ARTICLE WITH PEER COMMENTARIES AND RESPONSE

Neural plasticity and human development: the role of early experience in sculpting memory systems

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Abstract

The concept of sensitive or critical periods in the context of memory development is examined in this paper. I begin by providing examples of the role of experience in influencing sensory, linguistic and emotional functioning. This is followed by a discussion of the role of experience in influencing cognitive functioning, particularly memory. Based on this discussion, speculation is offered that the infant’s proclivity for novelty, which makes its appearance shortly after birth, provides critical input into a nervous system that will eventually be set up to learn and remember for the entire lifespan. Because learning and memory are fundamental to the survival of our species, those aspects of the nervous system that permit the encoding and retention of new information are remarkably malleable from the outset, even in the face of some types of neural trauma. This flexibility is retained for many years so long as the learning and memory ‘system’ is challenged. The implications of this model are discussed in the context of those life events that might undermine the longevity of memory systems.

Introduction

It has been known for decades that early experience plays an important role in many aspects of perceptual, linguistic and emotional development. A great deal is also known about the neural mechanisms that underlie the critical periods that are involved in these domains of behavior. We know, for example, that (a) visual experience is necessary for the development of stereoscopic vision and ocular dominance columns (e.g. Hubel, Wiesel & LeVay, 1977; LeVay, Wiesel & Hubel, 1980; Blakemore, 1991; Crair, Gillespie & Stryker, 1998), (b) exposure to particular speech contrasts is necessary for normal speech perception to develop and presumably for the auditory–thalamo–cortical pathways that facilitate the development of this ability (e.g. Neville, 1991; Kuhl, Williams, Lacerda, Stevens & Lindblom, 1992; Kuhl, 1993; Merzenich et al., 1996; Tallal et al., 1996), and (c) exposure to a healthy caretaking environment is necessary for normal emotional development to take place, and presumably the development of the cortico-limbic circuitry involved in emotion and emotion regulation (e.g. Dawson, Panagiotides, Grofer Klinger & Hill, 1992; Schore, 1994). Surprisingly, however, much less is known about the role of early experience in the domain of cognitive development; whether there is a critical period for the acquisition of cognitive skills such as memory and executive functions; and finally, why it is that many cognitive skills can be acquired and/or improved over the course of the lifespan, whereas, for example, developing new linguistic or visual competencies cannot.

In this paper I will attempt to determine whether there are critical experiences that occur in the first part of the lifespan that provide for the flexibility our species exhibits in the cognitive domain, particularly in the domain of learning and memory. Although I will consider this issue from a behavioral perspective, I will devote more attention to the neuroscience side of behavioral flexibility. In essence, what events occur in the brain that facilitate the long-term elasticity our cognitive systems enjoy? In order to address this issue, I begin by providing some background to the general problem of early experience and development. I then

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offer an overview of the many ways the brain is modified by experience. I conclude by speculating about the role of experience in cognitive development, particularly memory development, and how such experience may well set the brain up to remain remarkably plastic through much of the lifespan.

**History of the problem – studies of deprivation**

Without a doubt, the most common means by which investigators have demonstrated the important role of experience in behavioral and brain development has been through studies of deprivation. For example, it has been known for nearly 30 years that the ability of each eye to capture an image and then fuse this image so that it appears in depth – stereoscopic vision – depends on regions of the visual cortex that receive separate inputs from each eye. These inputs (which lead to layer IV of the visual cortex by way of the lateral geniculate) result in separate columns of cells that are distinct for the two eyes. Although experience is not essential to the early appearance of these columns, experience quickly becomes essential for their normal and complete elaboration (e.g. Crair et al., 1998). Thus, if the organism is deprived of vision in one eye or if the input to a given eye receives is abnormal (e.g. strabismus), these ocular dominance columns fail to develop normally, and stereo vision is compromised. Thus, there is a critical period for when these columns can develop normally and thus support normal vision. Lastly, this critical period coincides with the period of rapid overproduction of synapses in the visual cortex. The purpose of this exuberance of synapses is presumably to capture visual experience, and in so doing confirm those synapses involved in stereoscopic vision. (For a general review and discussion of this literature, see Hubel et al. (1977), LeVay and Stryker (1979), LeVay et al. (1980), Blakemore (1991)).

A far more dramatic and, indeed, tragic example of critical periods concerns what happens when a child is deprived of a normal caretaking environment. For example, it was demonstrated many years ago that early deprivation could, under some circumstances, lead to calamitous developmental outcomes (Spitz, 1945). Although subsequent studies revealed that the effects of institutionalization do not uniformly lead to disastrous consequences (e.g. see Provence & Lipton, 1962; Skeels, 1966; Tizard & Reese, 1975; Tizard & Hodges, 1977), the reality is that many such children fair poorly, particularly if they remain in that environment. Unfortunately, as a species, we appear not to have learned from our mistakes, as such institutions began to appear again in the late 1980s, first in Romania and more recently in China and Russia. Studies of children reared in Romanian institutions and adopted by parents in North America began to appear in the scientific literature in the early 1990s (e.g. Benoit et al., 1996; Marcovitch et al., 1997). On the whole, a disproportionate number of these children showed deficits in several domains (e.g. cognitive, emotional, linguistic; see Ames, 1997; Fisher, Ames, Chisholm & Savoie, 1997; Marcovitch et al., 1997). These children also suffered from growth retardation and a high morbidity rate due to a variety of infectious diseases (e.g. Hostetter, Iverson, Dole & Johnson, 1989; Hostetter et al., 1991; Johnson et al., 1993, 1996; Miller et al., 1995; Albers et al., 1997). More recent studies have indicated that the severity of the handicap increases as a function of the time spent in the institution. In particular, children who are adopted before their first birthday appear to have far better outcomes than children adopted at a later age (Benoit et al., 1996; Ames, 1997). This observation suggests, then, a rather narrowly defined sensitive period for being exposed to a normal caretaking environment.

