two theories that are already well developed and supported by an extensive literature, namely affective neuroscience on the one hand and neural Darwinism on the other. By supporting the two theories independently, that extensive literature serves to indicate that they are each valid in their own right, and if both are valid, this then provides some support for a proposal such as ours for combining the two into a unified whole.

Several pieces of evidence have been proposed to bolster the hypothesis of Neuronal Group Selection. These include the following:

- something like this is needed to account for the great variability in human brain structure, contrary to any process of construction according to a preset algorithm (Edelman, 1992, pp. 27, 82);
- this allows the brain to optimally adapt to the local physical and cultural environment (Deacon, 1997, p. 206; Siegel, 2001), while also being able to face up to new circumstances in a adaptive way;
- there is far too little genetic information available to structure the brain in a more direct way, as discussed above;
- it links to the fact that neuronal connections are set up in a random way on the micro level, and then pruned by micro processes.

On the other hand there is ever increasing recognition of developmental and neuronal importance of the affective dimension. The first part of our paper suggests these two developments fit well together. If this proposed syntheses is true, this would imply three key features:

- First, immune system, higher brain, and emotional system evolution, development, and function would all be based on the same generalised Darwinian selectional principles (the way this happens being set out in the main Hypothesis); a significant unification of understanding and extension of application of the basic Darwinian insight in terms of allowing developmental emergence of high level structures through processes of natural selection operating on various time scales; this is widely regarded as the only viable way of enabling teleonomic higher level structures to emerge

through self-structuring processes in evolutionary history, and extends that proposal to developmental processes. This unification has intriguing links to functional detail at the neuronal level (see Conjecture 4).

- Second, it makes concrete proposals as regards the neurobiological functioning underlying the role of emotions and the immune system in brain evolution and development as well as in learning, namely with primary emotions providing the essential part of the fitness function that shapes the result of natural selection processes operating developmentally in the phenotype (see Conjecture 3). This understanding provides sound links between evolutionary theory, neurology, developmental biology, and aspects of psychology (particularly learning theory) and ethology as outlined above, by explicating a key multilevel link of the kind envisioned as underlying social neuroscience (Cacioppo et al 2002). It also could provide proposals for the function of significant brain systems whose physiological role is otherwise unknown (e.g. some of the monoamine systems, see Kingsley, 2000, p.131).

- Third, it makes specific proposals as regard the age-old nature-nurture issue, see Conjectures 1 and 2; this issue has important implications for social policy and politics, as so clearly shown by Stephen Pinker in his book *The Blank Slate* (Pinker, 2002).

In the second part of the paper, we suggest that investigation of a corresponding link from the immune system to brain development and evolution could be interesting. This proposal is based on two features: first, there is a substantial literature on influences the other way, from the brain to the immune system. But given this causal connection, it then makes sense to look also for effects of the immune system on the brain (this may be thought of as an application of the heuristic principle, where there is an action, there is often a reaction)

Second, there is evidence that immune molecules do indeed have the capacity to influence neurons in the CNS. The question then is *what form that influence might take when considered at the macro level*, and a natural extension of the ideas of the first part suggest this might also take the form of a contribution to neural Darwinism, in this case with the immune system influencing both evolution and function of the affective systems (Conjecture 5). Indeed this interaction could possibly have played a significant role in the first evolutionary development of affective systems at the macro level and of chemical synapses at the micro level, and through this process have facilitated the emergence of neural Darwinism (Conjecture 6). This proposal does not deny the immense complexity of the immune system in its own right, but does indicate interesting lines to follow in terms of understanding its possible interactions with the CNS - another immensely complex system. This interaction would leave traces in the historical record; particularly one might attempt to show that immune system development preceded emergence of simple affective responses.

Overall, the point of this paper is that the macro-role of neural Darwinism is not fully explicated until the nature of the value system has been made clear. We have made such a proposal that unites neural Darwinism with a major aspect of recent neuroscience, namely the appreciation of the importance of affect. The resulting synthesis provides a unification with interesting implications as outlined above. It has a plausibility arising from the fact that it proposes a concrete mechanism to underlie the effectiveness of affective macro processes, for which there is an ever-growing body of evidence.

Our final major recommendations flowing from all of this (relating to section 4.3 above) are as follows:

Recommendation 1: A series of psychological tests should be devised that aim to determine the relative strengths $\mathbf{A(E_I)}$ of the basic emotional system **E1-E7** (see Section 4.1 above) as well as the strengths $\mathbf{A(S_I)}$ of a suitably chosen set **S1-S7** of secondary emotions;

Recommendation 2: These tests are then used to search for correlations of the primary emotional factor strengths $\mathbf{A(E_I)}$ with those of the secondary emotions $\mathbf{A(S_I)}$**;**

Recommendation 3**:** These tests are also used in conjunction with tests of the different aspects of intelligence (a general factor **g**, group factors $\mathbf{g_i}$, and specific factors $\mathbf{g_i(s)}$ within each group, see Deary, 2001 for a summary of such factors) to search for correlations with the intelligence factors **g**, $\mathbf{g_i}$, $\mathbf{g_i(s)}$ firstly of the primary emotional factor strengths $\mathbf{A(E_I)}$ and secondly of the secondary emotions $\mathbf{A(S_I)}$**.**

These tests should enable firmly experimentally based investigation of the basic hypothesis proposed here, in line with the strong experimental approach laid out by Deary (2001).