In both examples offered above, the importance of experience in influencing the development of a given behavior was inferred from what happens when such experience is withheld from the organism. Although there is a certain logical appeal to this approach, studies of deprivation are not without their shortcomings. For example, at least in the case of the human, one must leave open the possibility that infants who experience profound neglect or abuse may not represent the typically developing child (e.g. there could have been differences in the prenatal environment that account for portions of the variance in outcome, or selective adoption may play a role in which infants stay in the orphanage and which ones are adopted, or in which infants are targeted for abuse or neglect by perpetrators). In addition, the deprivation that occurs is generally not specific to one domain (particularly in the case of the human). Thus, for example, in the case of Genie, the young girl whose language delays were extensively studied by several investigators (e.g. see Curtis, 1977; Fromkin, Krashen, Curtiss & Rigler, 1974, for a review), the deprivation consisted of a great deal more than just being deprived of language input. Finally, even when the deprivation is targeted to a specific domain of function (as it often is in animal studies), one must consider the possibility that the domain that is first affected results in a spillover effect, ultimately resulting in deleterious effects in several domains (e.g. an animal deprived of visual input will also show disturbances in cognitive and social behaviors as well). None of this is to say that deprivation studies are not useful; clearly they are, and clearly such studies done with animals permit one to investigate phenomena that
are not so easily studied in the human. My point, however, is that it might be best to juxtapose deprivation studies against studies involving normally developing subjects. One such example comes from the domain of speech.

A number of investigators have now reported that exposure to language in the first year of life has a profound effect on how one later comes to discriminate and recognize the sounds of that language. For example, English-speaking adults who have not been exposed to languages such as Swedish or Thai are unable to discriminate speech contrasts from these languages, in contrast to the ceiling-level ability to discriminate speech contrasts from their own (English) language (e.g. the ability to make the categorical discrimination of ‘ba’ versus ‘ga’). Kuhl (e.g. Kuhl et al., 1992; Kuhl, 1993) demonstrated that between 6 and 12 months of life the ability to discriminate phonemes from languages to which infants are not exposed greatly diminishes. Thus, although a 6-month-old infant raised in an English-speaking home may be able to discriminate contrasts from English as well as those from Swedish or Thai, by 12 months of age such infants become more like English-speaking adults; i.e. they lose the ability to discriminate contrasts from their non-native language. Importantly, Cheour et al. (1998) have demonstrated that, by 12 months of age, brain activity (i.e. the match mismatch negativity of the event-related potential) recorded from vowels presented in a familiar (native tongue) or unfamiliar (non-native tongue) language differ, with the former giving rise to larger responses and the latter to smaller responses. The argument that Kuhl and others have proposed to account for these phenomena is that the speech system remains open to experience for a certain period of time, but if experience in a particular domain (such as hearing speech contrasts in different languages) is not forthcoming, the window begins to close early in life.

### Models of neural plasticity

Collectively, at least in the domains of speech, vision and emotion, crucial early experiences must occur for behavioral development to proceed on a normal tract, and for the brain systems that underlie these behaviors to develop normally. These three examples all illustrate an important principle of neural plasticity: that some neural systems remain open only so long to environmental input, and if such input fails to occur, or if the input is abnormal, the ‘window of opportunity’ closes and development goes awry. Greenough and colleagues have referred to this process as experience-expectant, by which they mean a process by which synapses form after some minimal experience has been obtained. Presumably this experience is common to all members of the species (e.g. the expectation that the young organism will confront a normal visual world with an intact visual system), thereby saving the genome from the trouble of orchestrating and regulating all aspects of development. In general, Greenough has proposed that the structural substrate of ‘expectation’ is the unpatterned, temporary overproduction of synapses distributed within a relatively wide area during a sensitive period, followed by a subsequent retraction of synapses that have not formed connections at all or that have formed abnormal connections. The expected experience produces patterns of neural activity, targeting those synapses that will be selected for preservation. The assumption is that synaptic contacts are initially transient and require some type of confirmation for their continued survival. If such confirmation is not obtained, synapses will be retracted according to a developmental schedule or due to competition from confirmed synapses (for elaboration on these ideas, see Greenough & Black, 1992; Black, Jones, Nelson & Greenough, 1998).

Experience-expectant synaptogenesis stands in marked contrast to another type of plasticity Greenough refers to as experience-dependent. This is a process that optimizes the individual’s adaptation to specific and possibly unique features of the environment, e.g. learning. Thus, for any given individual, diverse information will be obtained and stored for use at a later time, giving rise to individual differences in a variety of cognitive domains. The fundamental difference between experience-expectant and experience-dependent development is that the former applies in a similar fashion (presumably) to all members of a species, whereas the latter applies to individual members (again, for elaboration, see Greenough & Black, 1992; Black et al., 1998).

As may be obvious, experience-expectant development is probably behind several of the examples I provided earlier in this paper; notably the development of stereoscopic vision, speech perception and normal emotional development. In all three cases, one would hope that our species’ young is reared in an environment that promotes normal vision and hearing, and the potential to fall into the arms of a loving, consistent, sensitive caretaker (although this is not to deny the fact that these assumptions are not met in all cases). What about experience-dependent development? Presumably it is this type of plasticity that subserves changes in the nervous system at the level of the individual. In the section that follows a number of examples are provided, first in the context of the developing organism, and then

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in the context of the so-called ‘mature’ organism. These examples are provided to illustrate the general principle that, at least in certain domains, the nervous system can be modified across much of the lifespan. In the final section I attempt to address the question of whether there are critical periods for the acquisition of cognitive skills, such as memory, and if so, what experiences are essential to creating a learning and memory system that remains robust until old age.

**Neural plasticity in the juvenile organism**

It has been demonstrated in a variety of species that negative early life experiences can alter both the function and structure of the developing brain. Most often, these experiences constitute a form of stress, such as exposure to inescapable shock, loud noise or restraint. In the rat, for example, prenatal stress leads to increases in corticosterone and adrenocorticotropic hormone in both mothers and fetuses (Ward & Weisz, 1984; Takahashi, Baker & Kalin, 1992). Similarly, pregnant Rhesus monkeys exposed to stress (e.g. unpredictable loud sounds) give birth to newborns who show symptoms of neurobehavioural dysregulation at birth and beyond; in fact, these symptoms appear to persist well into postnatal life, including effects on noradrenergic and dopaminergic activity as long as 1.5 years after birth (see Schneider, 1992; Schneider et al., 1998). Moving back to the rat, it is known that rats born to mothers who were stressed during pregnancy show increased indices of emotionality in response to novelty. If such rats are observed in play behavior with other rats, they are found to be much slower to initiate play. If the rats are repeatedly exposed to this same play environment, their behavior improves (i.e. they show less wariness), but even a brief re-exposure to mild stress results in an increase in wariness (see Takahashi et al., 1992). Overall, these findings suggest that prenatal stress induces long-term wariness in offspring in unfamiliar environments. Such an effect may greatly diminish an animal’s ability to benefit from experience by reducing active seeking of new information.

These negative effects of stress on brain and behavior can be ameliorated, however, under the right conditions. For example, if prenatally stressed rats are reared in complex environments, and/or are handled at birth, they show fewer effects of prenatal stress (see Francis et al. (1996) and Black et al. (1998) for reviews of this literature). The mechanism responsible for this sparing and/or recovery of function has been hypothesized to be an increase in glucocorticoid receptors in the hippocampus (Meaney & Aitken, 1985; Meaney, Aitken, Viau, Sharma & Sarrazin, 1989). This, in turn, can have positive effects on hippocampal functions such as learning and memory. For example Meaney and colleagues have demonstrated that rats exposed to early stress but handled at the appropriate time perform better than non-handled stressed rats in a variety of visual–spatial memory tasks (Meaney, 1998).

In terms of the human, we have already alluded to three such effects: visual deprivation, emotional depriviation and linguistic depriviation. To elaborate on our discussion of visual depriviation, it has been known for some time that untreated strabismus can lead to amblyopia, a secondary condition in which the brain essentially fails to recognize the input from the non-dominant (crossed) eye (see Crawford, Harwerth, Smith & van Noorden, 1993, for discussion). Positron emission tomography studies of patients with untreated strabismus reveal the use of different regions of the visual cortex than for normal controls (Demer, 1993). As was the case with handled rats prenatally exposed to stress, if infants with strabismus are treated during the first months/years of life, there is no secondary amblyopia, and presumably the visual cortex is wired appropriately.

There are many other examples of the deleterious effects of early experience on brain–behavioral development in the human, including those already discussed (e.g. emotional, linguistic depriviation) as well as the effects of early neural trauma, physical or sexual abuse, and so forth. This literature, coupled with that reviewed herein, collectively suggests that early deleterious experience can have significant negative effects that may be long term; by the same token, it might be possible to 'protect' the animal from these effects by rearing them in complex environments (an example of sparing) or, in the case of strabismus, simply correcting the optical mismatch through, for example, surgery (an example of recovery of function). But, how easily can the nervous system be modified once the organism has matured? It is this topic to which I next direct my attention.

**Neural plasticity in the mature organism**

Let us begin with examples from the primate literature. Pons et al. (1991) reported on a group of monkeys that
12 years earlier had received deafferentations of an upper limb. Neuronal responses were elicited from a region of somatosensory cortex that would normally correspond to the deafferented portion of the limb, including the fingers, palm and adjacent areas (area S1). To the surprise of the investigators, this region of the brain now responded to stimulation in an area of the face (this region would normally border the cortical region innervated by the deafferented limb), pointing to a reorganization of somatosensory cortex of rather massive proportions (i.e. 10–14 mm).

This report, and others that followed (see Pons, 1995, for discussion), demonstrated that large-scale cortical reorganization can occur following injury even in the mature primate. Subsequent and comparable reports in the adult human followed. For example, in an extension of the monkey studies, Ramachandran, Rogers-Ramachandran and Stewart (1992) reasoned that an individual who had experienced a limb amputation (such as the forearm) should show sensitivity on the area of the body represented by the area of the brain adjacent to the amputated limb. To test this prediction, adults who had experienced various forms of amputation were examined. Such individuals experienced sensation in the limb that had, in fact, been amputated (i.e. ‘phantom limb phenomenon’). In one such individual, Ramachandran examined the patient’s sensitivity to tactile stimulation along the region of the face known to innervate the somatosensory cortex adjacent to the area previously innervated by the missing limb; the patient reported sensation in both the face and the missing limb. By mapping out the stimulated (facial) area, Ramachandran was able to determine the degree to which the cortical surface had been reorganized to take over responsibility for the area previously occupied by the missing limb. This report was subsequently replicated in other patients (for discussion, see Ramachandran, 1995) and by other groups (e.g. Flor et al., 1995; Chen, Corwell, Yaseen, Hallett & Cohen, 1998).

In both the monkey and human deafferentation/amputation work, cortical reorganization was presumably facilitated by stimulation of those parts of the body that were adjacent to the deafferented/amputated limb, suggesting a form of ‘natural’ intervention. In a more direct test of whether the motor and/or somatosensory cortex can be reorganized based on experience, Nudo, Wise, SIFuentes and Milliken (1996) mapped the motor cortex of monkeys using intracortical microstimulation (ICMS) before and after an ischemic lesion was made. Much as would occur in the human suffering a stroke in the same region of the brain, the infarct led to a deficit in use of that limb – in this case, the animal’s inability to retrieve food pellets. The animals then received intensive training in hand use, which resulted in a return to performance comparable to pre-injury levels. ICMS was used again to map the motor cortex, revealing substantial rearrangement of the area of the brain that represented the hand surrounding the lesion site. These findings, coupled with those reported by Pons and colleagues and Ramachandran and colleagues, suggest that the representation of the limbs in the adult primate can be altered as a function of experience.

In summary, there is now evidence to support the thesis that cortical reorganization is possible following injury to the peripheral nervous system in the adult human and non-human primate. Let us now ask whether similar reorganization can occur in the non-injured ‘healthy’ individual. To examine this question, Elbert, Pantev, Wienbruch, Rockstroh and Taub (1995) used magnetic encephalography (MEG) to map the somatosensory cortex of adults with and without experience playing a stringed instrument (e.g. guitar, violin). The investigators reported that, in the musicians, the area of the somatosensory cortex that represented the fingers of the left hand (the hand used on the finger board, thereby requiring greater dexterity) was larger than the area represented by the right hand (which was used to bow, presumably a skill requiring less dexterity) and larger than the left-hand area in the non-musicians. Moreover, there was a tendency for there to be greater cortical representation in individuals who had begun their musical training before the age of 10 years.