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Acknowledgements: GE thanks the members of the University of Cape Town Consciousness Study Group for helpful discussions, and particularly David Kibel for drawing my attention to the writings of Jaak Panksepp. We thank Jaak Panksepp and Alan St Clair Gibson for helpful communications, and Esther Sternberg for very helpful contributions .

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Paper Version: version 2004-07-31
to appear in Consciousness and Emotion, 2004.

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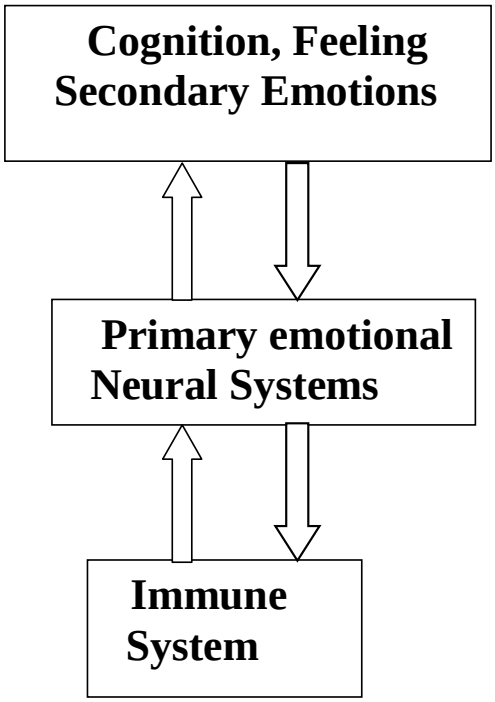

Figure 1a: The basic set of interactions between the higher level cognitive functions, the emotional system, and the immune system, go both ways. They involve immediate (physiological) effects, longer term (developmental) effects, and very long term (evolutionary) effects. The suggestion here is that the latter two proceed by basically the same evolutionary mechanism, albeit operating on very different timescales. Thus in broad brush terms the immune system underlies the emotions, which in turn underlie intellect.

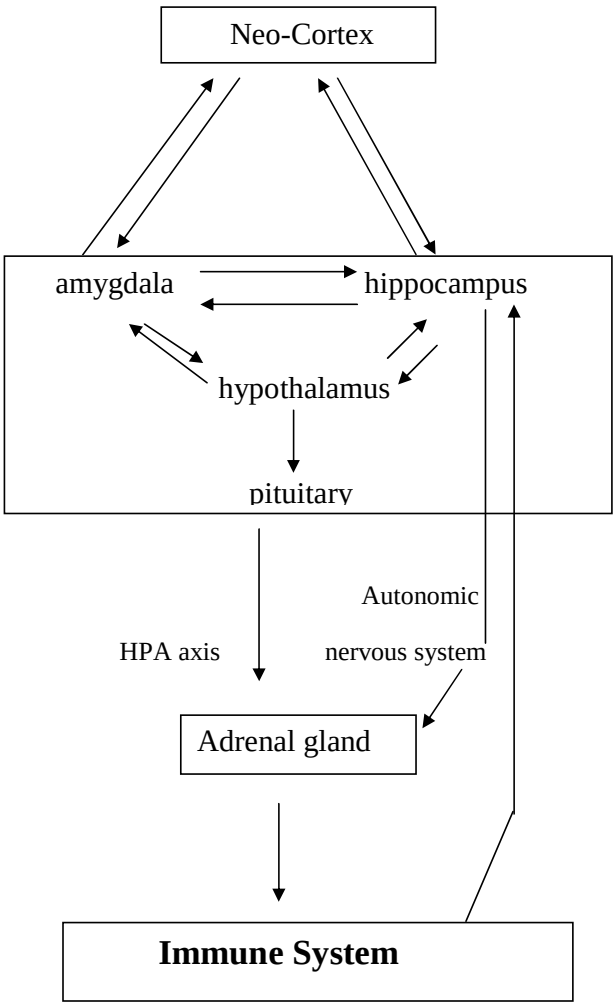

Figure 1b: More detailed view of the basic set of interactions between the higher level cognitive functions, the emotional system, and the immune system.