Collectively, this work suggests that the brain of the adult human can reorganize based not just on negative experience (e.g. injury) but also on positive experiences (e.g. musical training). However, in both cases the experience in question was limited to the motor domain, i.e. a limb was deafferented, amputated or stimulated. Might cortical reorganization occur in domains of functioning other than motor? One way to approach an answer to this question would be to examine intervention programs that target cognitive or linguistic functioning. One such example comes from the work of Paula Tallal and Michael Merzenich.

Tallal and colleagues have speculated that some children with language learning impairments have difficulty in parsing the phonemes that are embedded in ongoing speech. The basis for this disability is presumably the inability of the auditory system (specifically, the auditory–thalamic–cortical pathway; see Kraus, McGee, Carrell, Zecker and Koch (1996), for discussion and evidence) to keep up with the speed at which these phonemes are presented, leading to difficulty in discriminating speech sounds. More than two decades ago, Tallal reported that performance could be improved if the rate of change of the phonetic transitions was slowed down.
(e.g. Tallal & Piercy, 1973). Tallal and Merzenich (e.g. Merzenich et al., 1996; Tallal et al., 1996) reported that when children with language learning impairments were given 4 weeks of intensive training in the temporal processing of speech, a gain of approximately 2 years in both speech discrimination and language comprehension was realized. Although the investigators did not examine structural or physiological changes in the brains of these children, presumably the site of such changes was the auditory–thalamo–cortical pathway.

Summary

On the whole, it appears that reorganization of cortical pathways in the adult human brain is possible beyond childhood, and that such reorganization is not limited to motor or sensory pathways but also may include elements of language systems.

A summary of the main points offered thus far includes the following. First, stressors that occur even as early as the fetal stage of development can have long-term consequences for the developing brain. Second, reorganization of the motor cortex is possible through the daily activities of living (as revealed by the work with amputees) and by rehabilitation (as revealed by the work with squirrel monkeys that had incurred strokes, rendering them physically handicapped). The work with stroke rehabilitation was particularly dramatic, as it provided concrete, physiological evidence of motor cortex reorganization in the same animal before and after injury. Finally, at least in the domain of language, there appears to be evidence that elements of the speech perceptual apparatus can be improved through experience (i.e. intervention).

Implications of neural plasticity for cognitive development

What are the implications of this literature for our understanding of the malleability of cognitive systems such as memory? After all, the preponderance of examples of neural plasticity offered thus far have been confined to the sensory, perceptual and motor domains. Before turning to the issue of cognitive systems, let us first critically examine some of the factors that might account for the findings described for the motor and perceptual systems.

In some respects, the fact that the motor system is capable of being modified throughout much of the lifespan should not be surprising, given the lengthy period of input this system receives. For example, fetal movements occur long before the age of viability, and many infants are now born between 24 and 25 weeks gestation with intact (albeit immature) motor systems. Once infants reach 35–36 weeks, their movements begin to resemble those of the full-term infant, and in the following weeks and months the motor system grows in leaps and bounds, eventually resulting in creeping, crawling, walking and running; eventually, of course, motor skills of great complexity are possible (e.g. gymnastics, dance, squash etc.). One might argue, therefore, that the capacity for spontaneous movement coupled with movement in response to stimulation represents the perfect formula for strengthening the neural connections that underlie this system as a whole. In so doing, the system is set from very early in life to continually respond to the demands of the external world. By continually challenging the motor system, it is kept open to new experience. And, since most of us use our motor systems throughout our lifespan, we maintain the ability to acquire new motor skills. Lastly, there is good evidence that accelerated experience or training can have a profound impact on performance; witness the aim of athletic training.

Sensory systems appear to differ from motor systems in a number of important ways. Let us begin with a discussion of vision. The visual system of the newborn, although immature, nevertheless functions adequately. For example, as Salapatek and others demonstrated over 30 years ago, newborns engage in systematic eye movements that permit the external world to be processed in a coordinated manner (e.g. Salapatek & Kessen, 1966; Salapatek, 1968). The eye movement system, coupled with improvements in visual acuity and contrast sensitivity over the next 6–12 months, permits the infant to seek out and process increasingly complex information from the environment. Assuming the infant’s visual system has not been compromised (e.g. by strabismus or amblyopia or cataracts) and the experiences to which the infant has been exposed have been normal, by the end of the first year of life the visual system is functioning quite well (although it is still not fully mature). However, unlike the motor system, once the visual system has reached maturity, there is little improvement thereafter (for a review, see Banks & Salapatek, 1983); we do not, for example, see better and better as we get older.

The auditory system differs slightly from the visual system in that it can profit from experience even before birth, perhaps as early as the sixth prenatal week. As a result, hearing is relatively better than seeing in the first postnatal months. However, like the visual system, the ability to process auditory information improves enormously over the weeks and months following birth (again, assuming that the child’s auditory system is
intact and the experiences to which the child has been exposed have been normal). Finally, like the visual system, there may be a critical period for development to proceed normally. Speech perception may be an example of this. As discussed earlier, Kuhl and others have proposed that the speech perception system remains open to experience for a certain period of time, but if a particular experience in a particular domain (such as hearing speech contrasts in different languages) is not forthcoming, the window begins to close early in life. If the essential experience occurs, then this ability is maintained for the lifespan (i.e. if we grow up hearing and speaking English, we generally do not lose the ability to discriminate speech contrasts from English).

The motor system differs from the sensory systems in that the former can remain open for much of the lifespan, enabling us to acquire and master new motor tasks, whereas the latter plateaus within the first year or two of life and is not improved upon (except in the domain of esthetics) thereafter. Although the genes that regulate the development of these systems clearly play a role in this, another contributing factor appears to be the initial setting this system receives, coupled with its maintenance. Even in the motor domain, however, there may be some limitations. Thus, although adults with experience playing a stringed instrument showed evidence of cortical reorganization, there was a trend for this reorganization to be more pronounced in those individuals who had begun their musical training before the age of 10 (Elbert et al., 1995). Presumably the constraint here was not motor training per se, but the acquisition of the syntax of music (Elbert, personal communication). Thus, perhaps similar to the work on acrobatic rats (i.e. rats trained to perform complex motor skills), in which learning and not simply the repetitive use of synapses had to occur, motor learning may have a critical period, although motor skill may not.

Outside of the motor and sensory domains, there is a paucity of information on neural plasticity in the mature or normally developing organism. We know in the social/affective domain that there may be sensitive or critical periods (it is impossible to tell which, but it seems likely to be the former), at least as inferred from studies of deprivation. For example, in work reviewed earlier in this paper data were discussed suggesting that children reared in Romanian institutions adopted before the age of 1–2 years fare much better psychologically than those adopted after this. In terms of malleability in the social/affective domain, we know that both behavioral and pharmacological therapies are useful in treating a variety of emotional disorders in adulthood. It remains to be seen whether similar interventions can be developed to remediate the behavior of the older Romanian adoptees.

What about the cognitive domain? Let me begin by discussing some of the events that can have deleterious effects on learning and memory and then turn to a discussion of plasticity of a more positive nature.

There is a clear relation between circulating glucocorticoids (e.g. cortisol) and cognition, particularly in their effects on memory. For example, chronic exposure to glucocorticoids can lead to poor spatial (rats) and verbal (human) memory performance (for a review, see Monk, 1998). It is believed that the mechanism underlying this relation is the sensitivity of the hippocampus to such hormones. For example, rats exposed to high levels of exogenous glucocorticoids or to chronic stress reveal selective damage to the CA3 pyramidal neurons of the hippocampus (see McEwen & Sapolsky, 1995, for review). Similarly, monkeys exposed to social stress (e.g. separation, isolation) show extensive damage to the CA3 region of the hippocampus (Uno, Tarara, Else, Suleman & Sapolsky, 1989). Taken as a whole, these findings suggest that stress/cortisol leads to hippocampal damage, particularly damage to the CA3 region. This vulnerability appears not to be age-dependent and occurs throughout the lifespan; indeed, there is particularly strong evidence of this association in older rats and humans (e.g. Lupien et al., 1994, 1998).

Are there experiences that exert positive effects on brain and cognition? Let me begin with the rat. We know that rats raised in complex environments tend to be superior on a variety of learning tasks (see Greenough & Black, 1992, for discussion). At the level of the brain, being reared in such an environment results in an overall increase in the thickness, volume and weight of the visual cortex (Bennett, Diamond, Krech & Rosenweig, 1964), an increase in dendritic branching (e.g. Volkmar & Greenough, 1972) and more synapses per neuron (e.g. Turner & Greenough, 1983, 1985). Importantly, many of these synaptic changes regress when the rats are returned to a traditional laboratory cage. Rats extensively trained to use one forelimb to reach through a tube to receive cookies show dendritic growth within the region of the cortex involved in forelimb function in comparison to controls (Greenough, Larson & Withers, 1985). When rats are allowed to use only one forelimb for reaching, dendritic arborizations within the cortex opposite that of the trained limb are significantly increased relative to the cortex opposite the untrained forelimb (Withers & Greenough, 1989). Further, such training only affects some neurons (i.e. those in layer II/III). Finally, in rats required to master several new complex motor coordination tasks, an increased number of synapses per neuron within the cerebellum is observed in comparison to inactive controls (Black, Isaacs, Anderson, Alcantara & Greenough, 1990). In contrast,
animals exhibiting greater amounts of motor activity in running wheels or treadmills, where little information was learned, or yoked-control animals that made an equivalent amount of movement but in a simple straight alley, do not show significant alterations in synaptic connections in the cerebellum (Black et al., 1990; Kleim et al., 1997). Moreover, only those rats in the learning paradigm also showed structural changes in the brain, i.e. the density of capillaries in the involved region was significantly increased, corresponding to what would be seen if new blood vessels developed to support increased metabolic demand (Black et al., 1990). Thus, learning, and not simply the repetitive use of synapses that may occur during dull physical exercise, leads to changes in the cerebellum (for a review, see Black et al., 1998).

Less is known about the effects of enriched early experiences on human brain development, although a considerable amount is known about the effects on cognitive development. For example, there is evidence that children growing up in impoverished environments (e.g. low socio-economic standing, poor maternal education etc.) benefit from early intervention programs (which probably represent something akin to the complex environments discussed earlier). In most such programs, children are enrolled as infants and are maintained in the program until the age of 5. Under these circumstances, the average IQ gain is approximately 8 points (with the range varying from 4 to 11 points; e.g. Lee, Brooks-Gunn, Schnur & Liaw, 1990; see Barnett, 1995, for a review). This IQ gain (relative to the control group) generally persists until school age, and then diminishes as the children receiving early intervention move through the early years of school; conversely, as the control children enter school, their IQ scores increase slightly. Over and above IQ, however, many such programs report respectable and persistent effects on more functional aspects of cognition, such as greater school achievement and a decreased need for special education. Some projects, such as Abecedarian, have specifically examined whether there is an effect of early versus late experience. They have done so by comparing children who experienced (a) early intervention alone, (b) early intervention plus an enriched school-age program (carried out over the first 3 years of elementary school, roughly ages 6–9), (c) the school-age program alone or (d) no intervention at all. By the time these children reached adolescence, there were clear advantages conferred on IQ, school achievement and school progress by those who had early experience alone. Neither the school-age plus early intervention nor school age intervention alone children yielded significant gains in IQ and they showed only marginal effects in school achievement (see Ramey & Campbell, 1991, for a discussion). Once again, we infer the existence of sensitive periods and the importance of early experience based on studies of deprivation. However, if we only consider children who are developing in what might be called the ‘species-typical’ environment (i.e. access to resources, adequate parenting etc.; for discussion, see Boyce et al., 1998), it is unclear whether early intervention can facilitate cognitive skills above their already normative values; it is unclear because most interventions do not target such children, largely because of resource allocation. Lastly, it is also unclear whether exposure to stimulating and challenging information later in life (by way of a good education) improves performance because of the direct effects of experience on the brain, thereby compensating for otherwise poor environments and/or ‘weak’ genetic potential.