System	Neural Networks	Neuromodulators	Aspects
Seeking	ventral tegmental area (VTA), lateral hypothalamus, nucleus accumbens, PAG, diffuse mesolimbic and mesocortical outputs,	Dopamine (+), glutamate (+), neurotensin (+), Opioids (+), other neuropeptides	Appetitive states, anticipatory eagerness, exploration, (seeks non-specifically)
Rage	medial amygdala, BNST, medial and perifornical hypothalamus, dorsal PAG	substance P(+), Ach (+), glutamate(+)	Anger, frustration, hot aggression
Fear	lateral and central amygdala, medial hypothalamus, dorsal PAG	Glutamate(+), DBI, CRH, CCK, alpha-MSH, NPY	escaping danger
Lust	Amygdala ,BNST, preoptic and ventromedial hypothalamus, basal forebrain, ventral PAG	Steroids (+), vasopressin, oxytocin, LH-RH, CCK	pleasure, gratification
Panic	Anterior cingulate, thalamus, BNST, preoptic area, dorsal PAG	Opioids(-), oxytocin (-), prolactin (-), CRH	separation distress, social bonding
Caring	Anterior cingulate,BNST, preoptic hypothalamus, VTA, ventral PAG	oxytocin (+), prolactin (+), dopamine, opioids	Nurturance, maternal care
Play	Dorso-medial diencephalon, PAG	Opioids (+ in small amounts, -in larger amounts)	Play, joy, social affection

Table 1: Some of the basic emotional systems together with their associated brain areas and key neuromodulators. Serotonin and norepinephrine, which have more non-specific effects, are omitted, as are higher cortical areas. Derived from Panksepp (2004) and Watt (1999). Key: PAG=periaqueductal gray, BNST= bed nucleus of the stria terminalis, VTA=ventral tegmental area; CCK=cholecystokinin, CRH=corticotrophin releasing hormone, DBI=diazepam binding inhibitor, LH-RH= leutenizing hormone release hormone MSH=melanocyte stimulating hormone, NPY=neuropeptide Y;

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[3] See also Damasio (1995, 2000, 2003); Schore (1994); Le Doux (1998); Lane and Nadel (2000); Davidson et al (2002).
[4] See also Schore (1994); Deacon (1997); LeDoux (2002); and references therein.
[5] The name neural Darwinism can be criticised because there is no element of reproduction with genetic inheritance and variation; instead there is variation of connections created by imprecise synaptic formation, followed by neuronal group selection. This is however just an argument over semantics; it does not affect the nature of the theory, which centres on the core Darwinian feature that it is survival of the fittest that structures emergent complexity. It may be more accurate to call the proposal, "Neuronal Group Selection".
[6] Schore (1994) relates it to the idea of "parcellation" (pp.19, 250, 258).
[7] An antigen selects particular lymphocytes out of a very diverse population of pre-existing lymphocytes for clonal expansion, enabling the immune system to respond to antigens that it has never encountered before.
[8] Summarised in Pinker (2002), see the Appendix.
[9] See for example the concise survey of psychology by Butler and McManus (2000), where the role of emotions in behaviour is consigned to a few remarks on pages 67-68, commenting that for many they are regarded simply as an impediment to rational thinking.
[10] Many neo-cortical connections could also emerge in tissue-culture, but these connections would be broad and general and not represent detailed connectivity such as that provided by experience. If there is no experiential input, then the connections cannot be representative of such.
[11] In mathematical terms, they form an orthogonal basis for the space of primary emotions.
[12] It is usually claimed there are four types, because all of the conditions with one type of cone or no cones leave one with monochrome vision only (there must be two or more cone types to have different responses to different wavelengths). However these monochromatic images will each be different, corresponding to what can be seen with different colour filters.
[13] As another example, Evans (2001) lists hardwired basic emotions as Joy; Distress; Anger; Fear; Surprise; Disgust, and universal higher cognitive emotions as Love; Guilt; Shame; Embarrassment; Pride; Envy; Jealousy.
[14]There is not a unique relation here, as there is great overlap in the transmitter systems, plus many transmitters have both excitatory and inhibitory effects.
[15] Preliminary assessments in this regard are given by Damasio (2003, p.156).
[16] We assume from here on that by `E1-E7' we mean whatever classification of primary emotions emerges from the reconsideration just discussed.
[17] We thank Alan St Clair Gibson for raising this issue.
[18] This possibility is not taken into account by current models of synaptic plasticity rules (see Dayan & Abbot, ,2001, Section 8.2) and consequently the possibility of *value based learning* is not considered in present studies of the neuronal bases of learning (*ibid*, Sections 8.3 and 8.4). However the possibility of classical conditioning and reinforcement based learning (and specifically the role of dopamine) is recognised at the macro-level (*ibid*, Chapter 9).
[19]We thank Esther Sternberg for this suggestion.
[20] This theme will be pursued further in an upcoming paper (Toronchuk & Ellis, 2004).

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