If we move beyond childhood, what is clear is that, like the motor system, we are capable of learning new material across much of the lifespan. Conversely, there is also evidence that at least in some domains there is a decline in cognitive abilities later in life. The issue I would next like to address is the juxtaposition of these two phenomena – the ability to learn throughout much of the lifespan coupled with the decline in cognitive abilities later in the lifespan – against the role of experience.

Cognitive ‘development’ across the lifespan

Although little attention is currently directed to understanding changes in cognition across the lifespan relative to studies done with infants and children, there is still a respectable cognitive gerontology literature. A thorough review of this literature is beyond the scope of this paper. A few points are worth noting, however.

Although it is generally believed that cognitive abilities, broadly defined, decline with age, a careful reading of this literature reveals a number of important qualifiers. For example, Martin (1986) examined changes in everyday behaviors that make demands on memory and on simple and complex cognitive tasks in groups of young (23 years) and ‘old’ (66 years) subjects. The general conclusion drawn by the author was that aging does not produce a comprehensive impairment in cognitive performance; rather, there is a decline in some areas and an improvement in others. Thus, tasks that involve rote memorization (remembering names, phone numbers) decline with age, whereas tasks that require more complex, organized thought processes (e.g. remembering appointments or remembering to pay bills) improve with age. Admittedly, the ‘old’ subjects in this
study were not terribly old. What happens with more advanced aging? Ritchie, Touchon, Ledesert, Leibovicci and Dupuy Georce (1997) examined a variety of cognitive abilities in 60- to 100-year-old normally aging subjects using a variety of laboratory-based tasks. The authors reported no cross-sectional age differences in a range of abilities that included syntax comprehension, articulation, semantic matching, reading and implicit memory. In contrast, explicit memory, language skills and visuospatial skills deteriorated across time. However, when one took initial IQ levels and education (which covaried) into consideration, a different pattern emerged. Here the authors reported that individuals with higher levels of education showed relative stability across time in language and explicit memory, but deteriorated as rapidly on visuospatial abilities as those with lower levels of education. The authors drew two major conclusions from these findings. First, on the whole, the limbic structures that subserve explicit memory are more vulnerable to aging and/or disease than those that subserve implicit memory. Second, education appears to provide a protective factor for the decline in limbic-dependent abilities.

The Ritchie et al. (1997) findings appear to be consistent with the literature on cognitive changes in aging – essentially, in normally aging subjects (i.e. those with no disease), (a) verbal memory is more affected than non-verbal memory (Janowsky, Carper & Kaye, 1996), (b) recognition memory (a medial temporal lobe function) is spared relative to working memory (a prefrontal function; Fabiani & Friedman, 1996), (c) cognitive abilities that depend on the medial temporal lobe are most vulnerable to aging (Janowsky et al., 1996; Ritchie et al., 1997), (d) there are few differences between men and woman, although women might have a slight advantage (i.e. less decline) on verbal abilities and men on visuospatial abilities (Portin, Saarijarvi, Joukamaa & Salokangas, 1995; Ruoppila & Suutama, 1997), (e) education appears to be a protective factor among those aging normally as well as among those suffering from age-related dementias (Portin et al., 1995; Zec, 1995; Laursen, 1997), and (f) practice also provides a protective factor against cognitive decline, whereas disuse represents a risk factor (Zec, 1995). Regarding this last point, Zec (1995, p. 431) goes so far as to comment that

the best defense against age-related cognitive deterioration is practice. Practice tends to mitigate the effects of aging by not allowing disuse to occur. In addition, practice can overcompensate for age effects by building a larger reserve capacity to offset any real neurobiological effects of age.

Support for the hypothesis that education and practice can serve as protective factors in some forms of cognitive decline can also be found in the rodent literature. For example, Kempermann, Kuhn and Gage (1998) have reported that the opportunity for social interaction, exploration and physical activity (some of the experiences that define complex environments) for 68 days resulted in an increased survival of granule cells in the dentate gyrus in both adult and ‘aged’ mice. The mice reared in complex environments also showed better performance in a water maze (e.g. shorter times to reach the underwater platform). Thus, at least in one region of the hippocampus (the dentate gyrus) and at least in one species (the mouse) there can be regeneration of cells during senescence, presumably derived from enriched experience.

In terms of protective factors, Meaney, Aitken, van Berkel, Bhatnagar and Sapolsky (1988) have demonstrated that rats that are separated at birth from their mothers (a stressor) but are then handled show less age-related loss of pyramidal cells in the CA1 and CA3 regions of the hippocampus, and fewer deficits in spatial memory. The authors hypothesize that the mechanism underlying this effect is the down-regulation of glucocorticoid secretion. Interestingly, glucocorticoids have also been shown to inhibit neurogenesis in the dentate gyrus (Gould, 1994; Gould, McEwen, Tanapat, Galea & Fuchs, 1997).

Changes in the neural substrate underlying cognition across the lifespan

Given that explicit memory abilities appear somewhat more vulnerable to aging than cognitive functions subserved by the regions of the brain that subserve implicit memory (which includes a range of abilities, and thus a range of structures, all of which lie outside the medial temporal lobe and the prefrontal cortex), it would be appropriate to examine the literature on brain and aging.

Although it was once thought that neuronal loss occurred on a widespread scale with aging, the latest evidence is that these early reports were erroneous, due largely to inadequate measures. It is now thought that there is little or no loss of cortical neurons with aging (see Wickelgren, 1996, for a review). In normally aging subjects, this includes the entorhinal cortex, a cortical structure critically involved in explicit memory. In contrast, nearly half of the cells in the entorhinal cortex are lost in patients with early dementia. If we consider glia instead of neurons, the picture is slightly different. There is some evidence, at

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least in the monkey, that there may be up to a 10% loss of myelin with age (Peters, Morrison, Rosene & Hyman, 1998). Indeed, Peters et al. have speculated that myelin loss may account for some of the deficits in aging. I shall return to this point below.

Autopsy studies of the aging brain provide details that are not easily acquired using conventional neuroimaging approaches such as magnetic resonance imaging (MRI), but they preclude the possibility of testing a heterogeneous population and a large number of subjects. In this context, several recent MRI studies should be mentioned. Lars-Olof, Almkvist, Basun and Julin (1996) studied adults ranging in age from 75 to 85 years, with a mean age of 79 years at the time of the first test. All subjects were healthy and were examples of ‘successful aging’. MRIs were done serially, at the beginning of the study, 2 years later and then 3 years after that. Neuropsychological testing was also performed. The authors reported that there was no change in neuropsychological functioning across age (with the exception of a subject who developed cerebral vascular disease). Second, there was a slowing in reaction time on some tasks. Third, the authors reported an increase in signal hyperintensities in the cerebrum, basal ganglia and infratentorial regions as well as increased cerebrospinal fluid volumes; importantly, none of these changes (which were all mild) related to neuropsychological outcomes.

The observation of slowing in reaction times is consistent with the Peters et al. (1998) finding of decreased myelin, given the relation between myelin and conduction velocity. Thus, rather than a loss of neurons per se accounting for some cognitive decline, it may well be that general information processing is slowed due to myelin loss.

Overall, the neurobiological evidence of aging is consistent with the neuropsychological evidence. In the normal, healthy brain, there is remarkable sparing of most cognitive functions and most neural structures. The one exception may be a decline in some explicit memory abilities, due, perhaps, to vulnerability of the limbic structures related to memory. However, as discussed previously, at least in the rat, enriched environments may provide some protection against hippocampal damage and, correspondingly, deficits in explicit memory. Similarly, avoiding exposure to acutely or, more importantly, chronically elevated levels of glucocorticoids may also confer some protection against memory loss due to hippocampal sparing. And, at least in the mouse, there is some evidence of experience-induced neurogenesis of dentate cells into senescence.

Why is there sparing of memory function across age?

It is important to ask why, under certain circumstances, there is sparing of memory circuits in aging (over and above the effects of enriched environments or the avoidance of experiences that lead to elevated levels of glucocorticoids). There are, of course, the ‘just so’ explanations, such as that it is adaptive for the organism to retain an intact memory system (e.g. in the case of the human, to remember the names and faces of one’s offspring and friends; to remember to take life-saving medications; to remember to turn the stove off). However, as a class these explanations are unsatisfying, primarily because just as many contrary explanations can be offered (e.g. if at the end of the lifespan we must be cared for by others, then, like the infant, there is no need to remember things because others will remember for you). Rather, I would like to approach this question from a developmental perspective. Is there sparing (or even lack of sparing) in cognitive systems (including memory) because of one’s developmental history (e.g. a surfeit or, conversely, a relative lack of education, of cognitively stimulating challenges etc.). To address this question requires that I take a step back and briefly talk about the ontogeny of memory.

I have previously speculated (Nelson, 1995) that infants’ proclivity for novelty appears very early in development due largely to a relatively mature hippocampus. This early maturation is what is probably responsible for even the newborn infant’s ability to make simple discriminations between novel and familiar stimuli. However, because the full medial temporal lobe circuit is not developed (which involves not just the hippocampus but the entorhinal cortex and the inferior temporal cortex), I referred to this primitive form of memory as ‘pre-explicit’ memory. I also suggested that as the circuitry we have come to associate with explicit memory matures, this pre-explicit memory system evolves into an explicit memory system. This evolution takes place as the infant approaches his or her first birthday, and probably continues over the next few years of life. I also speculated (see Nelson, 1997) that the development of the prefrontal cortex and the rich connections between the hippocampus and the prefrontal cortex account for the improvements we see in memory through the age of 8–9 years, notably in the use of strategies for remembering information (see Cowan (1997) for an overview of memory development broadly defined).

Like the motor system, the learning and memory system is exercised from birth, perhaps even earlier. For example, we know that newborn infants recognize their
mother’s voice reading a nursery rhyme they had only
heard as fetuses (DeCasper & Fifer, 1980; DeCasper &
Spence, 1986, 1991); further, many investigators have
shown that newborns are capable of novelty preferences
(see Pascalis & de Schonen, 1994; Pascalis, de Schonen,
This proclivity for novelty is, of course, the quintessen-
tial manifestation of an early-maturing memory system
as it suggests that infants are actively seeking out new
information and that they do so automatically (and in
the case of pre-explicit memory, possibly involuntarily).
Further, because of rapid developments in the neural
circuits that underlie pre-explicit and explicit memory,
this learning and memory system improves by leaps and
bounds over the first year of life. (Although there are no
data to speak to the issue, presumably these changes are
activity-dependent and do not simply reflect the
maturation of neural systems, although this hypothesis
must be considered.) In a boot-strapping fashion, then,
the infant comes into the world prepared to learn and
remember and in so doing builds on this system at a
rapid pace.

Neural plasticity of memory circuits

Perhaps also like the motor system, if the memory
system is continuously challenged, it should remain
pliable. Clearly the evidence cited earlier in this paper on
the preservation of memory across the lifespan supports
this claim. In addition, if the memory system is
challenged in a sophisticated manner, it should be
capable of sophisticated performance. There are many
examples in the literature to support this claim. Let us
take chess as an example. Chess masters and novices
were shown a chess board that contained the chess
pieces placed in strategic locations. After 5 s the
pieces were removed and the subjects were given a
blank board and asked to reconstruct the locations of
the original playing surface. The chess masters could
reproduce all or nearly all of the pieces whereas the
novices could only recall seven or eight pieces.
Importantly, there was no evidence that the chess masters
had superior memory for other things; rather, it was
simply that they used their memory more efficiently and
strategically, due entirely to selective experience (i.e.
their extensive experience playing chess; e.g. Chase &

In contrast, in the child whose explicit memory system
has been compromised in some way, being reared in the
equivalent of an enriched environment (see earlier
discussion) may prove protective. This last point can be
illustrated by work by Vargha-Khadem et al. (1997).

These authors discuss three case studies in which
damage occurred to the structures in the medial
temporal lobe that subserve explicit memory. In two
cases the damage occurred at birth and in one other, at
age 9. When tested later in life (ages 14, 19 and 22 years),
all three of these patients were reported to have suffered
from significant anterograde amnesia since the time of
their injury; in addition, neuropsychological evaluations
confirmed significant impairments in memory at the
time of study participation. All patients showed impair-
ments in spatial ability, temporal ability and episodic
memory ability; thus, all patients reported getting lost
easily, not being oriented to time and place, and easily
forgetting phone conversations, television programs and
the like. MRI revealed bilateral hippocampal pathology
in all three patients, which would, of course, be
consistent with their memory impairments. Remarkably,
all three individuals were attending or had attended
regular schools, and all had performed in the average to
low average range on a variety of tests that collectively
reflected semantic memory. Thus, they had learned to
read, write and spell (although one patient was not in
the normal range for spelling) and their speech and
language functions were normal, including normal
acquisition of word meaning. Thus, all three patients
had reasonably intact semantic memory in the face of
significant disturbances in episodic memory, and in the
face of bilateral hippocampal damage. The authors
proposed that, because the rhinal cortex was intact in
these individuals, all retained the ability to form context-
free semantic memories; but, because of hippocampal
damage, none developed the ability to form context-rich
episodic memories. Although this is reasonable, an
alternative interpretation is that the hippocampus is
necessary for semantic memory as well (a subset of
explicit memory; see Squire & Zola, 1996) and under
these circumstances exhibited plasticity (see below).

These data provide a compelling example of neural
plasticity. Specifically, in the face of early, discrete brain
damage, leading to permanent disability in episodic
memory, compensation occurred that permitted normal
development in many memory-related domains. The
precise mechanisms underlying this compensation are
not known, although perhaps some insight might be
gained from work with the developing monkey. For
example, Webster, Ungerleider and Bachevalier (1991)
have reported that a transient projection is observed
from inferior cortical area TE to the lateral basal
nucleus of the amygdala in the normally developing
monkey. This projection is retracted later in develop-
ment and is not present in the adult. However, when
area TE (which lies adjacent to TEO) is removed during
the neonatal period, this normally transient projection is
seen in the adult. In addition, transient projections from area TEO to the dorsal part of the lateral nucleus of the amygdala tend to expand into the zone normally occupied by terminals from area TE when TE is lesioned in infancy; these projections normally disappear in the adult. Webster and colleagues have speculated that the sparing in performance on memory tasks such as the delayed non-match-to-sample that has been observed with early TE lesions may be due to the retention of these early transient projections. Similarly, the presence of these transient projections early in life in the intact animal, followed by their retraction, may be responsible for my observation that development of pre-explicit memory precedes development of explicit memory, as the former depends primarily on the hippocampus whereas the latter also depends on cortical area TE.

We do not know if something comparable to Webster’s monkeys occurred in Vargha-Khadem’s patients; for example, perhaps normally exuberant connections between the rhinal cortex and the hippocampus were retained instead of vanishing, and this was in part responsible for the preservation in semantic memory. Nor do we know if the sparing observed in these patients might have been due to the special education these children received, which was tantamount to an enrichment program. The outcome, however, is consistent with the literature reviewed earlier. At the neural level the sparing of the rhinal cortex probably enabled other structures in the explicit memory system to take over the functions of the hippocampus (assuming, of course, that the hippocampus plays a role in semantic memory). Presumably it was the enriched experiences these children were exposed to that facilitated these changes at the neural level.

In contrast to sparing and recovery of function, it must be acknowledged that there is life-long vulnerability of the memory circuits that underlie explicit memory. An example of such vulnerability concerns the effects of elevated glucocorticoids on the hippocampus and memory. For example, we know that children and adults who experience chronic stress have poorer memories than those not subjected to such environments (see Nelson & Carver, 1998, for a review). Thus, one might predict that a significant risk factor in disorders of memory development, or the lack of sparing in memory across the lifespan, might be due to exposure to chronic stress. This hypothesis, of course, remains to be evaluated.

Conclusions

Based on a critical examination of the role of early experience in influencing the development of the sensory, motor and speech systems, the following proposal is offered. We are born with the ability to learn and remember, in part because our hippocampus is sufficiently mature to direct the infant to novel events and experiences (what happens in premature birth is not known). If the infant is exposed to normal experiences and there is no damage to the hippocampus, the remaining structures that comprise the explicit memory system (e.g. entorhinal cortex, cortical area TE) will develop over the first year or so of life. These events, then, coupled with the further development of the hippocampus and related structures (which itself is possibly due to experience), essentially set the memory system to receive additional experience over the course of the lifespan. Assuming that this more mature memory system continues to be exercised by being exposed to enriched, challenging experiences, we will retain an intact memory across much of the lifespan. However, if this system is compromised in some way, such as by being exposed to chronic stress or overt damage (e.g. ischemia), or if we fail to use this system (the principle of disuse), then we increase the likelihood of experiencing deficits in memory or, perhaps more subtly, a decline in memory as we age.

The model I have proposed is more speculative than I would like. But it is consistent with the evidence reviewed from other modalities and systems. Collectively, the evidence suggests that the likelihood of a given behavioral system showing signs of recovery of function, or sparing, would depend on whether the system being challenged is one that has had the right early experience to ‘set’ the system (such as exposure to normal language or, in the case of memory, novel experiences) and is continually challenged thereafter. Thus, it may be that the success of the language intervention developed by Tallal and Merzenich rests on the fact that the auditory input these children received early in life was normal (although their brains did not respond normally to this input) and that this input was maintained. And it should also be the case that if we continuously challenge our cognitive systems (e.g. memory) and incur only routine decline in the neural systems that underlie cognition as we age, we should be spared the ravages of time, and perhaps even moderate insult. Certainly that is something we can all hope for.

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